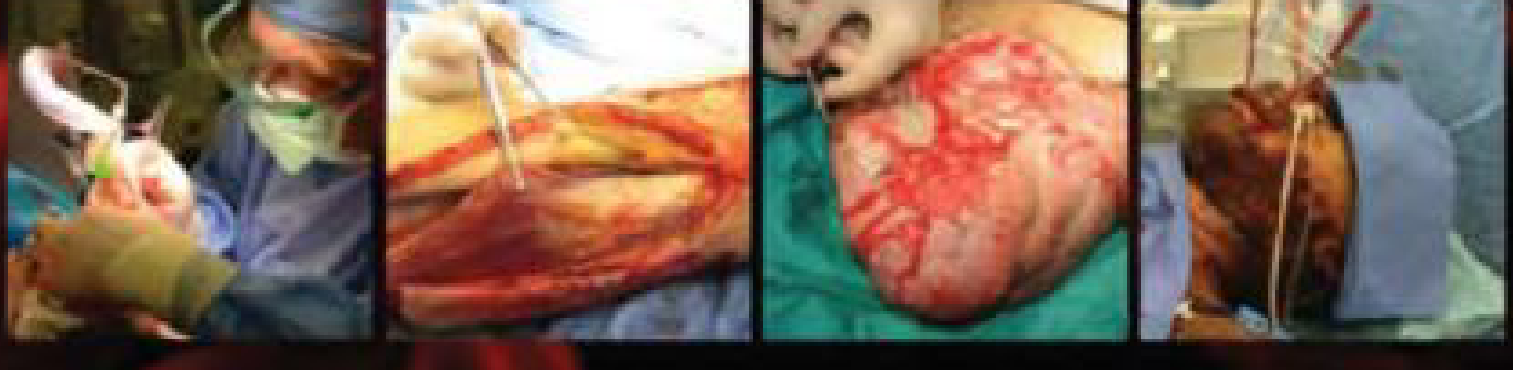
TOTAL BURN CARE

David N. Herndon



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ELSEVIER

Edinburgh London New York Oxford Philadelphia St Louis Sydney 2018

ELSEVIER

First edition 1996
Second edition 2002
Third edition 2007
Fourth edition 2012
Fifth edition 2018

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ISBN: 978-0-323-47661-4
eISBN: 978-0-323-49742-8
Printed in China
Last digit is the print number: 9 8 7 6 5 4 3 2 1

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Content Development Specialist: Nani Clansey
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Preface

Over the past three decades, vast improvements in survival from severe burns have been accompanied by a progressively greater understanding of the complex processes underlying this type of trauma. Basic science, and translational and clinical discoveries have provided new opportunities to advance burn care along its entire spectrum from management of burn shock, inhalation injury, sepsis, and hypermetabolism to scar reconstruction and rehabilitation. These and other key aspects of care, which are the focus of this book, share the goal of providing burn survivors more complete recovery from burns so that they can return to their communities as fully functioning members. All aspects of the physiological, psychological, and emotional care of acutely burned patients evolving through recovery, rehabilitation, and reintegration back into society and daily life are reexamined in this new, fifth edition.

The objective of the fifth edition of this book remains the same—to serve as a sophisticated instruction manual for a variety of health care professionals less experienced in burns. It is intended to be a resource not only for surgeons, anesthesiologists, and residents, but also for nurses and allied health professionals. Although this edition of the book covers many of the same fundamental concepts and techniques as the previous edition, the chapters have been extensively updated with new data and references to reflect advances in care and knowledge that have arisen over the past 5 years. In some cases, the chapters have been completely rewritten. The new edition also contains new chapters dealing with the care of unique populations, as well as newer topics in reconstruction and scarring. As before, demonstrative color illustrations are provided throughout the book. Moreover, many chapters are accompanied by online PowerPoint presentations to aid group discussion, as well as video clips to enhance understanding of complex concepts and techniques.

This new edition would not be possible without the many respected colleagues and friends who have volunteered their time and worked tirelessly to produce the various chapters. Grateful acknowledgment is also given to Elsevier publishing staff, who have maintained a high standard in the development and preparation of this fifth edition. Special thanks are offered to Dr. Derek Culnan, who graciously assisted in reviewing and updating material throughout the book, as well as to Genevieve Bitz and Dr. Kasie Cole for editorial assistance. Finally, I wish to thank my wife, Rose, for her invaluable support.

In Memorium of Ted Huang, MD

Derek Culnan, MD, Genevieve Bitz, Karel D. Capek, MD, David Herndon, MD

Last year, returning with his wife from a medical mission trip to Taiwan, Dr. Ted Huang died. On that day, we lost a colleague; a friend; and a surgeon of unquestioned skill, passion, and knowledge as well as a teacher unstinting in his advice and zeal to help others. Following a career as a leader in the fields of gender reassignment and cosmetic surgery, Dr. Huang retired to spend the next 20 years working to revolutionize the practice of surgical reconstruction of pediatric burns. He left behind a legacy in research and surgery in the papers he authored and the surgeons he mentored that few can achieve. He was the principal author of the previous four editions of the reconstructive section of this book. Stepping into the OR filled him with joy, for he was a man who truly loved and lived his career. When a surgical fellow once asked if he could assist, Dr. Huang responded, "I've been operating on burn scars since before you were born. If I need your help, then the patient and I both have a big problem. But, if you want, you can come have fun with me." We are better for having known him, and our principal regret is that we never figured out the recipe for his legendary bread, which, as with everything, he doled out generously to family, friends, patients, and colleagues. As he would undoubtedly have said, that's how the cookie crumbles. This book is a testimonial to his humanity and skill, from those he collaborated with and those he mentored. Thank you, Dr. Huang, for everything.

With greatest honor and humility we dedicate this book to you.

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1 A Brief History of Acute Burn Care Management

LUDWIK K. BRANSKI, DAVID N. HERNDON, and ROBERT E. BARROW

The recognition of burns and their treatment is evident in cave paintings that are more than 3500 years old. Documentation in the Egyptian Smith papyrus of 1500 BC advocated the use of a salve of resin and honey for treating burns.[1] In 600 BC, the Chinese used tinctures and extracts from tea leaves. Nearly 200 years later, Hippocrates described the use of rendered pig fat and resin-impregnated bulky dressings, which was alternated with warm vinegar soaks augmented with tanning solutions made from oak bark. Celsus, in the 1st century AD, mentioned the use of wine and myrrh as a lotion for burns, most probably for their bacteriostatic properties.[1] Vinegar and exposure of the open wound to air was used by Galen (130–210 AD) as a means of treating burns, while the Arabian physician Rhases recommended cold water for alleviating the pain associated with burns. Ambroise Paré (1510–1590 AD), who effectively treated burns with onions, was probably the first to describe a procedure for early burn wound excision. In 1607, Guilhelmus Fabricius Hildanus, a German surgeon, published *De Combustionibus*, in which he discussed the pathophysiology of burns and made unique contributions to the treatment of contractures. In 1797, Edward Kentish published an essay describing pressure dressings as a means to relieve burn pain and blisters. Around this same time, Marjolin identified squamous cell carcinomas that developed in chronic open burn wounds. In the early 19th century, Guillaume Dupuytren (Fig. 1.1) reviewed the care of 50 burn patients treated with occlusive dressings and developed a classification of burn depth that remains in use today.[2] He was perhaps the first to recognize gastric and duodenal ulceration as a complication of severe burns, a problem that was discussed in more detail by Curling of London in 1842.[3] In 1843, the first hospital for the treatment of large burns used a cottage on the grounds of the Edinburgh Royal Infirmary.

Truman G. Blocker Jr. (Fig. 1.2) may have been the first to demonstrate the value of the multidisciplinary team approach to disaster burns when, on April 16, 1947, two freighters loaded with ammonium nitrate fertilizer exploded at a dock in Texas City, killing 560 people and injuring more than 3000. At that time, Blocker mobilized the University of Texas Medical Branch in Galveston, Texas, to treat the arriving truckloads of casualties. This "Texas City Disaster" is still known as the deadliest industrial accident in American history. Over the next 9 years, Truman and Virginia Blocker followed more than 800 of these burn patients and published a number of papers and government reports on their findings.[4–6] The Blockers became renowned for their work in advancing burn care, with both receiving the Harvey Allen Distinguished Service Award from the American Burn Association (ABA). Truman Blocker Jr. was also recognized for his pioneering research in treating burns "by cleansing, exposing the burn wounds to air, and feeding them as much as they could tolerate."[7] In 1962, his dedication to treating burned children convinced the Shriners of North America to build their first Burn Institute for Children in Galveston, Texas.[7]

Between 1942 and 1952, shock, sepsis, and multiorgan failure caused a 50% mortality rate in children with burns covering 50% of their total body surface area (TBSA).[8] Recently burn care in children has improved survival such that a burn covering more than 95% TBSA can be survived in more than 50% of cases.[9] In the 1970s, Andrew M. Munster (Fig. 1.3) became interested in measuring quality of life after excisional surgery and other improvements led to a dramatic decrease in mortality. First published in 1982, his Burn Specific Health Scale became the foundation for most modern studies in burns outcome.[10] The scale has since been updated and extended to children.[11]

Further improvements in burn care presented in this brief historical review include excision and coverage of the burn wound, control of infection, fluid resuscitation, nutritional support, treatment of major inhalation injuries, and support of the hypermetabolic response.

Early Excision

In the early 1940s, it was recognized that one of the most effective therapies for reducing mortality from a major thermal injury was the removal of burn eschar and immediate wound closure.[12] This approach had previously not been practical in large burns owing to the associated high rate of infection and blood loss. Between 1954 and 1959, Douglas Jackson and colleagues at the Birmingham Accident Hospital advanced this technique in a series of pilot and controlled trials starting with immediate fascial excision and grafting of small burn areas and eventually covering up to 65% of the TBSA with autograft and homograft skin.[13] In this breakthrough publication, Jackson concluded that "with adequate safeguards, excision and grafting of 20% to 30% body surface area can be carried out on the day of injury without increased risk to the patient." This technique, however, was far from being accepted by the majority of burn surgeons, and delayed serial excision remained the prevalent approach to large burns. It was Zora Janzekovic (Fig. 1.4), working alone in Yugoslavia in the 1960s, who developed the concept of removing deep second-degree burns by tangential excision with a simple uncalibrated knife. She treated 2615 patients with deep second-degree burns by tangential excision of eschar between the third and fifth days after burn and covered the

Fig. 1.1 Guillaume Dupuytren.

Fig. 1.2 Truman G. Blocker Jr.

Fig. 1.3 Andrew M. Munster.

Fig. 1.4 Zora Janzekovic.

excised wound with skin autograft.[14] Using this technique, burned patients were able to return to work within 2 weeks or so from the time of injury. For her achievements, in 1974, she received the ABA Everett Idris Evans Memorial Medal and, in 2011, the ABA lifetime achievement award.

In the early 1970s, William Monafo (Fig. 1.5) was one of the first Americans to advocate the use of tangential excision and grafting of larger burns.[15] John Burke (Fig. 1.6), while at Massachusetts General Hospital in Boston, reported unprecedented survival in children with burns of more than 80% TBSA.[16] His use of a combination of tangential excision for the smaller burns (Janzekovic's technique) and excision to the level of fascia for the larger burns resulted in a decrease in both hospital time and mortality. Lauren Engrav et al.,[17] in a randomized prospective study, compared tangential excision to nonoperative treatment of burns. This study showed that, compared to nonoperative treatment, early excision and grafting of deep second-degree burns reduced hospitalization time and hypertrophic scarring. In 1988, Ron G. Tompkins et al.,[18] in a statistical review of the Boston Shriners Hospital patient population from 1968 to 1986, reported a dramatic decrease in mortality in severely burned children that he attributed mainly to the advent of early excision and grafting of massive burns in use since the 1970s. In a randomized prospective trial of 85 patients with third-degree burns covering 30% or more of their TBSA, Herndon et al.[19] reported a decrease in mortality in those treated with early excision of the entire wound compared to conservative treatment. Other studies have reported that prompt excision

Fig. 1.5 William Monafo.

Fig. 1.6 John Burke.

of the burn eschar improves long-term outcome and cosmesis, thereby reducing the amount of reconstructive procedures required.

Skin Grafting

Progress in skin grafting techniques has paralleled the developments in wound excision. In 1869, J. P. Reverdin, a Swiss medical student, successfully reproduced skin grafts.[20] In the 1870s, George David Pollock popularized the method in England.[21] The method gained widespread attention throughout Europe, but because the results were extremely variable it quickly fell into disrepute. J. S. Davis resurrected this technique in 1914 and reported the use of "small deep skin grafts," which were later known as "pinch grafts."[22] Split-thickness skin grafts became more popular during the 1930s, due in part to improved and reliable instrumentation. The "Humby knife," developed in 1936, was the first reliable dermatome, but its use was cumbersome. E. C. Padgett developed an adjustable dermatome that had cosmetic advantages and allowed the procurement of a consistent split-thickness skin graft.[23,24] Padgett also developed a system for categorizing skin grafts into four types based on thickness.[25] In1964 J. C. Tanner Jr. and colleagues revolutionized wound grafting with the development of the meshed skin graft;[26] however for prompt excision and immediate wound closure to be practical in burns covering more than 50% of the TBSA, alternative materials and approaches to wound closure were necessary. To meet these demands, a system of cryopreservation and long-term storage of human skin for periods extending up to several months was developed.[27] Although controversy surrounds the degree of viability of the cells within the preserved skin, this method has allowed greater flexibility in the clinical use of autologous skin and allogenic skin harvested from cadavers. J. Wesley Alexander (Fig. 1.7) developed a simple method for widely expanding autograft skin and then covering it with cadaver skin.[28] This so-called "sandwich technique" has been the mainstay of treatment of massively burned individuals.

Fig. 1.7 J. Wesley Alexander.

In 1981, John Burke and Ioannis Yannas developed an artificial skin that consists of a silastic epidermis and a porous collagen–chondroitin dermis and is marketed today as Integra. Burke was also the first to use this artificial skin on very large burns that covered more than 80% of the TBSA.[29] David Heimbach led one of the early multicenter randomized clinical trials using Integra.[30] Its use in the

coverage of extensive burns has remained limited partly due to the persistently high cost of the material and the need for a two-stage approach. Integra has since become popular for smaller immediate burn coverage and burn reconstruction. In 1989, J. F. Hansbrough and S. T. Boyce first reported the use of cultured autologous keratinocytes and fibroblasts on top of a collagen membrane (composite skin graft; CSS).[31] A larger trial by Boyce[32] revealed that the use of CSS in extensive burns reduces the requirement for harvesting of donor skin compared to conventional skin autografts and that the quality of grafted skin did not differ between CSS and skin autograft after 1 year. The search for an engineered skin substitute to replace all of the functions of intact human skin is ongoing; composite cultured skin analogs, perhaps combined with mesenchymal stem cells, may offer the best opportunity for better outcomes.[33,34]

Topical Control of Infection

Infection control is an important major advancement in burn care that has reduced mortality. One of the first topical antimicrobials, sodium hypochlorite (NaClO), discovered in the 18th century, was widely used as a disinfectant throughout the 19th century, but its use was frequently associated with irritation and topical reactions.[35] In 1915, Henry D. Dakin standardized hypochlorite solutions and described the concentration of 0.5% NaClO as most effective.[36] His discovery came at a time when scores of severely wounded soldiers were dying of wound infections on the battlefields of World War I. With the help of a Rockefeller Institute grant, Dakin teamed up with the then already famous French surgeon and Nobel Prize winner Alexis Carrel to create a system of mechanical cleansing, surgical débridement, and topical application of hypochlorite solution, which was meticulously protocolized and used successfully in wounds and burns.[37] Subsequently concentrations of sodium hypochlorite were investigated for antibacterial activity and tissue toxicity in vitro and in vivo, and it was found that a concentration of 0.025% NaClO was most efficacious because it had sufficient bactericidal properties but fewer detrimental effects on wound healing.[38]

Mafenide acetate (Sulfamylon), a drug used by the Germans for treatment of open wounds in World War II, was adapted for treating burns at the Institute of Surgical Research in San Antonio, Texas, by microbiologist Robert Lindberg and surgeon John Moncrief.[39] This antibiotic would penetrate third-degree eschar and was extremely effective against a wide spectrum of pathogens. Simultaneously, in New York, Charles Fox developed silver sulfadiazine cream (Silvadene), which was almost as efficacious as mafenide acetate.[40] Although mafenide acetate penetrates the burn eschar quickly, it is a carbonic anhydrase inhibitor that can cause systemic acidosis and compensatory hyperventilation and may lead to pulmonary edema. Because of its success in controlling infection in burns combined with minimal side effects, silver sulfadiazine has become the mainstay of topical antimicrobial therapy.

Carl Moyer and William Monafo initially used 0.5% silver nitrate soaks as a potent topical antibacterial agent for burns, a treatment that was described in their landmark publication[41] and remains the treatment of choice in many burn centers today. With the introduction of efficacious silver-containing topical antimicrobials, burn wound sepsis rapidly decreased. Early excision and coverage further reduced the morbidity and mortality from burn wound sepsis. Nystatin in combination with silver sulfadiazine has been used to control *Candida* at Shriners Burns Hospital for Children in Galveston, Texas.[42] Mafenide acetate, however, remains useful in treating invasive wound infections.[43]

Nutritional Support

P. A. Shaffer and W. Coleman advocated high caloric feeding for burn patients as early as 1909,[44] and D. W. Wilmore supported supranormal feeding with a caloric intake as high as 8000 kcal/day.[45] P. William Curreri (Fig. 1.8) retrospectively looked at a number of burned patients to quantify the amount of calories required to maintain body weight over a period of time. In a study of nine adults with 40% TBSA burns, he found that maintenance feeding at 25 kcal/kg plus an additional 40 kcal/% TBSA burned per day would maintain their body weight during acute hospitalization.[46] A. B. Sutherland proposed that children should receive 60 kcal/kg body weight plus 35 kcal/% TBSA burned per day to maintain their body weight.[47] D. N. Herndon et al. subsequently showed that supplemental parenteral nutrition increased both immune deficiency and mortality and recommended continuous enteral feeding, when tolerated, as a standard treatment for burns.[48]

The composition of nutritional sources for burned patients has been debated in the past. In 1959, F. D. Moore advocated that the negative nitrogen balance and weight loss in burns and trauma should be met with an adequate intake of nitrogen and calories.[49] This was supported by many others, including T. Blocker Jr.,[50] C. Artz, [51] and later by Sutherland.[47]

Fig. 1.8 P. William Curreri.

Fluid Resuscitation

The foundation of current fluid and electrolyte management began with the studies of Frank P. Underhill, who, as Professor of Pharmacology and Toxicology at Yale, studied 20 individuals burned in a 1921 fire at the Rialto Theatre.[52] Underhill found that the composition of blister fluid was similar to that of plasma and could be replicated by a salt solution containing protein. He suggested that burn patient mortality was due to loss of fluid and not, as previously thought, from toxins. In 1944, C. C. Lund and N. C. Browder estimated burn surface areas and developed diagrams by which physicians could easily draw the burned areas and derive a quantifiable percent describing the surface area burned.[53] This led to fluid replacement strategies based on surface area burned. G. A. Knaysi et al. proposed a simple "rule-of-nines" for evaluating the percentage of body surface area burned.[54] In the late 1940s, O. Cope and F. D. Moore (Figs. 1.9 and 1.10) were able to quantify the amount of fluid required per area burned for adequate resuscitation from the amount needed in young adults who were trapped inside the burning Coconut Grove Nightclub in Boston in 1942. They postulated that the space between cells was a major recipient of plasma loss, causing swelling in both injured and uninjured tissues in proportion to the burn size.[55] Moore concluded that additional fluid, over that collected from the bed sheets and measured as evaporative water loss, was needed in the first 8 hours after burn to replace "third space" losses. He then developed a formula for replacement of fluid based on the percent of the body surface area burned.[56] M. G. Kyle and A. B. Wallace showed that the heads of children were relatively larger and the legs relatively shorter than in adults, and they modified the fluid replacement formulas for use in children.[57] I. E. Evans and his colleagues made recommendations relating fluid requirements to body weight and surface area burned.[58] From their recommendations, intravenous infusion of normal saline plus colloid (1.0 mL per kg/% burn) along with 2000 mL dextrose 5% solution to cover insensible water losses was administered over the first 24 hours after burn. One year later, E. Reiss presented the Brooke formula, which modified the Evans formula by substituting lactated Ringer's for normal saline and reducing the amount of colloid given.[59] Charles R. Baxter (Fig. 1.11) and G. Tom Shires (Fig. 1.12) developed a formula without colloid, which is now referred to as the Parkland formula.[60] This is perhaps the most widely used formula today and recommends 4 mL of lactated Ringer's solution per kg/% TBSA burned during the first 24 hours after burn. All these formulas advocate giving half of the fluid in the first 8 hours

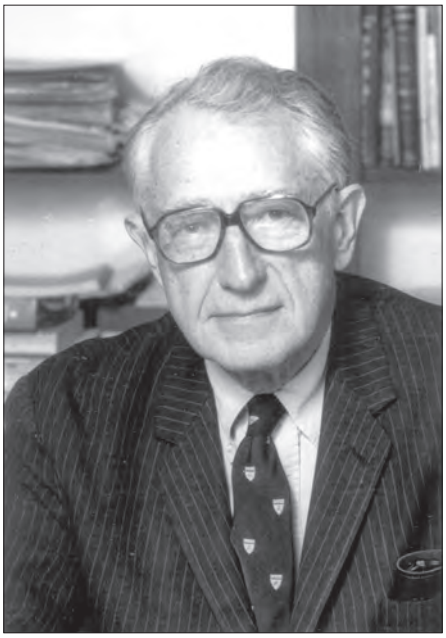

Fig. 1.10 Francis D. Moore.

Fig. 1.9 Oliver Cope.

Fig. 1.11 Charles R. Baxter.

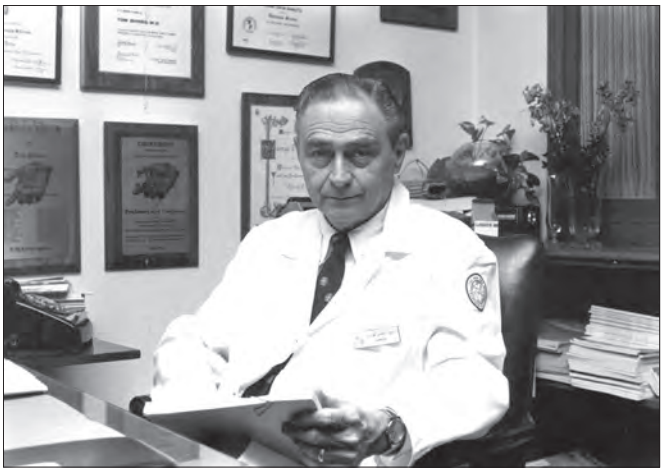

Fig. 1.12 G. Tom Shires.

after burn and the other half in the subsequent 16 hours. Baxter and Shires discovered that after a cutaneous burn, not only is fluid deposited in the interstitial space, but marked intracellular edema also develops. The excessive disruption of the sodium–potassium pump activity results in the inability of cells to remove excess fluid. They also showed that protein, given in the first 24 hours after injury, was not necessary and postulated that, if used, it would leak out of the vessels and exacerbate edema. This was later substantiated in studies of burn patients with toxic inhalation injuries.[61] After a severe thermal injury fluid accumulates in the wound, and, unless there is adequate and early fluid replacement, hypovolemic shock will develop. A prolonged systemic inflammatory response to severe burns can lead to multiorgan dysfunction, sepsis, and even mortality. It has been suggested that, for maximum benefit, fluid resuscitation should begin as early as 2 hours after burn.[9,62] Fluid requirements in children are greater with a concomitant inhalation injury, delayed fluid resuscitation, and larger burns.

Inhalation Injury

During the 1950s and 1960s, burn wound sepsis, nutrition, kidney dysfunction, wound coverage, and shock were the main foci of burn care specialists. Over the past 50 years, these problems have been clinically treated with increasing success; hence a greater interest in a concomitant inhalation injury evolved. A simple classification of inhalation injury separates problems occurring in the first 24 hours after injury, which include upper airway obstruction and edema, from those that manifest after 24 hours. These include pulmonary edema and tracheobronchitis, which can progress to pneumonia, mucosal edema, and airway occlusion due to the formation of airway plugs from mucosal sloughing.[63,64] The extent of damage from the larynx to tracheobronchial tree depends on the solubility of the toxic substance and the duration of exposure. Nearly 45% of inhalation injuries are limited to the upper passages above the vocal cords, and 50% have an injury to the major airways. Less than 5% have a direct

Fig. 1.13 Basil A. Pruitt.

parenchymal injury that results in early acute respiratory death.[64]

With the development of objective diagnostic methods, the incidence of an inhalation injury in burned patients can now be identified and its complications identified. Xenon-133 scanning was first used in 1972 in the diagnosis of inhalation injury.[65,66] When this radioisotope method is used in conjunction with a medical history, the identification of an inhalation injury is quite reliable. The fiberoptic bronchoscope is another diagnostic tool that, under topical anesthesia, can be used for the early diagnosis of an inhalation injury.[67] It is also capable of pulmonary lavage to remove airway plugs and deposited particulate matter.

K. Z. Shirani, Basil A. Pruitt (Fig. 1.13), and A. D. Mason reported that smoke inhalation injury and pneumonia, in addition to age and burn size, greatly increased burn mortality.[68] The realization that the physician should not underresuscitate burn patients with an inhalation injury was emphasized by P. D. Navar et al.[69] and D. N. Herndon et al.[70] A major inhalation injury requires 2 mL per kg/% TBSA burn more fluid in the first 24 hours after burn to maintain adequate urine output and organ perfusion. Multicenter studies looking at patients with acute respiratory distress syndrome (ARDS) have advocated respiratory support at low peak pressures to reduce the incidence of barotrauma. The high-frequency oscillating ventilator, advocated by C. J. Fitzpatrick[71] and J. Cortiella et al.,[72] has added the benefit of pressure ventilation at low tidal volumes plus rapid inspiratory minute volume, which provides a vibration to encourage inspissated sputum to travel up the airways. The use of heparin, *N*-acetylcysteine, nitric oxide inhalation, and bronchodilator aerosols have also been used with some apparent benefit, at least in pediatric populations.[73] Inhalation injury remains one of the most prominent causes of death in thermally injured patients. In children, the lethal burn area for a 10% mortality without a concomitant

inhalation injury is 73% TBSA; however with an inhalation injury, the lethal burn size for a 10% mortality rate is 50% TBSA.[74]

Hypermetabolic Response to Trauma

Major decreases in mortality have also resulted from a better understanding of how to support the hypermetabolic response to severe burns. This response is characterized by an increase in the metabolic rate and peripheral catabolism. The catabolic response was described by H. Sneve as exhaustion and emaciation, and he recommended a nourishing diet and exercise.[75] O. Cope et al.[76] quantified the metabolic rate in patients with moderate burns, and Francis D. Moore advocated the maintenance of cell mass by continuous feeding to prevent catabolism after trauma and injury.[77] Over the past 30 years, the hypermetabolic response to burn has been shown to increase metabolism, negative nitrogen balance, glucose intolerance, and insulin resistance. In 1974, Douglas Wilmore and colleagues defined catecholamines as the primary mediator of this hypermetabolic response and suggested that catecholamines were five- to sixfold elevated after major burns, thereby causing an increase in peripheral lipolysis and catabolism of peripheral protein.[78] In 1984, P. Q. Bessey demonstrated that the stress response required not only catecholamines but also cortisol and glucagon.[79] Wilmore et al. examined the effect of ambient temperature on the hypermetabolic response to burns and reported that burn patients desired an environmental temperature of 33°C and were striving for a core temperature of 38.5°C.[80] Warming the environment from 28°C to 33°C substantially decreased the hypermetabolic response, but did not abolish it. He suggested that the wound itself served as the afferent arm of the hypermetabolic response, and its consuming greed for glucose and other nutrients was at the expense of the rest of the body.[81] Wilmore also believed that heat was produced by biochemical inefficiency, which was later defined by Robert Wolfe as futile substrate cycling.[82] Wolfe et al. also demonstrated that burned patients were glucose intolerant and insulin resistant, with an increase in glucose transport to the periphery but a decrease in glucose uptake into the cells.[83] D. W. Hart et al. further showed that the metabolic response rose with increasing burn size, reaching a plateau at a 40% TBSA burn.[84]

In the past three decades, pharmacologic modulators, such as the β-receptor antagonist propranolol, the anabolic agent human recombinant growth hormone, the synthetic anabolic testosterone analog oxandrolone, insulin, and the glucose uptake modulator metformin, have all shown some beneficial effects in reducing the hypermetabolic response in burn patients.

Conclusion

The evolution of burn treatments has been extremely productive over the past 50 years. The mortality of severely burned patients has decreased significantly thanks to improvements in early resuscitation, infection control, nutrition, attenuation of the hypermetabolic response, and new and improved surgical approaches. In burned children, a 98% TBSA burn now has a 50% survival rate.[74] It is hoped that the next few years will witness the development of an artificial skin that combines the concepts of J. F. Burke [29] with the tissue culture technology described by E. Bell.[85] Inhalation injury, however, remains one of the major determinants of mortality in those with severe burns. Further improvements in the treatment of inhalation injuries are expected through the development of arterial venous carbon dioxide removal and extracorporeal membrane oxygenation devices.[86] Research continues to strive for a better understanding of the pathophysiology of burn scar contractures and hypertrophic scarring.[87] Although decreases in burn mortality can be expected, continued advances to rehabilitate patients and return them to productive life are an important step forward in burn care management.

Complete references available online at
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Further Reading

Baxter CR, Shires T. Physiological response to crystalloid resuscitation of severe burns. *Ann N Y Acad Sci*. 1968;150(3):874-894.

Burke JF, Yannas IV, Quinby WC Jr, et al. Successful use of a physiologically acceptable artificial skin in the treatment of extensive burn injury. *Ann Surg*. 1981;194(4):413-428.

Hansbrough JF, Boyce ST, Cooper ML, et al. Burn wound closure with cultured autologous keratinocytes and fibroblasts attached to a collagen-glycosaminoglycan substrate. *JAMA*. 1989;262(15):2125-2130.

Janzekovic Z. A new concept in the early excision and immediate grafting of burns. *J Trauma*. 1970;10(12):1103-1108.

Tompkins RG, Remensnyder JP, Burke JF, et al. Significant reductions in mortality for children with burn injuries through the use of prompt eschar excision. *Ann Surg*. 1988;208(5):577-585.

Wilmore DW, Long JM, Mason AD Jr, et al. Catecholamines: mediator of the hypermetabolic response to thermal injury. *Ann Surg*. 1974;180(4):653-669.

References

1. Majno G. *The Healing Hand: Man and Wound in the Ancient World*. Cambridge, MA: Harvard University Press; 1975.
2. Dupuytren G, Brierre de Boismont A-J-F, Paillard ALM. *Leçons Orales de Clinique Chirurgicale, Faites à l'Hôtel-Dieu de Paris*. Paris: Baillière; 1839.
3. Curling TB. On acute ulceration of the duodenum, in cases of burn. *Med Chir Trans*. 1842;25:260-281.
4. Blocker V, Blocker TG Jr. The Texas City disaster: a survey of 3,000 casualties. *Am J Surg*. 1949;78(5):756-771.
5. Hendrix JH Jr, Blocker TG Jr, Blocker V. Plastic surgery problems in the Texas City disaster. *Plast Reconstr Surg*. 1949;4(1):92-97.
6. Blocker TG Jr, Blocker V, Graham JE, et al. Follow-up medical survey of the Texas City disaster. *Am J Surg*. 1959;97(5):604-617.
7. Bremer J. Giant. The saga of the first man to be called president of UTMB: Truman Graves Blocker Jr., M.D. *UTMB Quarterly*. 2000;(Summer/Fall):6-13.
8. Bull JP, Fisher AJ. A study of mortality in a burns unit: a revised estimate. *Ann Surg*. 1954;139(3):269-274.
9. Wolf SE, Rose JK, Desai MH, et al. Mortality determinants in massive pediatric burns. An analysis of 103 children with > or = 80% TBSA burns (> or = 70% full-thickness). *Ann Surg*. 1997;225(5):554-565, discussion 565-559.
10. Blades B, Mellis N, Munster AM. A burn specific health scale. *J Trauma*. 1982;22(10):872-875.
11. Munster AM, Horowitz GL, Tudahl LA. The abbreviated Burn-Specific Health Scale. *J Trauma*. 1987;27(4):425-428.
12. Cope O, Langohr JL, et al. Expeditious care of full-thickness burn wounds by surgical excision and grafting. *Ann Surg*. 1947;125(1):1-22.
13. Jackson D, Topley E, Cason JS, et al. Primary excision and grafting of large burns. *Ann Surg*. 1960;152:167-189.
14. Janzekovic Z. A new concept in the early excision and immediate grafting of burns. *J Trauma*. 1970;10(12):1103-1108.
15. Monafo WW. Tangential excision. *Clin Plast Surg*. 1974;1(4):591-601.
16. Burke JF, Bondoc CC, Quinby WC. Primary burn excision and immediate grafting: a method shortening illness. *J Trauma*. 1974;14(5):389-395.
17. Engrav LH, Heimbach DM, Reus JL, et al. Early excision and grafting vs. nonoperative treatment of burns of indeterminant depth: a randomized prospective study. *J Trauma*. 1983;23(11):1001-1004.
18. Tompkins RG, Remensnyder JP, Burke JF, et al. Significant reductions in mortality for children with burn injuries through the use of prompt eschar excision. *Ann Surg*. 1988;208(5):577-585.
19. Herndon DN, Barrow RE, Rutan RL, et al. A comparison of conservative versus early excision. Therapies in severely burned patients. *Ann Surg*. 1989;209(5):547-553.
20. Reverdin JP. Greffe epidermique. *Bull Soc Chir Paris*. 1869;101.
21. Freshwater MF, Krizek TJ. Skin grafting of burns: a centennial. A tribute to George David Pollock. *J Trauma*. 1971;11(10):862-865.
22. Davis JP. The use of small deep skin grafts. *JAMA*. 1914;63:985-989.
23. Padgett EC. Calibrated intermediate skin grafts. *Surg Gynecol Obstet*. 1939;69:779-793.
24. Padgett EC. Skin grafting and the 'three-quarter'-thickness skin graft for prevention and correction of cicatricial formation. *Ann Surg*. 1941;113(6):1034-1049.
25. Padgett EC. Indications for determination of the thickness of split skin grafts. *Am J Surg*. 1946;72(5):683-693.
26. Tanner JC Jr, Vandeput J, Olley JF. The mesh skin graft. *Plast Reconstr Surg*. 1964;34:287-292.
27. Bondoc CC, Burke JF. Clinical experience with viable frozen human skin and a frozen skin bank. *Ann Surg*. 1971;174(3):371-382.
28. Alexander JW, MacMillan BG, Law E, et al. Treatment of severe burns with widely meshed skin autograft and meshed skin allograft overlay. *J Trauma*. 1981;21(6):433-438.
29. Burke JF, Yannas IV, Quinby WC Jr, et al. Successful use of a physiologically acceptable artificial skin in the treatment of extensive burn injury. *Ann Surg*. 1981;194(4):413-428.
30. Heimbach D, Luterman A, Burke J, et al. Artificial dermis for major burns. A multi-center randomized clinical trial. *Ann Surg*. 1988;208(3):313-320.
31. Hansbrough JF, Boyce ST, Cooper ML, et al. Burn wound closure with cultured autologous keratinocytes and fibroblasts attached to a collagen-glycosaminoglycan substrate. *JAMA*. 1989;262(15):2125-2130.
32. Boyce ST. Cultured skin substitutes: a review. *Tissue Eng*. 1996;2(4):255-266.
33. Supp DM, Boyce ST. Engineered skin substitutes: practices and potentials. *Clin Dermatol*. 2005;23(4):403-412.
34. Butler KL, Goverman J, Ma H, et al. Stem cells and burns: review and therapeutic implications. *J Burn Care Res*. 2010;31(6):874-881.
35. Barillo DJ. Topical antimicrobials in burn wound care: a recent history. *Wounds*. 2008;20(7):192-198.
36. Dakin HD. On the use of certain antiseptic substances in the treatment of infected wounds. *Br Med J*. 1915;2(2852):318-320.
37. Haller JS Jr. Treatment of infected wounds during the Great War, 1914 to 1918. *South Med J*. 1992;85(3):303-315.
38. Heggers JP, Sazy JA, Stenberg BD, et al. Bactericidal and wound-healing properties of sodium hypochlorite solutions: the 1991 Lindberg Award. *J Burn Care Rehabil*. 1991;12(5):420-424.
39. Lindberg RB, Moncrief JA, Switzer WE, et al. The successful control of burn wound sepsis. *J Trauma*. 1965;5(5):601-616.
40. Fox CL Jr, Rappole BW, Stanford W. Control of pseudomonas infection in burns by silver sulfadiazine. *Surg Gynecol Obstet*. 1969;128(5):1021-1026.
41. Moyer CA, Brentano L, Gravens DL, et al. Treatment of large human burns with 0.5 per cent silver nitrate solution. *Arch Surg*. 1965;90:812-867.
42. Heggers JP, Robson MC, Herndon DN, et al. The efficacy of nystatin combined with topical microbial agents in the treatment of burn wound sepsis. *J Burn Care Rehabil*. 1989;10(6):508-511.
43. Monafo WW, West MA. Current treatment recommendations for topical burn therapy. *Drugs*. 1990;40(3):364-373.
44. Shaffer PA, Coleman W. Protein metabolism in typhoid fever. *Arch Intern Med*. 1909;IV(6):538-600.
45. Wilmore DW, Curreri PW, Spitzer KW, et al. Supranormal dietary intake in thermally injured hypermetabolic patients. *Surg Gynecol Obstet*. 1971;132(5):881-886.
46. Curreri PW, Richmond D, Marvin J, et al. Dietary requirements of patients with major burns. *J Am Diet Assoc*. 1974;65(4):415-417.
47. Sutherland AB. Nitrogen balance and nutritional requirement in the burn patient: a reappraisal. *Burns*. 1976;2(4):238-244.
48. Herndon DN, Barrow RE, Stein M, et al. Increased mortality with intravenous supplemental feeding in severely burned patients. *J Burn Care Rehabil*. 1989;10(4):309-313.
49. Moore FD. *Metabolic Care of Surgical Patients*. Philadelphia: Saunders; 1959.
50. Blocker TG Jr, Levin WC, Nowinski WW, et al. Nutrition studies in the severely burned. *Ann Surg*. 1955;141(5):589-597.
51. Artz CP, Reiss E. *The Treatment of Burns*. Philadelphia: Saunders; 1957. Available at: http://books.google.com/books?id=0M9rAAAAMAAJ.
52. Underhill FP. The significance of anhydremia in extensive surface burns. *JAMA*. 1930;95:852.
53. Lund CC, Browder NC. The estimation of areas of burns. *Surg Gynecol Obstet*. 1944;79:352-358.
54. Knaysi GA, Crikelair GF, Cosman B. The role of nines: its history and accuracy. *Plast Reconstr Surg*. 1968;41(6):560-563.
55. Cope O, Moore FD. The redistribution of body water and the fluid therapy of the burned patient. *Ann Surg*. 1947;126(6):1010-1045.
56. Moore FD. The body-weight burn budget. Basic fluid therapy for the early burn. *Surg Clin North Am*. 1970;50(6):1249-1265.
57. Kyle MJ, Wallace AB. Fluid replacement in burnt children. *Br J Plast Surg*. 1950;3(3):194-204.
58. Evans EI, Purnell OJ, Robinett PW, et al. Fluid and electrolyte requirements in severe burns. *Ann Surg*. 1952;135(6):804-817.
59. Reiss E, Stirmann JA, Artz CP, et al. Fluid and electrolyte balance in burns. *JAMA*. 1953;152(14):1309-1313.
60. Baxter CR, Shires T. Physiological response to crystalloid resuscitation of severe burns. *Ann N Y Acad Sci*. 1968;150(3):874-894.
61. Tasaki O, Goodwin CW, Saitoh D, et al. Effects of burns on inhalation injury. *J Trauma*. 1997;43(4):603-607.
62. Barrow RE, Jeschke MG, Herndon DN. Early fluid resuscitation improves outcomes in severely burned children. *Resuscitation*. 2000;45(2):91-96.
63. Foley FD, Moncrief JA, Mason AD Jr. Pathology of the lung in fatally burned patients. *Ann Surg*. 1968;167(2):251-264.
64. Moylan JA, Chan CK. Inhalation injury—an increasing problem. *Ann Surg*. 1978;188(1):34-37.
65. Agee RN, Long JM 3rd, Hunt JL, et al. Use of 133xenon in early diagnosis of inhalation injury. *J Trauma*. 1976;16(3):218-224.
66. Moylan JA Jr, Wilmore DW, Mouton DE, et al. Early diagnosis of inhalation injury using 133 xenon lung scan. *Ann Surg*. 1972;176(4):477-484.

67. Moylan JA, Adib K, Birnbaum M. Fiberoptic bronchoscopy following thermal injury. *Surg Gynecol Obstet*. 1975;140(4):541-543.
68. Shirani KZ, Pruitt BA Jr, Mason AD Jr. The influence of inhalation injury and pneumonia on burn mortality. *Ann Surg*. 1987;205(1):82-87.
69. Navar PD, Saffle JR, Warden GD. Effect of inhalation injury on fluid resuscitation requirements after thermal injury. *Am J Surg*. 1985;150(6):716-720.
70. Herndon DN, Barrow RE, Traber DL, et al. Extravascular lung water changes following smoke inhalation and massive burn injury. *Surgery*. 1987;102(2):341-349.
71. Fitzpatrick JC, Cioffi WG Jr. Ventilatory support following burns and smoke-inhalation injury. *Respir Care Clin N Am*. 1997;3(1):21-49.
72. Cortiella J, Mlcak R, Herndon D. High frequency percussive ventilation in pediatric patients with inhalation injury. *J Burn Care Rehabil*. 1999;20(3):232-235.
73. Desai MH, Mlcak R, Richardson J, et al. Reduction in mortality in pediatric patients with inhalation injury with aerosolized heparin/N-acetylcystine [correction of acetylcystine] therapy. *J Burn Care Rehabil*. 1998;19(3):210-212.
74. Barrow RE, Spies M, Barrow LN, et al. Influence of demographics and inhalation injury on burn mortality in children. *Burns*. 2004;30(1):72-77.
75. Sneve H. The treatment of burns and skin grafting. *JAMA*. 1905;45(1):1-8.
76. Cope O, Nardi GL, Quijano M, et al. Metabolic rate and thyroid function following acute thermal trauma in man. *Ann Surg*. 1953;137(2):165-174.
77. Moore FD. Metabolism in trauma: the reaction of survival. *Metabolism*. 1959;8:783-786.
78. Wilmore DW, Long JM, Mason AD Jr, et al. Catecholamines: mediator of the hypermetabolic response to thermal injury. *Ann Surg*. 1974;180(4):653-669.
79. Bessey PQ, Watters JM, Aoki TT, et al. Combined hormonal infusion simulates the metabolic response to injury. *Ann Surg*. 1984;200(3):264-281.
80. Wilmore DW, Mason AD Jr, Johnson DW, et al. Effect of ambient temperature on heat production and heat loss in burn patients. *J Appl Physiol*. 1975;38(4):593-597.
81. Wilmore DW, Aulick LH, Mason AD, et al. Influence of the burn wound on local and systemic responses to injury. *Ann Surg*. 1977;186(4):444-458.
82. Wolfe RR, Durkot MJ, Wolfe MH. Effect of thermal injury on energy metabolism, substrate kinetics, and hormonal concentrations. *Circ Shock*. 1982;9(4):383-394.
83. Wolfe RR, Durkot MJ, Allsop JR, et al. Glucose metabolism in severely burned patients. *Metabolism*. 1979;28(10):1031-1039.
84. Hart DW, Wolf SE, Chinkes DL, et al. Determinants of skeletal muscle catabolism after severe burn. *Ann Surg*. 2000;232(4):455-465.
85. Bell E, Ehrlich HP, Buttle DJ, et al. Living tissue formed in vitro and accepted as skin-equivalent tissue of full thickness. *Science*. 1981;211(4486):1052-1054.
86. Zwischenberger JB, Cardenas VJ Jr, Tao W, et al. Intravascular membrane oxygenation and carbon dioxide removal with IVOX: can improved design and permissive hypercapnia achieve adequate respiratory support during severe respiratory failure? *Artif Organs*. 1994;18(11):833-839.
87. Gurtner GC, Werner S, Barrandon Y, et al. Wound repair and regeneration. *Nature*. 2008;453(7193):314-321.

2 Teamwork for Total Burn Care: Burn Centers and Multidisciplinary Burn Teams

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Introduction

Severe burn injuries evoke strong emotional responses in most people including health professionals who are confronted by the specter of pain, deformity, and potential death. Intense pain and repeated episodes of sepsis, followed by either death or survival encumbered by pronounced disfigurement and disability, have been the expected sequelae to serious burns for most of mankind's history.[1] However, these dire consequences have been ameliorated so that, although burn injury is still intensely painful and tragic, the probability of death has been significantly diminished. During the decade prior to 1951, young adults (15–43 years of age) with total body surface area (TBSA) burns of 45% or greater had a 49% mortality rate (Table 2.1).[2] Forty years later, statistics from the pediatric and adult burn units in Galveston, Texas, show that a 49% mortality rate is associated with TBSA burns of 70% or greater in the same age group. Over the past decade, these mortality figures have improved even more dramatically, so that almost all infants and children can be expected to survive when resuscitated adequately and quickly.[3] Although improved survival has been the primary focus of burn treatment advancement for many decades, today the major goal—since survival rates have highly increased—is rehabilitation of burn survivors to maximize quality of life and reduce morbidity.

Such improvement in forestalling death is a direct result of the maturation of burn care science. Scientifically sound analyses of patient data have led to the development of formulas for fluid resuscitation[4–6] and nutritional support.[7,8] Clinical research has demonstrated the utility of topical antimicrobials in delaying onset of sepsis, thereby contributing to decreased mortality of burn patients. Prospective randomized clinical trials have shown that early surgical therapy is efficacious in improving survival for many burned patients by decreasing blood loss and diminishing the occurrence of sepsis.[9–14] Basic science and clinical research have helped decrease mortality by characterizing the pathophysiological changes related to inhalation injury and suggesting treatment methods that have decreased the incidence of pulmonary edema and pneumonia.[15–18] Scientific investigations of the hypermetabolic response to major burn injury have led to improved management of this life-threatening phenomenon, not only enhancing survival, but also promising an improved quality of life.[19–32]

Optimal treatment of severely burned patients requires significant healthcare resources and has led to the development of highly specialized burn centers over the past decades. Centralizing services to regional burn centers has made implementation of multidisciplinary acute critical care and long-term rehabilitation possible. It has also enhanced opportunities for study and research over the past several decades. This has led to great advances both in our knowledge and in clinical outcomes, with further advancements being expected.

Implementation of a wide range of medical discoveries and innovations has improved patient outcomes following severe burns over the past half century. Key areas of advancements in recent decades include fluid resuscitation protocols; early burn wound excision and closure with grafts or skin substitutes, nutritional support regimens, topical antimicrobials and treatment of sepsis, thermally neutral ambient temperatures, and pharmacological modulation of hypermetabolic and catabolic responses. These factors have helped to decrease morbidity and mortality following severe burns by improving wound healing, reducing inflammation and energy demands, and attenuating hypermetabolism and muscle catabolism.

Melding scientific research with clinical care has been promoted in recent burn care history largely because of the aggregation of burn patients into single-purpose units staffed by dedicated healthcare personnel. Dedicated burn units were first established in Great Britain to facilitate nursing care. The first U.S. burn center was established at the Medical College of Virginia in 1946. The same year, the U.S. Army Surgical Research Unit (later renamed the U.S. Army Institute of Surgical Research) was established. Directors of both centers and later, the founders of the burn centers at University of Texas Medical Branch in 1947 and Shriners Hospitals for Children–Galveston in 1963 emphasized the importance of collaboration between clinical care and basic scientific disciplines to improve the patient's outcome.[1]

The organizational design of these centers engendered a self-perpetuating feedback loop of clinical and basic scientific inquiry. In this system, scientists receive first-hand information about clinical problems, while clinicians receive provocative ideas about patient responses to injury from experts in other disciplines. Advances in burn care attest to the value of a dedicated burn unit organized around a collegial group of basic scientists, clinical researchers, and

Table 2.1 Percent total body surface area (TBSA) burn producing an expected mortality of 50% in 1952, 1993, and 2006

Age (years)	1953† (% TBSA)	1993* (% TBSA)	2006° (% TBSA)
0–14	49	98	99
15–44	46	72	88
45–65	27	51	75
65	10	25	33

†Bull, JP, Fisher, AJ. *Annals of Surgery* 1954;139.
*Shriners Hospital for Children and University of Texas Medical Branch, Galveston, Texas.
°Pereira CT et al. *J Am Coll Surg* 2006; 202(3): 536–548 and unpublished data. PP. 1138–1140 (PC65).

clinical caregivers, all asking questions of each other, sharing observations and information, and seeking solutions to improve patient welfare.

Findings from the group at the Army Surgical Research Institute point to the necessity of involving many disciplines in the treatment of patients with major burn injuries and emphasize the utility of a team concept.[1] For this reason the International Society of Burn Injuries and its journal, *Burns*, as well as the American Burn Association and its publication, *Journal of Burn Care and Research*, have publicized the notion of successful multidisciplinary work by burn teams to widespread audiences.

Members of a Burn Team

The management of severe burn injuries benefits from concentrated integration of health services and professionals, with care being significantly enhanced by a true multidisciplinary approach. The complex nature of burn injuries necessitates a diverse range of skills for optimal care. A single specialist cannot be expected to possess all skills, knowledge, and energy required for the comprehensive care of severely injured patients. For this reason, reliance is placed on a group of specialists to provide integrated care through innovative organization and collaboration.

In addition to including burn-specific providers, the burn team consists of epidemiologists, molecular biologists, microbiologists, physiologists, biochemists, pharmacists, pathologists, endocrinologists, and numerous other scientific as well as medical specialists. Because burn injury is a complex systemic injury, the search for improved treatments leads to inquiry from many approaches. Each scientific finding stimulates new questions and the potential involvement of additional specialists.

At times, the burn team can be thought of as including the environmental service workers responsible for cleaning the unit, the volunteers who may assist in a variety of ways to provide comfort for patients and families, the hospital administrator, and many others who support the day-to-day operations of a burn center and significantly impact the well-being of patients and staff. However, the traditional burn team consists of a multidisciplinary group of direct-care providers. Although burn surgeons, plastic surgeons, nurses, nutritionists, and physical and occupational therapists form the skeletal core; most burn units also include anesthesiologists, respiratory therapists, pharmacists, spiritual therapists, and music therapists. The increasing number of survivors has consequently also added psychologists, psychiatrists, and, more recently, exercise physiologists to the burn team. In pediatric units, child life specialists and school teachers are also significant members of the team of caregivers.

Patient satisfaction can be formally measured through questionnaires to provide positive feedback to caregivers and highlight potential areas of improvement. Allowing patients to feel as if they are part of decisions about their care, listening and responding to concerns, providing encouragement, and displaying empathy are all important for maintaining satisfaction in patients and their families. These approaches also reduce fear, apprehension, and misunderstandings.

Healing relies on a complex array of factors. These include individual factors such as motivation, pre-existing health status, obesity, malnutrition, comorbidities, family support, and social support. They also include wider societal factors such as reintegration, individual perception, and coping strategies as well as factors specific to the mechanism of injury such as trauma, bereavement, grief, and loss.

Patients and their families are infrequently mentioned as members of the team but are obviously important in influencing the outcome of treatment. Persons with major burn injuries contribute actively to their own recovery, and each brings individual needs and agendas into the hospital setting that may influence the way treatment is provided by the professional care team.[33] The patient's family members often become active participants. This is even more important in the case of children, but is also true in the case of adult patients. Family members become conduits of information from the professional staff to the patient. At times, they act as spokespersons for the patient, and, at other times, they become advocates for the staff in encouraging the patient to cooperate with dreaded procedures.

With so many diverse personalities and specialists potentially involved, purporting to know what or who constitutes a burn team may seem absurd. Nevertheless, references to "burn teams" are plentiful, and there is agreement on the specialists and care providers whose expertise is required for the optimal care of patients with significant burn injuries (Fig. 2.1).

BURN SURGEONS

Ultimate responsibility and overall control for the care of a patient lies with the admitting burn surgeon, the key figure of the burn team. The burn surgeon is either a general surgeon or plastic surgeon with expertise in providing emergency and critical care, as well as in performing skin grafting and amputations. The burn surgeon provides leadership and guidance for the rest of the team, which may include several surgeons. The surgeon's leadership is particularly important during the early phase of patient care when moment-to-moment decisions must be made based on the surgeon's knowledge of physiologic responses to injury, current scientific evidence, and appropriate medical/surgical treatments. The surgeon must not only possess

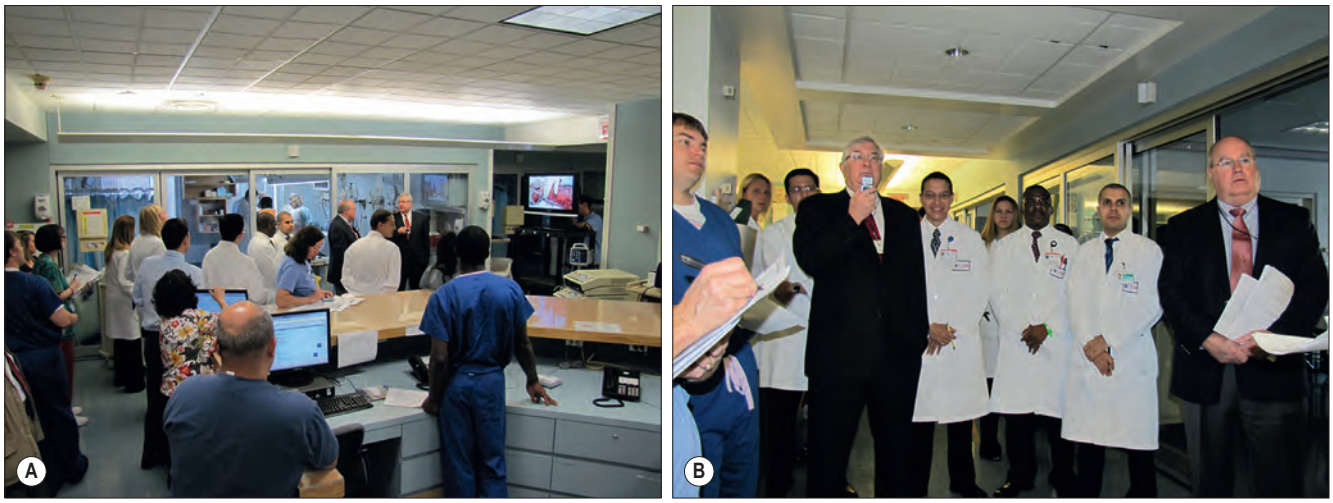

Fig. 2.1 (**A, B**) Experts from diverse disciplines gather together with common goals and tasks and overlapping values to achieve their objectives.

knowledge and skills in medicine, but also be able to clearly exchange information with a diverse staff of experts in other disciplines and lead the team. The surgeon alone cannot provide comprehensive care but must be wise enough to know when and how to seek counsel as well as how to clearly and firmly give directions to direct activities surrounding patient care. The senior surgeon of the team is accorded the most authority and control of any member of the team and thus bears the responsibility and receives accolades for the success of the team as a whole.[33]

PLASTIC SURGEONS

Next to burn surgeons, who are particularly involved in the immediate and acute phase of surgical treatment, are the plastic surgeons, who are typically involved instead in long-term surgical treatment. The plastic surgeons aim to deliver care that yields the best functional and aesthetic results for the burn survivor. The burn surgeon should always work in close collaboration with the plastic surgeon. Most burn surgeons are plastic surgeons, but in instances where this is not the case, the presence of plastic surgeons in the team is essential. Ideally, this collaboration should start during the initial phase of surgical treatment. The plastic surgeon's duty is primarily to care for the patient in terms of functional improvement through surgeries that aim to lessen scarring and decrease the functional limitations created by scarring. This surgical treatment often requires numerous operations that may take place for years after the burn injury.

ANESTHESIOLOGISTS

An anesthesiologist who is an expert in the altered physiologic parameters of burned patients is critical to the survival of the patient who usually undergoes multiple acute surgical procedures. Anesthesiologists on the burn team must be familiar with the phases of burn recovery and the physiologic changes to be anticipated as burn wounds heal.[1] Anesthesiologists play significant roles in facilitating comfort for burned patients, not only in the operating room, but also during the painful ordeals of dressing changes, staple removal, and physical exercise.

NURSES

Nurses represent the largest single disciplinary segment of the burn team, providing continuous coordinated care to the patient. The nursing staff is responsible for technical management of the 24-hour physical treatment of the patient. They control the therapeutic milieu that allows the patient to recover. They also provide emotional support to the patient and patient's family.[34] Nursing staff are often the first to identify changes in a patient's condition and initiate therapeutic interventions. Because recovery from a major burn is rather slow, burn nurses must merge the qualities of sophisticated intensive care nursing with the challenging aspects of psychiatric nursing. Nursing case management can play an important role in burn treatment, extending the coordination of care beyond hospitalization through the lengthy period of outpatient rehabilitation.

PHYSICAL AND OCCUPATIONAL THERAPISTS

Occupational and physical therapists begin planning therapeutic interventions at the patient's admission to maximize functional recovery. Burned patients require special positioning and splinting, early mobilization, strengthening exercises, endurance activities, and pressure garments to promote healing while controlling scar formation. These therapists must be very creative in designing and applying the appropriate appliances. Knowledge of the timing of application is necessary. In addition, rehabilitation therapists must become expert behavioral managers since their necessary treatments are usually painful to the recovering patient who will resist in a variety of ways. While the patient is angry, protesting loudly, or pleading for mercy, the rehabilitation therapist must persist with aggressive treatment to combat quickly forming and very strong scar contractures. The same therapist, however, is typically rewarded

with adoration and gratitude from an enabled burn survivor.

RESPIRATORY THERAPISTS

Inhalation injury, prolonged bed rest, fluid shifts, and the threat of pneumonia, all concomitant with burn injury, render respiratory therapists essential to the patient's welfare. Respiratory therapists evaluate pulmonary mechanics, perform therapy to facilitate breathing, and closely monitor the status of the patient's respiratory functioning and improvements during the recovery.

EXERCISE PHYSIOLOGIST

The exercise physiologist has recently been recognized as a key member of the comprehensive burn rehabilitation team. Traditionally, exercise physiologists study acute and chronic adaptations to a wide range of exercise conditions. At our institution, the exercise physiologist performs clinical duties and conducts clinical research.

Clinical duties include monitoring and assessing cardiovascular and pulmonary exercise function, as well as muscle function. Additional clinical duties include writing exercise prescriptions for cardiopulmonary and musculoskeletal rehabilitation. Clinical research conducted by the exercise physiologist mainly focuses on the effect of exercise on burn sequelae and the mechanisms by which exercise can reduce or reverse burn-induced catabolic and hypermetabolic conditions and improve a patient's quality of life.

There is no licensing body or requirements for exercise physiologists to practice their profession. However, many organizations, such as the American College of Sports Medicine and the Clinical Exercise Physiology Association, offer national certifications. These certifications include the exercise test technologist, exercise specialist, health/fitness director, and clinical exercise specialist. We recommend that if the exercise physiologist is primarily involved in clinical duties, he or she should have a minimum of a master's degree and be nationally certified by a well-known and respected organization. If clinical or basic research will be part of his or her duties, then we recommend a doctorate degree as well as a national certification.

NUTRITIONISTS

A nutritionist or dietitian monitors daily caloric intake and weight maintenance. These specialists also recommend dietary interventions to provide optimal nutritional support to combat the hypermetabolic and catabolic responses to burn injury. Caloric intake as well as intake of appropriate vitamins, minerals, and trace elements must be managed to promote wound healing and facilitate recovery. Nutritionists and exercise physiologists may work together in implementing methods to increase daily physical activity (caloric expenditure) to counteract any sequelae due to a sedentary lifestyle.

PSYCHOSOCIAL EXPERTS

Psychiatrists, psychologists, and social workers with expertise in human behavior and psychotherapeutic interventions provide continuous sensitivity in caring for the emotional and mental well-being of patients and their families. These professionals must be knowledgeable about the process of burn recovery as well as human behavior to make optimal interventions. They serve as confidants and supports for patients, families of patients, and, on occasion, other burn team members.[35] They often assist colleagues from other disciplines in developing behavioral interventions for problematic patients, allowing the colleague and patient to achieve therapeutic success.[36] During initial hospitalization, these experts manage the patient's mental status, pain tolerance, and anxiety level to provide comfort to the patient and facilitate physical recovery. As the patient progresses toward rehabilitation, the role of the mental health team becomes more prominent in supporting optimal psychological, social, and physical rehabilitation.

SPIRITUAL THERAPISTS

Not all patients and relatives are religious, but for those who are religious, the presence of a spiritual therapist can be extremely important and can help to overcome or deal with the difficult times the burn survivors are experiencing. The power and efficacy of prayer and religious-spiritual involvement during illness and recovery have been often discussed and have been demonstrated to be very important for many patients.[37] For these reasons, hospitals and especially burn centers should have a spiritual therapist in the team to assist not only the burn survivors but also their relatives.[38]

MUSIC THERAPISTS

Music therapy is the use of music interventions to accomplish individualized goals within a therapeutic relationship between the patient and the figure of the music therapist. The principal goals and interventions can be designed to promote wellness, manage stress, alleviate pain, express feelings, enhance memory, improve communication, and promote physical rehabilitation.[39] As reported, music therapy can improve a patient's range of motion and help during the hospitalization and rehabilitation periods.[40] The music therapist has an important role to play for burn patients and should be considered an essential member of the burn team.

STUDENTS, RESIDENTS, AND FELLOWS

Medical students, graduate students, postdoctoral fellows, and residents are vital members of the burn care team. Burn care professionals often do not have the time or energy to perform activities outside of work hours or set responsibilities. However, these young students, fellows, and residents frequently have the time, energy, and desire to take on additional work, whether in the form of clinical work or research. The close working relationship between these individuals and the rest of the burn care team yields numerous benefits, including the conception of new clinical and translational questions that, when answered, directly improve patient care.

Dynamics and Functioning of the Burn Team

Gathering a group of experts from diverse disciplines does not form a team.[41] In fact, the diversity of the disciplines, along with individual differences in gender, ethnicity, values, professional experience, and professional status, render such teamwork a process fraught with opportunities for disagreements, jealousies, and confusion.[42] The process of working together to accomplish the primary goal (i.e., returning burn survivors to a normal, functional life) is further complicated by the fact that the patient and the patient's family must collaborate with these professionals. It is not unusual for the patient to attempt to diminish his or her immediate discomfort by pitting one team member against another or "splitting" the team. Much as young children will try to manipulate parents by first going to one and then the other, patients will complain about one staff member to another or assert to one staff member that another staff member allows less demanding rehabilitation exercises or some special privilege.[43] Time must be devoted to a process of trust building among the team members. It is also imperative that the team communicate openly and frequently or the group will lose effectiveness.

Communicating and discussing a daily, weekly, and long-term management plan among team members allows for clarification and organization of early plans to flag issues early on with regard to further surgery, rehabilitation, discharge planning, nutritional goals, patient understanding, and patient compliance. Such issues are all simultaneously addressed in a holistic approach.

The group becomes a team when they share common goals and tasks as well as when they have overlapping values that will be served by accomplishing their goals.[44,45] The team becomes an efficient work group through a process of establishing mechanisms of collaboration and cooperation that facilitate focusing on explicit tasks rather than on covert distractions of personal need and interpersonal conflict.[44,46] Work groups develop best under conditions that allow each individual to feel acknowledged as valuable to the team.[47]

Multidisciplinary burn care involves taking into account all aspects of patient care when treatment decisions are made as well as considering subsequent effects and consequences of decisions. With good communication and coordination among all team members, the team can optimize outcome for a patient in every aspect of their care (Fig. 2.1).

Research into the area of multidisciplinary teams has highlighted the wide application of such teams in healthcare settings as well as some of the shortcomings affecting their efficacy.[41] Clearly defining the various components of these teams will allow improved analysis. Some of the factors that are useful for assessing how well a team is functioning are listed in Box 2.1.

A burn team has defined and shared goals with clear tasks. For a group of burn experts to become an efficient team, skillful leadership that facilitates the development of shared values among team members and ensures the validation of team members as they accomplish tasks is necessary. The burn team consists of many experts from diverse professional backgrounds; each profession has its own culture, problem-solving approach, and language.[48] For the team to benefit fully from the expertise of its members, every expert voice must be heard and acknowledged. Team members must be willing to learn from each other, eventually developing their own culture and language that all can understand. Attitudes of superiority and prejudice are most disruptive to the performance of the team.

Disagreement and conflict will be present, but these can be expressed and resolved in a respectful manner. Research suggests that intelligent management of emotions is linked with successful team performance in problem-solving and conflict resolution.[49] When handled well, conflicts and disagreements can increase understanding and provide new perspectives, in turn enhancing working relationships and leading to improved patient care.[50]

The acknowledged formal leader of the team is the senior surgeon, who may find the arduous job of medical and social leadership difficult and perplexing (Fig. 2.1). Empirical studies indicate, with remarkable consistency, that the functions required for successful leadership can be grouped into two somewhat incompatible clusters: (1) directing the group toward tasks and goal attainment and (2) facilitating interactions among group members and enhancing their feelings of worth.[44,47,50]

At times, task-oriented behavior by the leader may clash with the needs of the group for emotional support. During those times, the group may inadvertently impede the successful performance of both the leader and the team by seeking alternate means of establishing feelings of self-worth. When the social/emotional needs of the group are not met, the group begins to spend more time attempting to satisfy individual needs and less time pursuing task-related activities.

Studies of group behavior demonstrate that high-performance teams are characterized by synergy between task accomplishment and individual need fulfillment.[44,51] Since one formal leader cannot always attend to task and interpersonal nuances, groups informally or formally allocate leadership activities to multiple persons.[44,46,47] According to the literature in organizational behavior, the most

Box 2.1 Factors for analyzing multidisciplinary team effectiveness and function

Size of team
Composition (professions represented)
Specific responsibilities
Leadership style (individual or co-leadership/voluntary or assigned/stable or rotating/authoritarian or nonauthoritarian)
Scope of work (consultation or intervention or both/idea generating/decision-making)
Organizational support
Communication and interactional patterns within the team (e.g., frequency/intensity/type)
Contact with the patient, family, or care system (e.g., frequency/intensity/type)
Point in treatment process when team is involved (e.g., intake through to discharge, one phase only, only if case not progressing)

(From Al-Mousawi et al., Burn Teams and Burn Centers,[52] adapted from Schofield & Amodeo[41])

effective leader is one who engages the talents of others and empowers them to utilize their abilities to further the work of the group.[44,46] Failure to empower the informal leaders limits their ability to contribute fully.

For the identified leader of the burn team (i.e., the senior surgeon) to create a successful, efficient burn team, the leader must be prepared to share leadership with one or more "informal" leaders in such a way that all leadership functions are fulfilled.[44,46,47] The prominence and identity of any one of the informal leaders will change according to the situation. The successful formal leader will encourage and support the leadership roles of other members of the team, developing a climate in which the team members are more likely to cooperate and collaborate toward achievement beyond individual capacity.

For many physicians, the concept of sharing leadership and power initially appears threatening, for it is the physician, after all, who must ultimately write the orders and be responsible for the patient's medical needs. However, sharing power does not mean giving up control. The physician shares leadership by seeking information and advice from other team members and empowers them by validating the importance of their expertise in the decision-making process. However, the physician maintains control and responsibility over the patient's care and medical treatment.

Summary

Centralized care provided in designated burn units has promoted a team approach to both scientific investigation and clinical care that has demonstrably improved the welfare of burn patients. Multidisciplinary efforts are imperative to continue improving and understanding the rehabilitation and emotional, psychological, and physiologic recovery of burn patients. Tremendous scientific and technological advances have led to dramatic increases in the survival of burn victims.

Wider issues to be considered by leaders in the field include burn prevention, access to care in rural regions and developing countries, and promotion of investment and funding for burn care. Centralization of care at burn centers as well as enhanced care have provided tremendous opportunities for research and education.

We hope that, in the future, scientists and clinicians will follow the same model of collaboration to pursue solutions to the perplexing problems that burn survivors must encounter. Physical discomforts such as itching still interfere with patient rehabilitation. New techniques for controlling hypertrophic scars and surgical reconstruction could do much to diminish disfigurement.[52] The use of treatments to attenuate hypermetabolism, use of anabolic agents,[19,27] and supervised strength and endurance training[22,23] are all currently being investigated as means of enhancing the well-being of survivors of massive burn injuries. Further development of psychological expertise within burn care and increased public awareness of the competence of burn survivors may ease the survivor's transition from an incapacitated patient to a functional member of society. We hope that, in the future, burn care will continue to devote the same energy and resources that have produced such tremendous advances in saving lives and optimizing the quality of life for survivors.

Complete references available online at
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References

1. Artz CP, Moncrief JA. The burn problem. In: *The Treatment of Burns*. 2nd ed. Philadelphia, PA: W B Saunders; 1969:1-21.
2. Bull JP, Fisher AJ. A study of mortality in a burns unit: a revised estimate. *Ann Surg*. 1954;139(3):269-274.
3. Pereira CT, Barrow RE, Sterns AM, et al. Age-dependent differences in survival after severe burns: a unicentric review of 1,674 patients and 179 autopsies over 15 years. *J Am Coll Surg*. 2006;202(3):536-548.
4. Baxter CR, Marvin J, Curreri PW. Fluid and electrolyte therapy of burn shock. *Heart Lung*. 1973;2(5):707-713.
5. Carvajal HF. Fluid therapy for the acutely burned child. *Compr Ther*. 1977;3(3):17-24.
6. Evans EI, Purnell OJ, Robinett PW, Batchelor A, Martin M. Fluid and electrolyte requirements in severe burns. *Ann Surg*. 1952;135(6):804-817.
7. Curreri PW, Richmond D, Marvin J, Baxter CR. Dietary requirements of patients with major burns. *J Am Diet Assoc*. 1974;65(4):415-417.
8. Hildreth MA, Herndon DN, Desai MH, Duke MA. Reassessing caloric requirements in pediatric burn patients. *J Burn Care Rehabil*. 1988;9(6):616-618.
9. Burke JF, Bondoc CC, Quinby WC. Primary burn excision and immediate grafting: a method shortening illness. *J Trauma*. 1974;14(5):389-395.
10. Desai MH, Herndon DN, Broemeling L, et al. Early burn wound excision significantly reduces blood loss. *Ann Surg*. 1990;211(6):753-759, discussion 759-762.
11. Desai MH, Rutan RL, Herndon DN. Conservative treatment of scald burns is superior to early excision. *J Burn Care Rehabil*. 1991;12(5):482-484.
12. Engrav LH, Heimbach DM, Reus JL, Harnar TJ, Marvin JA. Early excision and grafting vs. nonoperative treatment of burns of indeterminant depth: a randomized prospective study. *J Trauma*. 1983;23(11):1001-1004.
13. Herndon DN, Barrow RE, Rutan RL, et al. A comparison of conservative versus early excision. Therapies in severely burned patients. *Ann Surg*. 1989;209(5):547-552, discussion 552-543.
14. Janzekovic Z. A new concept in the early excision and immediate grafting of burns. *J Trauma*. 1970;10(12):1103-1108.
15. Cioffi WG Jr, Rue LW 3rd, Graves TA, et al. Prophylactic use of high-frequency percussive ventilation in patients with inhalation injury. *Ann Surg*. 1991;213(6):575-580, discussion 580-572.
16. Herndon DN, Barrow RE, Linares HA, et al. Inhalation injury in burned patients: effects and treatment. *Burns Incl Therm Inj*. 1988;14(5):349-356.
17. Herndon DN, Barrow RE, Traber DL, et al. Extravascular lung water changes following smoke inhalation and massive burn injury. *Surgery*. 1987;102(2):341-349.
18. Shirani KZ, Pruitt BA Jr, Mason AD Jr. The influence of inhalation injury and pneumonia on burn mortality. *Ann Surg*. 1987;205(1):82-87.
19. Hart DW, Wolf SE, Ramzy PI, et al. Anabolic effects of oxandrolone after severe burn. *Ann Surg*. 2001;233(4):556-564.
20. Wilmore DW, Long JM, Mason AD Jr, Skreen RW, Pruitt BA Jr. Catecholamines: mediator of the hypermetabolic response to thermal injury. *Ann Surg*. 1974;180(4):653-669.
21. Hart DW, Wolf SE, Chinkes DL, et al. Determinants of skeletal muscle catabolism after severe burn. *Ann Surg*. 2000;232(4):455-465.
22. Celis MM, Suman OE, Huang TT, Yen P, Herndon DN. Effect of a supervised exercise and physiotherapy program on surgical interventions in children with thermal injury. *J Burn Care Rehabil*. 2003;24(1):57-61, discussion 56.
23. Suman OE, Thomas SJ, Wilkins JP, Mlcak RP, Herndon DN. Effect of exogenous growth hormone and exercise on lean mass and muscle function in children with burns. *J Appl Physiol*. 2003;94(6):2273-2281.
24. Low JF, Herndon DN, Barrow RE. Effect of growth hormone on growth delay in burned children: a 3-year follow-up study. *Lancet*. 1999;354(9192):1789.
25. Cucuzzo NA, Ferrando A, Herndon DN. The effects of exercise programming vs traditional outpatient therapy in the rehabilitation of severely burned children. *J Burn Care Rehabil*. 2001;22(3):214-220.
26. Suman OE, Mlcak RP, Herndon DN. Effects of exogenous growth hormone on resting pulmonary function in children with thermal injury. *J Burn Care Rehabil*. 2004;25(3):287-293.
27. Murphy KD, Thomas S, Mlcak RP, et al. Effects of long-term oxandrolone administration in severely burned children. *Surgery*. 2004;136(2):219-224.
28. Herndon DN, Stein MD, Rutan TC, Abston S, Linares H. Failure of TPN supplementation to improve liver function, immunity, and mortality in thermally injured patients. *J Trauma*. 1987;27(2):195-204.
29. Herndon DN, Barrow RE, Stein M, et al. Increased mortality with intravenous supplemental feeding in severely burned patients. *J Burn Care Rehabil*. 1989;10(4):309-313.
30. Thomas S, Wolf SE, Murphy KD, Chinkes DL, Herndon DN. The long-term effect of oxandrolone on hepatic acute phase proteins in severely burned children. *J Trauma*. 2004;56(1):37-44.
31. Demling RH, DeSanti L. Oxandrolone induced lean mass gain during recovery from severe burns is maintained after discontinuation of the anabolic steroid. *Burns*. 2003;29(8):793-797.
32. Hart DW, Wolf SE, Mlcak R, et al. Persistence of muscle catabolism after severe burn. *Surgery*. 2000;128(2):312-319.
33. Shakespeare PG. Who should lead the burn care team? *Burns*. 1993;19(6):490-494.
34. Callejas Herrero A, Cuadrado Rodriguez C, Pena Lorenzo A, Diez Sanz MJ. [Psychosocial nursing care patient with major burns]. *Rev Enferm*. 2014;37(2):59-64.
35. Morris J, McFadd A. The mental health team on a burn unit: a multidisciplinary approach. *J Trauma*. 1978;18(9):658-663.
36. Hughes TL, Medina-Walpole AM. Implementation of an interdisciplinary behavior management program. *J Am Geriatr Soc*. 2000;48(5):581-587.
37. Ameling A. Prayer: an ancient healing practice becomes new again. *Holist Nurs Pract*. 2000;14(3):40-48.
38. Saad M, de Medeiros R. Programs of religious/spiritual support in hospitals: five "whies" and five "hows". *Philo Ethics Humanit Med*. 2016;11(1):5.
39. Koelsch S. Music-evoked emotions: principles, brain correlates, and implications for therapy. *Ann NY Acad Sci*. 2015;1337:193-201.
40. Neugebauer CT, Serghiou M, Herndon DN, Suman OE. Effects of a 12-week rehabilitation program with music & exercise groups on range of motion in young children with severe burns. *J Burn Care Res*. 2008;29(6):939-948.
41. Schofield RF, Amodeo M. Interdisciplinary teams in health care and human services settings: are they effective? *Health Soc Work*. 1999;24(3):210-219.
42. Fallowfield L, Jenkins V. Effective communication skills are the key to good cancer care. *Eur J Cancer*. 1999;35(11):1592-1597.
43. Perl E. Treatment team in conflict: the wishes for and risks of consensus. *Psychiatry*. Summer 1997;60(2):182-195.
44. Harris P, Harris DL. High performance team management. *Leadership Org Dev J*. 1989;10(4):28-32.
45. Miller E, Rice A. Systems of organization. In: Coleman A, Bexton W, eds. *Group Relations Reader*. Sausalito, CA: Grex; 1975:43-68.
46. Yank GR, Barber JW, Hargrove DS, Whitt PD. The mental health treatment team as a work group: team dynamics and the role of the leader. *Psychiatry*. 1992;55(3):250-264.
47. Litterer J. *The Analysis of Organizations*. 2nd ed. John Wiley & Sons; 1973.
48. Hall P. Interprofessional teamwork: professional cultures as barriers. *J Interprof Care*. 2005;19(suppl 1):188-196.
49. Jordan PJ, Troth AC. Managing emotions during team problem solving: emotional intelligence and conflict resolution. *Hum Perform*. 2004;17(2):195-218.
50. Van Norman G. Interdisciplinary team issues – online publication. 1998. Available from: https://depts.washington.edu/bioethx/topics/team.html.
51. Al-Mousawi AM, Mecott-Rivera GA, Jeschke MG, Herndon DN. Burn teams and burn centers: the importance of a comprehensive team approach to burn care. *Clin Plast Surg*. 2009;36(4):547-554.
52. Constable JD. The state of burn care: past, present and future. *Burns*. 1994;20(4):316-324.

3 Epidemiological, Demographic and Outcome Characteristics of Burns

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Introduction

In 2014, approximately 200,000 deaths occurred in the United States from all injuries, and 31 million sustained nonfatal injuries. In a population of 318,857,056 persons, this represents a per capita death rate from injury of 0.063% (or approximately 6 per 10,000), and a nonfatal injury rate of 9.73% (or approximately 1 in 10). Therefore injury is common but related death is uncommon. For injuries from fire and burns specifically, 3,194 deaths occurred (1/100,000 population), which represented 1.6% of all injury fatalities but only 1.3% of injuries. In all, 408,945 nonfatal burns occurred in the United States in 2014, giving a rate of 0.129% of persons in the United States sustaining a burn, or about 1 per 1000.

We constructed trend lines in addition to the preceding data in the rate of reported injuries and death since 2005. These data were found on the WISQAR database produced by the U.S. Centers for Disease Control and Prevention (CDC).[1] We found that total injuries were relatively unchanged in this period from 2005 to 2009, then saw a large spike (a 10% increase) from 2010 to 2012. This spike has since receded (Fig. 3.1). When seen on a per capita basis, a 7.5% increase in the rate of reported injury occurred in the 2010–2012 period; therefore the spike in reported injuries was not from an increase in population; this is an interesting societal trend. Of further interest is the increase in injury fatalities which began at the same time and is mostly associated with an increased injury mortality rate (a 12.3% increase from 0.57% to 0.64%). This continues to rise despite a subsequent decline in total and per capita injuries. Whether this is from an increase in injury severity or age distribution cannot be answered in these data. A potential reason is a perceived increase in the use of palliative withdrawal of care, suggesting that those who might live with known treatments are unnecessarily adding to the mortality rate.

The incidence of total burns saw a similar spike in the 2010–2012 period, but this was not reflected in the per capita statistics, likely because of blunting by the relatively low incidence of burns (Fig. 3.2). Interestingly burn fatalities continue to decrease overall with a flattening trajectory in 2013–2014. The per capita numbers also showed a decline that has leveled at 0.001% (1 in 100,000). What is not seen is an increase in burn fatality rate that is evident in the all-injury fatality rate.

Burns occur unequally among the age groups in the WISQAR data, and the interim changes from 2005 to 2014 are interesting. The total number of burns have generally decreased in those aged 0–45, whereas the total number of burns in those older than 45 have increased dramatically, 31% from 2005 to 2014 in those aged 46–65, and 12% in those aged over 65 (Table 3.1).

The spike seen in total injuries between 2010 and 2012 is parallel with burns in those aged 0–4 but has settled back to a 6% decline in this age group from that in 2005. For those aged 5–18, we see a similar steady decline in the number of burns, and also in those aged 19–45. However the numbers of burns in those aged 46–65 and in those older than 65 years have seen a steady and dramatic increase. When indexed to population, this is almost completely accounted for by the increase in population in these age groups. Therefore no increase in per capita rate has occurred, and the increased numbers are from an increase in the population of those aged over 45 years.

When considering plans in health care utilization to respond to changes in the incidence of burns, strategies should be for the *total* number of burns likely to be encountered. For regional plans, per capita estimations should be used as specific regions grow and contract. In this light, the past 10 years have seen a significant decrease in the total number of burns in those aged 45 years and younger. Populations in the United States are generally stable for these age groups in the past 10 years, thus the decline in total numbers of burns must be attributed to cultural changes and prevention efforts, both legislative and educational. Therefore future resource utilization for the care of burns in this age group in the United States will likely continue to diminish unless some change occurs in the population. However those older than 45 years continue to increase in many areas, and thus considerations might be made to plan for further growth in burns in older persons.

We then analyzed the epidemiologic data from the National Burn Repository (NBR) available from the American Burn Association for the years 2006–2015.[2] In this, we examined recent trends in burn incidence and qualities in the United States. The NBR contains data from 96 of the128 self-designated burn centers in the United States as well as 7 burn centers in Canada, Sweden, and Switzerland. Of these 96 centers, 65 were verified as a burn center using American Burn Association criteria. The data we include here come only from the reporting US centers.

The distribution of burns among age groups in the NBR data has more granularity than does the WISQAR data. Burn distribution has a major grouping in those younger than 10 years of age. Those aged 11–20 have a smaller incidence, which then increases in those aged 21–60;

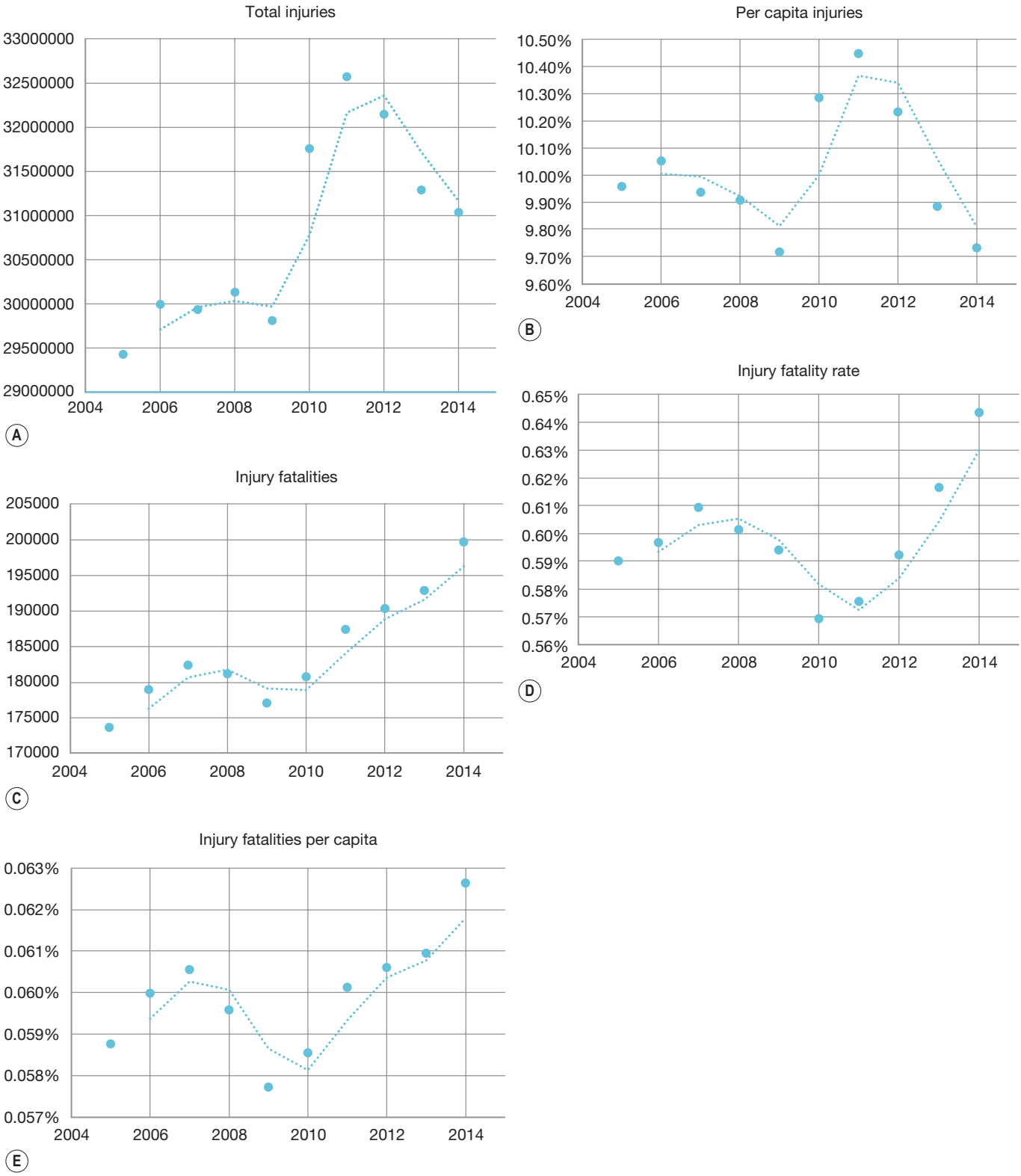

Fig. 3.1 Injury statistics taken from the WISQARS database maintained by the U.S. Centers for Disease Control and Prevention. Panel A describes the total number of reported injuries from the period 2005–2014. The y-axis is the total number of injuries. The trendline is the moving average of the adjoining two values. Panel B describes the per capita incidence of reported injuries in %, calculated by dividing the number of injuries by population for that year. Panel C describes the total number of fatalities ascribed to injury for the years 2005–2014. Panel D is the injury fatality rate by year calculated by dividing the number of fatalities by the number of reported injuries. Panel E is the injury fatalities per capita, calculated by dividing the number of fatalities by the population for that year.

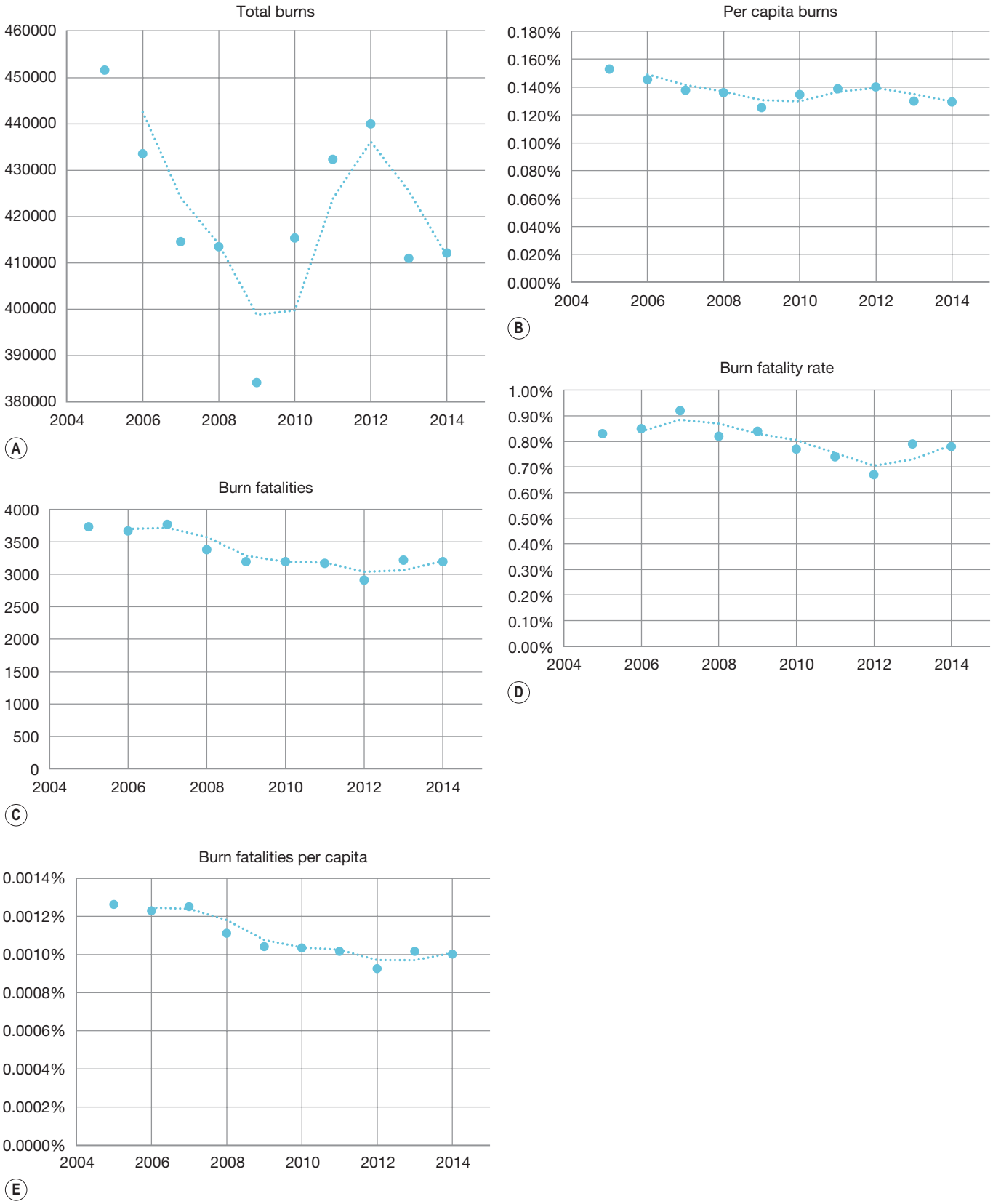

Fig. 3.2 Burn injury statistics taken from the WISQARS database maintained by the U.S. Centers for Disease Control and Prevention. Panel A describes the total number of injuries from the period 2005–2014. The y-axis is the number of injuries, with the included trendline the moving average of the two adjoining values. Panel B describes the per capita incidence with a trendline similarly calculated. Panel C is the number of fatalities with Panel D as the corresponding fatality rate. Finally, Panel E is the per capita burn fatalities.

Table 3.1 Burn Mortality Rates Over Time.

		BURNS					ALL	FATAL
Age	**Year**	**Nonfatal**	**Fatal**	**Total**	**Mortality (%)**	**Population**	**Per Capita Burn (%)**	**Per Capita Burn (%)**
0–4	2005	71935	279	72214	0.4	19917400	0.36	0.0014
	2006	64821	250	65071	0.4	19938883	0.33	0.0013
	2007	63207	266	63473	0.4	20125962	0.32	0.0013
	2008	60571	219	60790	0.4	20271127	0.30	0.0011
	2009	58400	208	58608	0.4	20244518	0.29	0.0010
5-yr Avg		63787	244	64031	0.4	20099578	0.32	0.0012
	2010	61091	212	61303	0.3	20201362	0.30	0.0010
	2011	67225	172	67397	0.3	20125958	0.33	0.0009
	2012	68130	141	68271	0.2	19980310	0.34	0.0007
	2013	63297	165	63462	0.3	19867849	0.32	0.0008
	2014	57117	151	57268	0.3	19876883	0.29	0.0008
5-yr Avg		63372	168	63540	0.3	20010472	0.32	0.0008
10-yr Avg		63579	206	63786	0.3	20055025	0.32	0.0010
5–18	2005	74159	312	74471	0.4	57831395	0.13	0.0005
	2006	66652	279	66931	0.4	58119881	0.12	0.0005
	2007	61400	300	61700	0.5	58288081	0.11	0.0005
	2008	63831	229	64060	0.4	58421598	0.11	0.0004
	2009	52910	208	53118	0.4	58424283	0.09	0.0004
5-yr Avg		63790	266	64056	0.4	58217048	0.11	0.0005
	2010	60711	198	60909	0.3	58480960	0.10	0.0003
	2011	61699	187	61886	0.3	58193935	0.11	0.0003
	2012	62847	154	63001	0.2	58091861	0.11	0.0003
	2013	58077	197	58274	0.3	58038492	0.10	0.0003
	2014	55991	170	56161	0.3	57932325	0.10	0.0003
5-yr Avg		59865	181	60046	0.3	58147515	0.10	0.0003
10-yr Avg		61828	223	62051	0.4	58182281	0.11	0.0004
19–45	2005	208907	929	209836	0.4	112647339	0.19	0.0008
	2006	203442	878	204320	0.4	112514315	0.18	0.0008
	2007	191442	874	192316	0.5	112442872	0.17	0.0008
	2008	182288	694	182982	0.4	112505361	0.16	0.0006
	2009	173432	717	174149	0.4	112716130	0.15	0.0006
5-yr Avg		191902	818	192721	0.4	112565203	0.17	0.0007
	2010	190820	632	191452	0.3	112814655	0.17	0.0006
	2011	194082	627	194709	0.3	113358991	0.17	0.0006
	2012	197541	549	198090	0.3	114032337	0.17	0.0005
	2013	181735	620	182355	0.3	114758868	0.16	0.0005
	2014	178110	628	178738	0.4	115429655	0.15	0.0005
5-yr Avg		188458	611	189069	0.3	114078901	0.17	0.0005
10-yr Avg		190180	715	190895	0.4	113322052	0.17	0.0006
46–65	2005	70827	1028	71855	1.4	70711525	0.10	0.0015
	2006	72704	1124	73828	1.5	72928734	0.10	0.0015
	2007	74386	1132	75518	1.5	74994337	0.10	0.0015
	2008	79990	1110	81100	1.4	76870172	0.11	0.0014
	2009	74215	1035	75250	1.4	78416768	0.10	0.0013
5-yr Avg		74424	1086	75510	1.4	74784307	0.10	0.0015
	2010	79685	1068	80753	1.3	79661338	0.10	0.0013
	2011	84717	1095	85812	1.3	81352090	0.11	0.0013
	2012	82370	1044	83414	1.3	82417467	0.10	0.0013
	2013	79213	1120	80333	1.4	82497447	0.10	0.0014
	2014	92813	1081	93894	1.2	82759431	0.11	0.0013
5-yr Avg		83760	1082	84841	1.3	81737555	0.10	0.0013
10-yr Avg		79092	1084	80176	1.4	78260931	0.10	0.0014
>65	2005	22054	1183	23237	5.1	34408940	0.07	0.0034
	2006	22277	1136	23413	4.9	34878099	0.07	0.0033
	2007	20393	1196	21589	5.5	35379955	0.06	0.0034
	2008	23449	1127	24576	4.6	36025708	0.07	0.0031
	2009	22034	1026	23060	4.4	36969830	0.06	0.0028

Continued

Table 3.1 Burn Mortality Rates Over Time.—cont'd

		BURNS					ALL	FATAL
Age	**Year**	**Nonfatal**	**Fatal**	**Total**	**Mortality (%)**	**Population**	**Per Capita Burn (%)**	**Per Capita Burn (%)**
5-yr Avg		22041	1134	23175	4.9	35532506	0.07	0.0032
	2010	19872	1083	20955	5.2	37587223	0.06	0.0029
	2011	21465	1087	22552	4.8	38690658	0.06	0.0028
	2012	26219	1021	27240	3.7	39590103	0.07	0.0026
	2013	25449	1114	26563	4.2	41334875	0.06	0.0027
	2014	24914	1164	26078	4.5	42858762	0.06	0.0027
5-yr Avg		23584	1094	24678	4.5	40012324	0.06	0.0027
10-yr Avg		22813	1114	23926	4.7	37772415	0.06	0.0030

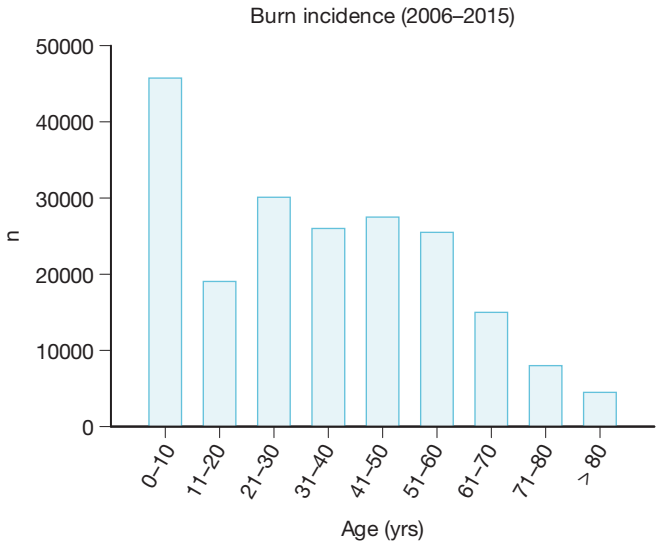

Fig. 3.3 Burn-specific injury statistics taken from the WISQARS database. These are the number of recorded injuries in each age group.

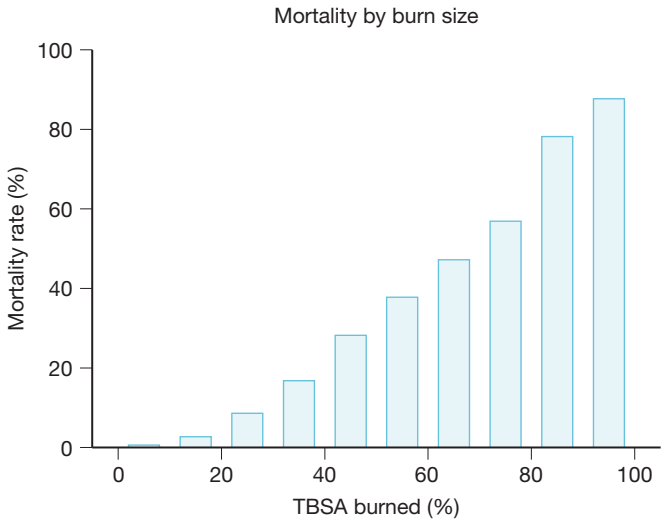

Fig. 3.4 Reported mortality by burn size.

thereafter the total numbers decline (Fig. 3.3) for a bimodal distribution when grouped in this way. Among these, 67% were in men, which is similar to previous reports of burns by gender. In terms of ethnicity, 58% of burns in the United States were in European-Americans, 21% in African-Americans, 13% in Hispanic-Americans, 5% in other ethnicities, and 3% in Asian-Americans.

Most burns were below 10% total body surface (TBSA), which included 78% of the burned population. Another 14% measured 11–20% TBSA, and the remaining 8% were greater than 20% TBSA. These numbers are all from designated burn centers, and it is likely that many additional burns below 10% TBSA were treated in nonburn centers. With this in mind, it is likely that almost all burns over 10% were treated at burn centers, thus the distribution in the NBR data is likely to be biased to larger burns from the true incidence in the United States.

Most burns were the result of injuries due to fire and flame at 41% of the total. Scalds accounted for another 33%, followed by contact with hot objects at 9%, and then chemical and electrical burns at 3% each. Overall mortality for those with burns was 3.1% during this period, which declined by almost 25% from 4.0% in 2006. Mortality was generally higher in women, except in 2015. Deaths did increase significantly with burn size (as expected), which was almost linear with increasing burned area (regression formula $y = x - 13.7$, $r^2 = 0.97$) (Fig. 3.4). This is a change from previous mortality rates, which was mostly a first-order distribution. According to this formula, probability of mortality for a burn (without considering age) can be estimated at %TBSA burned minus 14.

We did a probit analysis on the overall mortality data which revealed an LD50 for a 55% TBSA burn among all age groups. Thus a 55% TBSA burn would be expected to have a mortality rate of 50%; this is an improvement from previous reports.[3] When the Baux score (age plus TBSA burned) was examined for mortality, a 50% mortality was reported at about 105 and a 90% mortality was reported at 130.

Demography

Geographic and housing tract location significantly influences the rate of house fires and the subsequent death rates from associated burns. Age of the home, economic status, number of vacant houses, and immigration status affect the house fire rate.[4–5] House fire death rates are higher in

Table 3.2 Causes of Burn Injuries.

	Fires (%)	Injuries (%)	Deaths (%)	Odds Ratio of Death
Cooking Equipment	46	44	19	0.4
Heating Equipment	16	12	19	1.2
Electrical Equipment	9	9	16	1.8
Intentional	8	7	14	1.8
Smoking	5	10	22	4.4

the Eastern part of the United States, particularly the Southeast, compared to the West.[6] Cooking is the leading cause of house fires in the United States: 46% of house fires and 44% of fire-related injuries are by this cause.[7] Another leading cause of house fires is from heating equipment at 16% of instances. Other causes include electrical system fires (9%), intentional fires (8%), and fires from cigarette smoking (5%). Interestingly the cause of fire with the highest mortality is that from cigarette smoking, comprising 22% of residential fire-related deaths (Table 3.2). The ratio of deaths compared to other causes is also much higher in this group, at 4.4.

Gratifyingly the number of residential fires has dramatically decreased since 2004, falling 22%; similarly related fire death rates have fallen by the same amount. Injuries, however, have only gone down by 7%, suggesting that in those fires that do occur, more injuries are occurring.[8] Interestingly fire death rates are reduced by 50% with working fire alarms.[9] When the rate of fire deaths is considered by state, we find these are highest in Alabama, Alaska, Arkansas, District of Columbia, Mississippi, Oklahoma, Tennessee, and West Virginia. The lowest rates are Arizona, California, Colorado, Florida, Massachusetts, Nevada, New Jersey, Texas, and Utah.

The economic consequences of residential fires are also great. The highest fire-related losses in recent history were in 2008, with $16.7 billion in property damage and other direct costs. This has significantly fallen since then, with a reported $11.5 billion in losses in 2013.[8] The healthcare costs of burns are also prodigious. Each year in the United States, 40,000–60,000 people undergo in-hospital care for burns. The average charges for hospital care of a burned patient range from $47,557.00 to $1,203,410.00 (average $92,377), with much higher costs incurred by patients with extensive burns. The length of hospital stay ranges from one day to hundreds of days (mean 9.7), and, for patients 80 years and older is more than twice as long as that for children under 5.[2]

High-Risk Populations

CHILDREN

The number of pediatric burn patients admitted to hospitals is influenced by cultural differences, resource availability, and medical practice. Consequently the number of pediatric burn patients admitted to a hospital for treatment varies by geographic area from a low rate of 1.4/100,000 population in North America to a high of 10.8/100,000 population in Africa.[1,10] It has been estimated that 113,108 children aged 18 and younger were treated for burns in the United States in 2014. Of those injuries, approximately 60% were scald burns in those under 5 years of age; contact burns, 20%; fire/flame, 15%; and 5%, other.[2] For those aged 5–18, scalds accounted for approximately 33% of injuries; fire/flame, 45%; contact, 10%; and other, 12%, demonstrating a shift from scalds to fire and flame with increasing age. In 2013, 334 children died from fires or burns, and 44% of these were 4 years of age and younger.[9]

Scald burns are the most common cause of burns in the particularly young. The occurrence of tap water scalds can be prevented by adjusting the temperature settings on hot water heaters or by installing special faucet valves so that water does not leave the tap at temperatures above 120°F (48.8°C).[9,11] All code-making bodies at the national and regional levels have established standards for new or reconstructed dwellings requiring antiscald technology and a maximum water temperature of 120°F.

Home exercise treadmills represent a recently identified source of burns in pediatric patients. The injuries are a consequence of contact with a moving treadmill and almost always involve the upper extremity (97%), often the volar surface of the hand.[12] Approximately 50% undergo surgical intervention in the form of skin grafting, and some develop hypertrophic scars.[13]

ELDERLY

The elderly represent an increasing population segment, as previously described, and they have an increased prevalence in the burned population due to increased numbers as well as increased risk of being burned. Furthermore mortality from burns increases with age. The WISQAR data demonstrate that about 6% of all burns occur in those older than 65 years, although other reports from single centers approach 16% of all admissions for burns,[14] and mortality in this age group is significantly higher than that of all other ages, at 4.7% of all over 65 years of age who are burned compared to between 0.4% and 1.4% in all other age groups.

Interestingly the rates of burn by gender are almost even in the elderly who are burned, 51% in men and 49% in women. In an older paper, it was noted that 67% of injuries in the elderly are caused by flame or explosion, 20% by scalds, 6% by electricity, 2% by chemicals, and 6% by other causes. Forty-one percent of the injuries occurred in the bedroom and/or living room, 28% out of doors or in the workplace, 18% in the kitchen, 8% in the bathroom, and 5% in the garage or basement. Seventy-seven percent of the patients had one or more preexisting medical conditions.[15] Examination of predictors of mortality revealed that the usual signals such as increasing age, burn size, and inhalation injury continue to remain the most useful in this age group, but each of these had much more impact on mortality than in other age groups, as reflected by the much higher mortality rate.[14] Several authors reported lower mortality rates in the elderly than expected from standard prediction models, such as those from Bull, ASBI, and Ryan,[16] indicating that we are improving in this age group as well.

A recently identified factor in burns in the elderly are those in relation to dementia. Harvey and others identified a 1.6 odds ratio of burns between the aged with and without dementia. In addition, the burns were more likely to be larger, were more likely associated with ignition of clothing or scalds, and hospital length of stay was twice as long.[17]

DISABLED

The disabled are a group of patients considered to be burn-prone and are often injured in the home in incidents associated with scalds. From a report in 1993, the effects of disability and preexisting disease in those patients are evident in the duration of hospital stay (27.6 days on average) and the death rate (22.2%) associated with the modest average extent of burn (10% TBSA).[18] Another report on burns in generally elderly patients with dementia (who were also disabled) emphasized prevention measures to reduce the incidence of burns when such patients are performing the activities of daily living.[19]

MILITARY PERSONNEL

In wartime, military personnel are at high risk for burns both related to combat and nonintentional causes. The incidence of burns is associated with the types of weapons employed and combat units engaged and has ranged from 2.3% to as high as 85% in a number of conflicts over the past 8 decades. The detonation of a nuclear weapon at Hiroshima in 1945 instantaneously generated an estimated 57,700 burned patients and destroyed many treatment facilities, which thereby compromised their care.[20] In the Vietnam conflict, as a consequence of the total air superiority achieved by the U.S. Air Force and the lack of armored fighting vehicle activity, those with burns constituted only 4.6% of all patients admitted to Army medical treatment facilities from 1963 to 1975.[21] Approximately 60% of the 13,047 burned patients were nonbattle injuries. Furthermore in the Panama police action in late 1989, the low incidence of burns (only 6 or 2.3% of the total 259 casualties had burns) has been attributed to the fact that the action involved only infantry and airborne forces using small-arms weaponry.

Burns during conflicts have not always been this low, as exemplified by the Israeli conflicts of 1973 and 1982, and the British Army of the Rhine experience in World War II. Both of these conflicts were dense, with personnel in armored fighting vehicles who had a relatively high incidence of burns.[22,23] Burns have also been common injuries in war at sea, such as in the Falkland Islands campaign of 1982: 34% of all casualties from the British Navy ships were burns.[24,25] The increased incidence of burns, 10.5% and 8.6% in the Israeli conflicts of 1973 and 1982, respectively, as compared to the 4.6% incidence in the 1967 Israeli conflict, was considered to reflect what has been termed "battlefield saturation" with tanks and antitank weaponry.[22,26] Decreasing incidence of burns in armored vehicle combat has been attributed to enforced use of flame-retardant garments and the effectiveness of an automatic fire extinguishing system within tanks.[26] Those factors have also been credited with reducing the extent of the burns that did occur. For example, in the 1973 Israeli conflict 29% of burned patients had injuries of more than 40% TBSA, and only 21% had burns of less than 10% TBSA. After institution of garment and fire-extinguisher policies, in the 1982 Israeli conflict those same categories of burns represented 18% and 51%, respectively, of all burn injuries.

Modern weaponry may have eliminated the differential incidence of burns between armored fighting vehicle personnel and those in other combat elements. One of every seven casualties had burns in the British and Argentinean forces in the 1982 Falkland Islands conflict in which there was little if any involvement of armored fighting vehicles.[24,25] Conversely only 36 (7.8%) burns were sustained in the total 458 casualties in the U.S. Forces during Operation Desert Shield/Desert Storm in 1990–1991, in which there was extensive involvement of armored fighting vehicles.

In the most recent armed conflicts, Operations Iraqi Freedom and Enduring Freedom, the U.S. Army Burn Center (U.S. Army Institute of Surgical Research [ISR]) in San Antonio, Texas, provided care for all military patients who sustained burns. Trained burn surgeons from the ISR provided care at the Burn Center in San Antonio; at a general hospital in Landstuhl, Germany, while in transit from the theater of operations to the continental United States; as well as at the Level III hospital in-theater (Balad, Iraq). During this conflict, approximately 900 combat casualties were admitted to the burn center, among whom 34 expired (3.9%).[27] Interestingly another 11 expired within 10 years of injury from either a drug overdose (5), another combat injury (3), or a motor vehicle crash (3).[28] Therefore about 10% of deaths occurred from self-induced overdose, which should be investigated further and mitigated. On average, definitive care was administered in the United States within 96 hours of injury, which was accomplished through active use of the Global Patient Movement Regulating Center and the Burn Flight Team. This team consists of Army personnel who work with existing Air Force crews to support and rapidly transport severely burned patients from theater. In this conflict, more than 250 critically ill patients were transported successfully, with only one mortality during the flight.[29]

The U.S. Army Burn Center maintains readiness by caring for civilians in south Texas, and this activity continued during the conflict. When examined, these two populations who were cared for by the same personnel with the same equipment showed no differences in outcomes when those of the same ages were compared. Interestingly the burn size distributions of both groups were the same and were similar to that reported from the general databases at the beginning of this chapter.[30]

Burn Etiologies

FIRE/FLAME

Flame is the predominant cause of burns (43%) in patients admitted to burn centers, particularly in the adult age group.[2] Misuse of fuels and flammable liquids is a common cause of burns, constituting 66% of flame injuries.[31] The predominant affected population is young men, and the distribution of burn sizes is similar to that of all burns.[32] However mortality rates are higher than in the general

burn population (50% increase), and length of hospital stay is up to twice as long as for other causes of burns. This might be related to a higher incidence of full-thickness burns due to the higher temperatures associated with gasoline, which results in more excision and grafting procedures, ICU care, and the like.[33] Because of these findings, the use of gasoline for purposes other than as a motor fuel, and any indoor use of a volatile petroleum product, should be discouraged as part of any prevention program.

Another commonly encountered cause of flame burns is that associated with automobile crashes. A comprehensive study done in Germany demonstrated that about 1% of car crashes had associated burns; these injuries were more common in frontal and high-energy collisions.[34] In a review of 178 patients who had been burned in an automobile crash, it was noted that slightly more than one-third had other injuries, most commonly involving the musculoskeletal system, and that approximately 1 in 6 had inhalation injury (1 in 3 of those who died).[35] A review of patients admitted to a referral burn center revealed that burns sustained while operating a vehicle involved an average of more than 30% TBSA and were associated with mechanical injuries (predominantly fractures) much more frequently than those burns incurred in the course of vehicle maintenance activities, which involved an average of less than 30% TBSA.[36]

Automotive-related flame burns can also be caused by fires and explosions resulting from "carburetor-priming" with liquid gasoline, although this is much less common now that almost all automobile engines are equipped with fuel injectors. The burns sustained in boating accidents are also most often flash burns due to an explosion of gasoline or butane and typically affect the face and hands.[37]

The ignition of clothing is the second leading cause of burn admissions for most ages. The fatality rate of patients with burns due to the ignition of clothing is second only to that of patients with burns incurred in house fires.[9] More than three-quarters of deaths due to the ignition of clothing occur in patients older than 64.[6] Clothing ignition deaths, which were a frequent cause of death in young girls, have decreased as clothing styles have changed and are now rare among children, with little overall gender difference at the present time.

SCALD

Burns due to hot liquids cause approximately 33% of all burns in any age group, but this incidence in much higher in children, particularly those under 4 years of age, at up to 60% of admissions.[38–40] These injuries are generally partial-thickness; however full-thickness injury can occur. In particular, full-thickness burns have a much higher incidence with hot oil burns. Young children are most commonly injured by pulling a container of hot liquid onto themselves,[40] while older children and adults are most commonly injured by improper handling of hot oil appliances.[41–43]

Burns from scalds and contacts with hot materials cause approximately 100 deaths per year.[6] The case fatality rate of scald injury is low (presumably due to the usually modest extent and limited depth of the burn), but scalds are major causes of morbidity and associated healthcare costs, particularly in children younger than 5 years of age and in the elderly.

CONTACT

Contact burns are the third most encountered cause of injury and are most common in children and young adults. For children, the incidence is higher due to lack of safety awareness and grasping hot objects. Another cause recently identified was contact burns due to glass-fronted fireplaces.[44] In this study, 402 children were identified with this injury in the United States in a 5-year period. This rate was 20 times higher than that estimated by the U.S. Consumer Product Safety Commission.

For younger adults, motorcycle exhaust pipes are another common cause of injury related to the use of vehicles. In Greece, the incidence of burns from motorcycle exhaust pipes has been reported to be 17/100,000 person-years, or 208/100,000 motorcycle-years. The highest occurrence was in children. In adults, the incidence is 60% higher in women than in men. As anticipated, the most frequent location of the burns was on the right leg below the knee, where contact with the exhaust pipe occurs. The authors concluded that a significant reduction of incidence could be achieved by wearing long pants and by the use of an external exhaust pipe shield.[45]

WORK-RELATED BURNS

Work-related burns account for 20–25% of all serious burns and also account for about 2% of all workplace injuries.[46] Interestingly, in a recent study from Michigan, accommodation and food services as well as the healthcare and social assistance industries accounted for more than 50% of the injuries.[47] Restaurant-related burns, particularly those due to deep fryers, represent a major and preventable source of occupational burn morbidity and, in restaurants, account for 12% of work-related injuries.[6] Other significant causes of work-related injuries are associated with electrical injuries, chemical injuries, and contact burns. Also as anticipated, the risk of burns due to hot tar is greatest for roofers and paving workers. Of all incidents involving roofers and sheet metal workers, 16% are burns caused by hot bitumen, and 17% of those injuries are of sufficient severity to prevent work for a variable period of time.

CHEMICAL BURNS

Chemicals are a well-known cause of burns, and these burns are generally caused by either acidic or alkali chemicals, although chemical burns can also occur with organic solvents. In a recent review of the literature for chemical burns, the reported percentage of burns related to chemical agents is between 2% and 10% of injuries. Most of those affected are men who were injured either in the workplace or domestic setting. Acids caused about 25% of the injuries and bases 55%.[48] The limited extent of burns reported from chemicals may be affected by many being treated as outpatients.

The greatest risk of injury due to strong acids occurs in patients who are involved in plating processes and fertilizer

manufacture, whereas the greatest risk from alkalis is associated with soap manufacturing and in the home with the use of oven cleaners. The greatest risk of organic solvent injuries is associated with the manufacture of dyes, fertilizers, plastics, and explosives, and that for hydrofluoric acid injury is associated with etching processes, petroleum refining, and air conditioner cleaning. Anhydrous ammonia injury is most common in agricultural workers and cement injury (an alkali injury with associated thermal injury) is most common in construction workers.

ELECTRICAL CURRENT INJURY

Electrical current is another cause of injury seen in burn centers. Approximately one-third of electrical current injuries occur in the home, with another one-quarter occurring on farms or industrial sites and the rest occurring in the occupational setting.[6] A once common cause of electrical injury by household current occurred in children who inserted uninsulated objects into electrical receptacles or bit or sucked on electrical cords in sockets, resulting in oral commissure burns;[49] this has significantly diminished with the universal adoption of alternating electrical current for household use. Low-voltage direct current injury can be caused by contact with automobile battery terminals or by defective or inappropriately used medical equipment such as electrical surgical or external pacing devices,[50] or defibrillators.[51] Although such injuries may involve the full thickness of the skin, they are characteristically of limited extent.

Employees of utility companies, electricians, construction workers (particularly those working with cranes), farm workers moving irrigation pipes, oil field workers, truck drivers, and individuals installing antennae are at greatest risk of work-related high-voltage electric injury.[52] The greatest incidence of electrical current injury occurs during the summer as a reflection of farm irrigation activity, construction work, and work on outdoor electrical systems and equipment.[53]

During the period 1994 to 2008, 26 patients with high-voltage injury and 30 with low-voltage injury were treated at a regional burn center. Mortality was only 3.6%, which is likely biased in that those who died at the scene of injury were not included.[54] In another study, about one-half of patients with high-voltage injury underwent fasciotomy, and, even so, amputation was necessary in almost all of these. Of note, about 15% developed some long-term neurologic deficit, and 3% developed cataracts.[55] Another study reported the outcome of 195 patients with high-voltage electrical injury treated at a single burn center during a 19-year period. A total of 187 (95.9%) of the 195 patients survived and were discharged. Fasciotomy was undertaken in the first 24 h following injury in 56 patients, and 80 patients underwent an amputation because of extensive tissue necrosis. The presence of hemochromogens in the urine predicted amputation with an overall accuracy of 73.3%.[56]

LIGHTNING BURNS

Death due to lightning strikes has now fallen to the third most common cause of death during storms[57] and is now down to less than 30 deaths per year in the United States. Most lightning strikes (70%) occur between clouds; however approximately 30% hit the ground or other site. In the United States, these are most common in Florida and the Southeast coast and occur most often in the warmer months. Only about 3–5% of injuries result from a direct lightning strike; instead most of the energy is mediated by other objects, such as the ground or a tree.[58] Most injuries in survivors are superficial, and deep injuries are rare.

Lightning injuries and deaths occur most often in individuals who work outside or participate in outdoor recreational activities. Thus men are five times more likely to be struck by lightning than are women.[59] In some older studies, the annual death rate from lightning was greatest among those aged 15–19 years (6 deaths per 10 million population; crude rate: 3 per 10 million) and is seven times greater in men than in women. Approximately 30% of those struck by lightning die, with the greatest risk of death being in those patients with cranial or leg burns. Fifty-two percent of patients who died from lightning injury were engaged in outdoor recreational activity, such as playing golf or fishing, and 25% were engaged in work activities when struck.[60]

FIREWORKS

Fireworks are another seasonal cause of burns. Approximately 8% of patients with fireworks injuries undergo hospitalization for care, and approximately 60% of those injuries are for burns of specific areas, mostly those of the hands, head, and eyes.[61] Other data estimate that 1.86–5.82 fireworks-related burns per 100,000 persons occurred in the United States during the Fourth of July holiday.[62] Sparklers, firecrackers, and bottle rockets caused the greatest number of burns.[63] Of note, the incidence of injuries has decreased by 30% over the past 25 years. Boys, especially those aged 10–14, are at the highest risk for fireworks-related injuries. Children aged 4 and under are at highest risk for sparkler-related injuries.[9] Proposed prevention measures include reducing the explosive units per package, package warnings, and limiting the sale of the devices to children.[64]

INTENTIONAL BURNS

Burns can be intentional, either self-inflicted or done purposefully by another. It is estimated that 4% of burns (published range 0.37–10%) are self-inflicted. The region of the world has great import in determining the rates of intentional burns, with a particularly high rate in young women in India and middle-aged men in Europe. The average burn size in intentional burns is larger than other causes, at approximately 20% TBSA. The reasons for intentional burns, specifically assaults, are reported to be due to conflict between persons including spouses, elderly abuse, and economic transactions. For self-inflicted injuries, these are related to domestic discord, difficulty between family members, and social distress from unemployment. Mortality rates worldwide for intentional burns are reported at 65%.[65] Rates for Europe and the United States are also higher, with a twofold increase in the risk of mortality compared to nonintentional injuries.[66] Data from the NBR in 2007 indicated that 3% of admitted burns were intentional,

with about 50% self-inflicted and the other 50% from assault. Similar to the prior report, burn size was on average 22% TBSA compared to 11% for nonintentional and exhibited a fourfold higher mortality rate.[67]

In some other studies, interesting findings were noted. In those with self-inflicted injuries, 43% occurred at home and another 33% occurred while in a psychiatric institution. Importantly 73% had a history of psychiatric disease; these were predominantly affective disorders or schizophrenia in the suicide attempts and personality disorders in self-mutilation. Also, 55% of suicide attempts had previously attempted suicide; 66% of the self-mutilators had made at least one previous attempt at self-mutilation. The authors concluded that the very fact of self-burning warranted psychiatric assessment.[68]

Assault by burning is most often caused by throwing liquid chemicals at the face of the intended victim or by the ignition of a flammable liquid with which the victim has been doused. These types of injuries are generally rare in the developed world but are quite common in low- and middle-income countries.[65] In those injuries that do occur in such places as the United States, most are African-American women who were unemployed and are associated with premorbid substance abuse.[69] Occasionally injuries will be induced by spouses characteristically dousing the face or genitalia.[70] In India, a common form of spouse abuse is burning by intentional ignition of clothing. When such burns are fatal, they have been called "dowry deaths" because they have been used to establish the widower's eligibility for a new bride and her dowry.

Child abuse represents a special form of burns perpetrated by parents, siblings, caregivers, or child care personnel. Child abuse has been associated with teenage parents, mental deficits in either the child or the abuser, illegitimacy, a single-parent household, and low socioeconomic status, although child abuse can occur in all economic groups. Abuse is usually inflicted on children younger than 2 years of age who, in addition to burns, may exhibit signs of poor hygiene, psychological deprivation, and nutritional impairment.[71] The most common form of child abuse involving burns is caused by hot water in bathing. In a recent report, it was noted that about 5% of pediatric burn admissions were associated with abuse, and most were due to scalds (90%). Mortality was double that of patients with nonintentional injuries (5.4% vs. 2.3%).[72]

A distribution typical of child abuse immersion scald burns (i.e., feet, posterior legs, buttocks, and hands) should heighten the suspicion of child abuse. The presence of such burns mandates a complete evaluation of the circumstances surrounding the injury and the home situation. The importance of identifying child abuse in the case of a burn injury resides in the fact that if such abuse goes undetected and the child is returned to the abusive environment, there is a high risk of fatality due to repeated abuse.

Elder abuse can also take the form of severe burn. A congressional report published in 1991 indicated that 2 million older Americans are abused each year, and some estimates claim a 4–10% incidence of neglect or abuse of the elderly.[73] A recent retrospective review of 28 patients 60 years and older admitted to a single burn center during a calendar year identified self-neglect in seven, neglect by others in three, and abuse by others in one.[74] Adult protective services were required in two cases. The authors of that study concluded that abuse was likely to be underreported because of poor understanding of risk factors and a low index of suspicion on the part of the entire spectrum of healthcare personnel.

HOSPITAL BURNS

Patients may also sustain burns while in the hospital for diagnosis and treatment of other disease. Approximately 2% of surgical anesthesia malpractice claims involve fire incidents, and 85% of these were in head and neck surgery. These were most commonly associated with the use of electrocautery around oxygen sources.[75,76] Application of excessively hot soaks or towels or inappropriate use of heat lamps or a heating blanket are other causes of burn injury to patients.[77] Localized high-energy ultrasound may also produce coagulative necrosis, as exemplified by full-thickness cutaneous injury and localized subcutaneous fat necrosis of the abdominal wall in a patient who had received focused-beam high-intensity ultrasound treatment for uterine fibroids.[78] A common cause of burn injury, particularly in disoriented hospital or nursing home patients, is the ignition of bed clothes and clothing by a burning cigarette. Smoking should be banned in healthcare facilities or at least restricted to adequately monitored situations.

Burn Patient Transport and Transfer

As noted earlier, distance between viable burn centers and variable population density implies that many burned patients undergo transfer to burn centers from other locations. For transfer across short distances and in congested urban areas, ground transportation is frequently the most expeditious. For longer distances, aeromedical transfer for major burns is often indicated when ground transportation takes more than 2 hours.[79] In the United States, helicopters are most frequently employed for distances of less than 200 miles. The instance of vibration, poor lightning, restricted space, and high noise make in-flight monitoring and therapeutic interventions difficult, a fact that emphasizes the importance of carefully evaluating the patient and modifying treatment prior to the transfer. If distances of more than 200 miles are considered, fixed-wing aircraft are often a better option. The patient compartment of such an aircraft should be well lighted, permit movement of attending personnel, and have some measure of temperature control. In general, burned patients travel best in the immediate period after the burn injury has occurred, as soon as hemodynamic and pulmonary stability has been attained. This is particularly true in those with inhalation injury, whereby an increased mortality rate was shown in those taking more than 16 hours to arrive at definitive care.[80]

Physician-to-physician case review to assess the patient's need for and ability to tolerate aeromedical transfer, prompt initiation of the aeromedical transfer mission, examination of the patient in the hospital of origin by a burn surgeon from the receiving hospital and correction of organ dysfunction prior to undertaking aeromedical transfer, and in-flight monitoring by burn-experienced personnel ensure

both continuity and quality of care during the transport procedure. During the first half of the Iraq/Afghanistan conflicts (2003–2007), the U.S. Army ISR Burn Care Flight Teams using such a regimen completed 380 patient transfers from theater to the burn center in San Antonio using dedicated burn transport teams including physicians, nurses, respiratory therapists, and support personnel. One-third of the patients (33.6%) received ventilatory support throughout the transport, but no in-flight deaths occurred.[81] This demonstrates that burned patients can be transported safely throughout the world if indicated.

Mass Casualties

Mass casualty incidents may be caused by forces of nature or by accidental or intentional explosions and conflagrations. Interest in man-made mass casualties has been heightened by recent terrorist activities and the threat of future incidents. The incidence of severe burns in a mass casualty incident varies with the cause of the incident, the magnitude of the inciting agent, and the site of occurrence (indoors vs. outdoors). The terrorist attacks in which airplanes laden with aviation fuel crashed into the Pentagon and the World Trade Center on September 11, 2001, produced 10 and 39 patients with burns, respectively, for treatment at burn centers.[82,83] Since then, many events have occurred throughout the world, with the most recent taking place at a festival in Taiwan in 2015, where 499 persons were burned who were between the ages of 12 and 38: 281 sustained burns over 40% TBSA. These patients were distributed between many hospitals, and the eventual mortality rate was 3%, akin to that normally seen in burn centers. The assembled response was massive, including thousands of providers, and was effectively coordinated at the federal level.[84] Another prominent burn event occurred in Bali, in 2002, caused by an explosion and fire that killed more than 200 people and generated 60 burn patients who, after triage and emergency care, were transported by aircraft to Australia and treated at various hospitals.[85] The casualties produced in terrorist attacks often have associated blast injury and mechanical trauma in addition to burns.

Recent nonterrorist mass casualty incidents have been of greater magnitude in terms of numbers of burn casualties. In the Station nightclub fire in Warwick, Rhode Island, in February 2003, 96 people died at the scene and 215 people were injured. Forty-seven of the 64 burned patients were evaluated at one burn center and admitted for definitive care.[86] Additionally an explosion at a pharmaceutical plant in North Carolina in January 2003 killed 3 and injured more than 30 to an extent that necessitated admission to a hospital. Ten of the injured patients, all with inhalation injury and 6 with associated mechanical trauma, required admission to the regional burn center.[87]

To deal effectively and efficiently with a mass casualty situation burn treatment facilities must have an operational and tested mass casualty disaster plan and be prepared to provide burn care to a highly variable number of patients injured in either natural or man-made disasters.[88] In reality, mass casualty events are likely to involve some form of burns, particularly in those with explosions. All regions should be prepared for such an event with established plans that are reviewed regularly and drilled.

Outcome Analysis in Burns

The importance of the extent of injury to burn outcomes was recognized by Holmes in 1860, and further evidence was produced to relate either measured area or the specific parts of the body to outcomes in the latter 19th and early 20th centuries.[89,90] Formal expression of burn size as a percentage of total body surface area, however, awaited the work of Berkow in 1924.[91] Although not well known, this single finding in accurately estimating severity of injury made burns the first form of trauma in which the injury was measured and easily communicated. This measurement, then, was the first "trauma score" and made assessing burn size the basis for the accurate prediction of mortality, direct comparison of populations of burned patients, and the measurement of the effects of treatment on outcomes.

The earliest comprehensive statistical technique used for such assessment was univariate probit analysis.[92,93] Before the age of desktop computing, this approach was quite laborious and thus uncommon. An early attempt at multivariate evaluation was made by Schwartz, who used probit plane analysis to estimate the relative contributions of partial- and full-thickness burns to mortality.[94] The advent of computers of suitable power and the further development of statistical techniques has reduced the difficulty of analyzing burn mortality, removed the necessity for arbitrary partitioning, and made these techniques much more accessible.

One of the first comprehensive analyses of this sort was done on a population of 8448 patients admitted for burn care to the U.S. Army ISR between January 1, 1950, and December 31, 1991. To ensure the validity of such studies, an important first step is to achieve uniformity among the population to be analyzed. Variables of interest include time from injury, burn size, and age; these patients were encountered between the day of injury and day 531 after burn (mean 5.86 days, median 1 day), with burns averaging 31% (range 1–100%, median 26%) TBSA. The ages were biphasic, with one peak at 1 year of age and another at age 20; the mean age of the entire population was 26.5 years (range 0–97 years, median 23 years). From this group, 7893 (93.4%) who had flame or scald burns were selected, excluding patients with electrical or chemical injuries. Some of these were from the Vietnam conflict and were first transferred to Japan and then selectively transferred to the Institute; arriving late at the Institute biased this cohort toward survival. To account for this, the analysis focused on the 4870 with flame or scald burns who reached the Institute on or before the second day after burn. Burn size in these patients averaged 34% TBSA (range 1–100%, median 29%), and age was again biphasic, with peaks at 1 and 21 years and a mean of 27.1 years (range 0–93 years, median 24 years).

Between 1950 and 1965, most of the admissions were young soldiers; mean age approximated 22.5 years and was relatively stable. During the succeeding decade, this value rose to an irregular plateau centering on 30 years of age, a

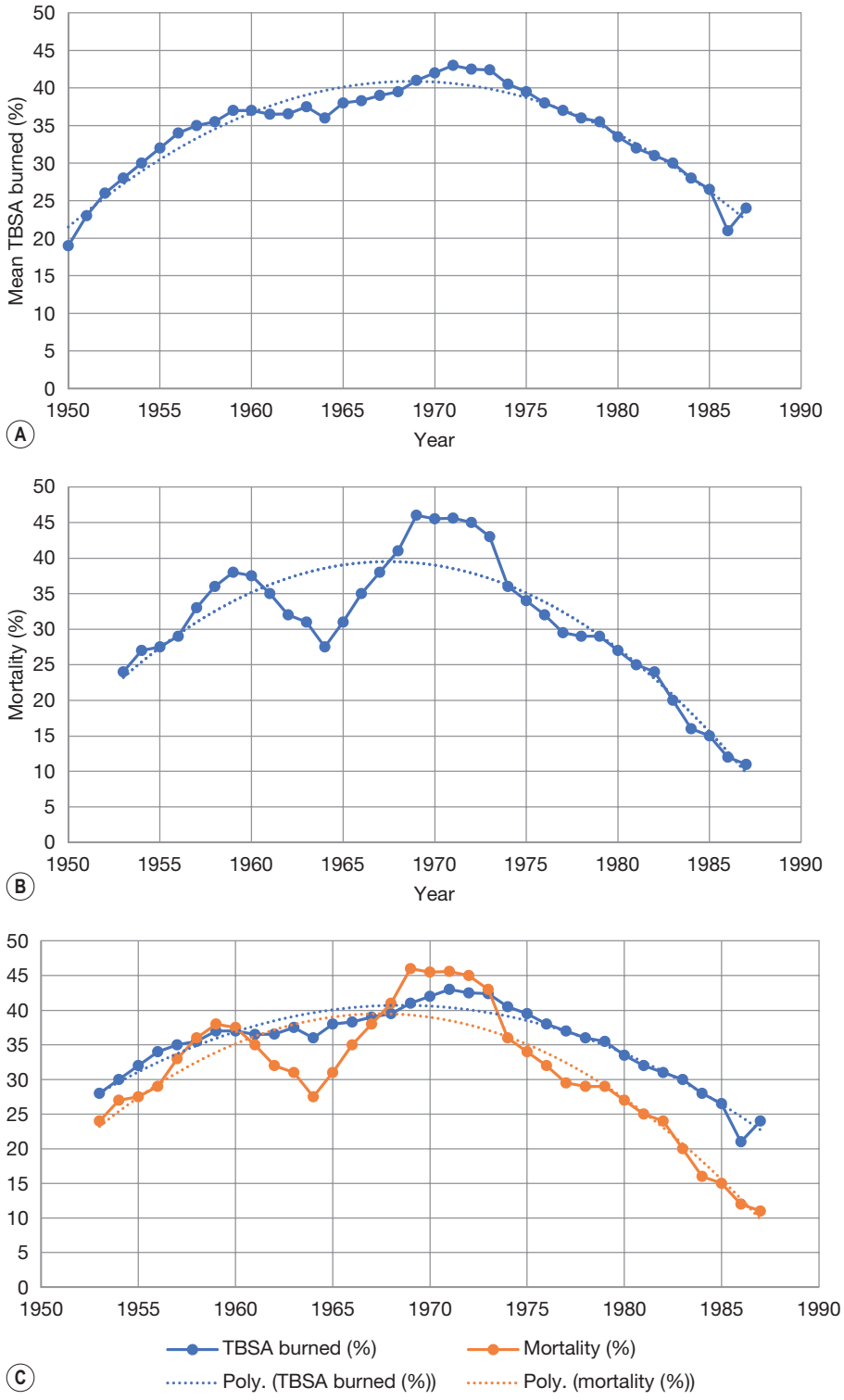

Fig. 3.5 U.S. Army Institute for Surgical Research Burn Incidence and Outcomes Data (1950–1988). Panel A describes the mean burn size encountered among admissions. The figure includes a polynomial trendline. Panel B shows the overall mortality rate and also includes a polynomial trendline. Panel C is a combination of these curves over time and shows both trendlines.

change reflecting a greater number of civilian admissions and increasing age in the military population.

Fig. 3.5A shows the variation in mean burn size during the study interval, and Fig. 3.5B shows the roughly parallel mortality. Mean burn size peaked in the two intervals spanning 1969 to 1974 and decreased steadily after that time. Mortality peaked at 46% during those years. The two datasets are shown together in Fig. 3.5C and suggest a crude index of the results of burn care in this population. When comparing the polynomial lines derived from

the data, it appears that a separation favoring improved survival occurred in about 1970. This was about the time of the development of effective topical antimicrobial chemotherapy.

Raw percent mortality, even in conjunction with burn size, is never an adequate index of the effectiveness of treatment since the frequency of death after burn injury is also determined by prior patient condition, age, inhalation injury, and the occurrence of pneumonia and burn wound sepsis. Each of these elements, except for prior condition, can be addressed in analysis, but only burn size, age, and the presence or absence of inhalation injury are known at the time of admission. Furthermore the definition of significant comorbidities and development of complications are constantly being revised, making addition of these to prediction formulas difficult, and this must be kept in mind by the reader.

For a uniform population of specific age, a plot of the relationship between burn size and percent mortality is S-shaped, or sigmoid: small burns produce relatively few deaths, but, generally, as burn size increases mortality rises steeply and then plateaus as it approaches its maximum of 100%. Of note, in our recent analysis presented early in the chapter (Fig. 3.4), this appears to be more linear as burn size increases when age is not considered. When age is added, children and young adults will fit this more accurately, and older adults will have a more first-order distribution. When these are added, the curve flattens, yielding that is seen in Fig. 3.5. Although this experience conforms with that of most burn centers in the United States, it should be noted that there are still many areas of the world where the survival of patients with burns of more than 40% TBSA is rare.

The U.S. Army Burn Center (at the U.S. Army ISR, Fort Sam Houston, Texas) is the second oldest continuously operating burn center in the United States. Thus data from this burn center provide an invaluable opportunity to understand long-term changes in patient care and their effects on outcome. To further address the changes previously found up to 1991, we analyzed changes in mortality risk occurring over time from 1950 to 2013. In this analysis, only patients admitted to the burn center on the day of burn or 1 or 2 days after burn were included. Furthermore only patients with fire/flame and scald injuries were included; those with electrical, chemical, or other thermal processes and exfoliative dermatitides were excluded. Patients of all ages and burn sizes were included. Mortality was assessed as death at any time during the index hospitalization at the burn center, regardless of cause.

Data were analyzed using binomial logistic regression (backward likelihood-ratio method). In the analysis, age was represented as cubic age function, given by the equation

$$\text{Age Function} = (-5 * \text{AGE} + 14 * \text{AGE}^2/100 - 7 * \text{AGE}^3/10000)/100$$

This permits use of a single term that captures the observation that the relationship between age and outcome is not linear but rather "bathtub-shaped," with a nadir at about 20 years and a leveling off in advanced age.[95] Year of admission was entered into the analysis as a categorical variable, permitting calculation of odds ratios for mortality for each individual year from 1950–2013.

A total of 9755 patients met study inclusion criteria and were analyzed. The mortality rate was 18.1%. The mean age was 31.6 years (standard deviation [SD] 19.8 years). Mean total burn size was 24.4% (SD 23.5%). Odds ratios of mortality as a function of year of admission are shown in Fig. 3.6. The graph is remarkable for two peaks in mortality risk, marked "A" and "B." Peak A, in the late 1950s and early 1960s, represents increased mortality associated with invasive Gram-negative burn wound infections. This peak was followed by a striking decrease in mortality risk in 1964 with the introduction of topical mafenide acetate cream for antimicrobial chemoprophylaxis. Peak B, in 1969–72, reflects the emergence of other virulent Gram-negative organisms less sensitive to mafenide acetate (e.g., *Klebsiella* spp.). With the introduction of silver sulfadiazine cream, first as a single agent and then as an alternating

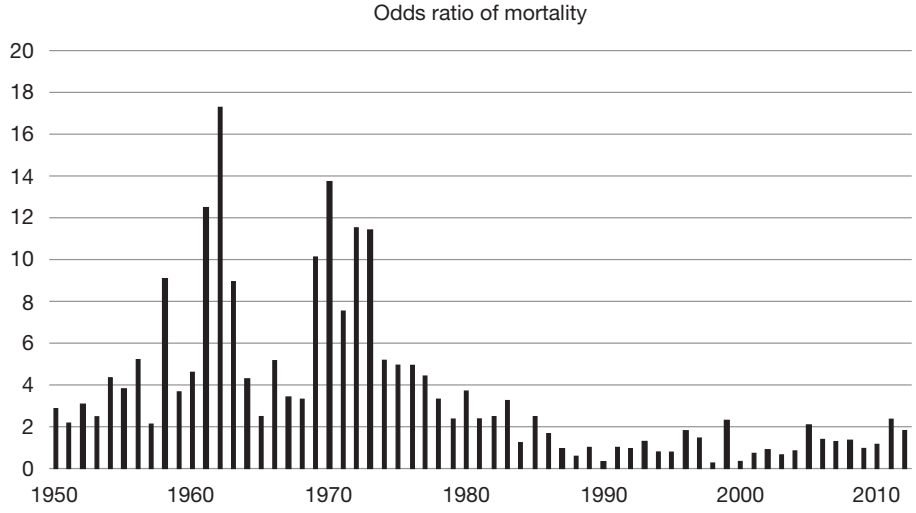

Fig. 3.6 Odds ratio of mortality distributed across a 63-year period from a single center (U.S. Army Institute of Surgical Research). These data show two spikes, in the 1960s and 1970s, that have subsequently significantly diminished in size to reach the current ratios.

agent along with mafenide acetate, a subsequent decline in mortality risk occurred. Further decreases in mortality risk were observed with the introduction and then essentially standardized use of burn wound excision in the late 1970s, enhanced infection control in the early 1980s, and improvements in mechanical ventilation in the early 1990s. The reduction in mortality risk has been maintained over the past two decades.

Conclusion

Much has been accomplished in acute burn care during the past half century, and further improvement in outcome will probably occur as inhalation injury and pneumonia come under better control and new wound coverage techniques are developed, but such improvement will be harder won and smaller in magnitude. Preservation of function, reconstruction, and rehabilitation, areas which have received less attention in the past, appear the more likely primary targets of future burn research and may be expected to materially enhance the quality of life for burn survivors.

Complete references available online at
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References

1. WISQARS Data and Statistics, Centers for Disease Control and Prevention. Available at: www.ded.gov/injury/wisqars/index.html.
2. National Burn Repository, American Burn Association. Available at: www.ameriburn.org/2016/%20ABA%20Full.pdf.
3. Olser T, Glance LG, Hosmer DW. Simplified estimates of the probability of death after burn injuries: extending and updating the Baux score. *J Trauma*. 2010;68:690-697.
4. Shai D. Income, housing, and fire injuries: a census tract analysis. *Pub Health Rep*. 2006;121:149-154.
5. Schachterle SE, Bishai D, Shields W, et al. Proximity to vacant buildings is associated with increased fire risk in Baltimore Maryland homes. *Inj Prev*. 2012;18:98-102.
6. Baker SP, O'Neill B, Ginsberg NJ, et al. Fire, burns, and lightning. In: *The Injury Fact Book*. 2nd ed. New York: Oxford University Press; 1992:161-173.
7. National Fire Protection Association, News and Research Page. Available at: NFPA.org/news-and-research/fire-statistics-and-reports.
8. United States Fire Administration, US Fire Statistics. Available at: usfa.fema.gov/data/statistics.
9. Safe Kids Worldwide, Burn Injury Fact Sheet 2015. Available at: www.safekids.org/sites/default/files/documents/skw_burns_fact_sheet_feb_2015.pdf.
10. Albertyn R, Berg A, Numanoglu A, et al. Traditional burn care in sub-Saharan Africa: a long history with wide acceptance. *Burns*. 2015;41:203-211.
11. Baptiste MS, Feck G. Preventing tap water burns. *Am J Public Health*. 1980;70:727-729.
12. Lohana P, Hemington-Gorse S, Thomas C, et al. Pediatric injuries due to home treadmill use: an emerging problem. *Ann R Coll Surg Engl*. 2012;94:121-123.
13. Goltsman D, Li Z, Connolly S, et al. Pediatric treadmill burns: assessing the effectiveness of prevention strategies. *Burns*. 2016;42:1581-1587.
14. Lumenta DB, Hautier A, Desouches C, et al. Mortality and morbidity among elderly people with burns – evaluation of data on admission. *Burns*. 2008;34:965-974.
15. McGill V, Kowal-Vern A, Gamelli RH. Outcome for older burn patients. *Arch Surg*. 2000;135:320-325.
16. Khadim MF, Rashid A, Fogarty B, et al. Mortality estimates in the elderly burn patients: a Northern Ireland experience. *Burns*. 2009;35:107-113.
17. Masud D, Norton S, Smailes S, et al. The use of a frailty scoring system for burns in the elderly. *Burns*. 2013;39:30-36.
18. Harvey L, Mitchell R, Brodaty H, et al. Dementia: a risk factor for burns in the elderly. *Burns*. 2016;42:282-290.
19. Backstein R, Peters W, Neligan P. Burns in the disabled. *Burns*. 1993;19:192-197.
20. Glasstone S Effects on personnel. In: *The effects of nuclear weapons*. Department of the Army Pamphlet No. 39-3. United States Atomic Energy Commission; June 1957: 455–464.
21. Burns sustained in Vietnam, 1965–1973. Data tables supplied by Department of the Army, the Chief of Military History and the Center of Military History, Washington D.C. 20314;1980.
22. Shafir R Burn injury and care in the recent Lebanese conflict. Presentation on behalf of the Surgeon General, Israeli Defense Forces and staff. The Israeli Society of Plastic and Reconstructive Surgery; 1984.
23. Owen-Smith MS. Armoured fighting vehicle casualties. *J R Army Med Corps*. 1977;123:65-76.
24. Chapman CW. Burns and plastic surgery in the South Atlantic campaign 1982. *J R Navy Med Serv*. 1983;69:71-79.
25. Sereday C MAJ, Major, Argentine Navy Medical Corps. Personal communication; 1990.
26. Eldad A, Torem M. Burns in the Lebanon War 1982: "the blow and the cure". *Mil Med*. 1990;155:130-132.
27. Renz EM, King BT, Chung KK, et al. The US Army burn center: professional service during 10 years of war. *J Trauma*. 2012;73:S409-S416.
28. Escolas SM, Archuleta DJ, Orman JA, et al. Postdischarge cause of death analysis of combat related burned patients. *J Burns Care Res*. 2017;38:e158-e164.
29. Chan RK, Aden J, Wu J, et al. Operative utilisation following severe combat-related burns. *J Burns Care Res*. 2015;36:287-296.
30. Wolf SE, Kauvar DS, Wade CE, et al. Comparison between burns and combat burns from Operation Iraqi Freedom and Operation Enduring Freedom. *Ann Surg*. 2006;243:786-792.
31. Williams JB, Ahrenholz DH, Solem LD, et al. Gasoline burns: the preventable cause of thermal injury. *J Burn Care Rehabil*. 1990;11:446-450.
32. Gough J, Cheng ES, Pegg SP. Ten-year Brisbane experience in petrol burns: a preventable health burden. *Burns*. 2006;32:597-601.
33. Barillo DJ, Stetz CK, Zak AL, et al. Preventable burns associated with the misuse of gasoline. *Burns*. 1998;24:439-443.
34. Brand S, Otte D, Stubig T, et al. Mechanisms of motor vehicle crashes related to burns – an analysis of the German in depth accident study (GIDAS) database. *Burns*. 2013;39:1535-1540.
35. Purdue GF, Hunt JL, Layton TR, et al. Burns in motor vehicle accidents. *J Trauma*. 1985;25:216-219.
36. Barillo DJ, Cioffi WG, McManus WF, et al. Vehicle-related burn injuries. *Proc Assoc Adv Automot Med*. 1993;11:209-218.
37. Shergill G, Scerri GV, Regan PJ, et al. Burn injuries in boating accidents. *Burns*. 1993;19:229-231.
38. Battle CE, Evans V, James K, et al. Epidemiology of burns and scalds in children presenting to the emergency department of a regional burns unit: a 7-year retrospective study. *Burns Trauma*. 2016;4:19.
39. Rimmer RB, Weigand S, Foster KN, et al. Scald burns in young children – a review of Arizona burn center pediatric patients and a proposal for prevention in the Hispanic community. *J Burns Care Res*. 2008;29:595-605.
40. Sanyaolu L, Javed MU, Eales M, et al. A 10-year epidemiological study of pediatric burns at the Welsh Centre for burns and plastic surgery. *Burns*. 2017;43:632-637.
41. Hankins CL, Tang XQ, Phipps A. Hot beverage burns: an eleven-year experience of the Yorkshire Regional Burns Centre. *Burns*. 2006;32:87-91.
42. Hankins CL, Tang XQ, Phipps A. Hot oil burns-a study of predisposing factors, clinical course and prevention strategies. *Burns*. 2006;32:92-96.
43. Klein MB, Gibran NS, Emerson D, et al. Patterns of grease burn injury: development of a classification system. *Burns*. 2005;31:765-767.
44. Wibbenmeyer L, Gittelman MA, Kluesner K, et al. A multicenter study of preventable contact burns from glass fronted fireplaces. *J Burns Care Res*. 2015;36:240-245.
45. Matzavakis I, Frangakis ZE, Charalampopolulou A, et al. Burn injuries related to motorcycle exhaust pipes: a study in Greece. *Burns*. 2005;31:372-374.
46. Clouatre E, Gomez M, Banfield JM, et al. Work-related burn injuries in Ontario, Canada: a follow-up 10-year retrospective study. *Burns*. 2013;39:1091-1095.
47. Kica J, Rosenman KD. Multisource surveillance system for work-related burns. *J Occup Environ Med*. 2012;54:642-647.
48. Hardwicke J, Hunter T, Staruch R, et al. Chemical burns – an historical comparison and review of the literature. *Burns*. 2012;38:383-387.
49. Leeming MN, Ray C, Howland WS. Low-voltage direct current burns. *JAMA*. 1970;214:1681-1684.
50. Pride HB, McKinley DF. Third-degree burns from the use of an external cardiac pacing device. *Crit Care Med*. 1990;18:572-573.
51. Reisin L, Baruchin AM. Iatrogenic defibrillator burns. *Burns*. 1990;16:128.
52. Baker SP, O'Neill B, Ginsberg NJ, et al. Unintentional injury. In: Baker SP, O'Neill B, Ginsberg NJ, eds. *The Injury Fact Book*. 2nd ed. New York: Oxford University Press; 1992:39-64.
53. Vierhapper MF, Lumenta DB, Beck H, et al. Electrical injury: a long-term analysis with review of regional differences. *Ann Plast Surg*. 2011;66:43-46.
54. Arnoldo BD, Purdue GF, Kowalske K, et al. Electrical injuries: a 20-year review. *J Burn Care Rehabil*. 2004;25:479-484.
55. Cancio LC, Jimenez Reyna JF, Barillo DJ, et al. One hundred ninety five cases of high-voltage electric injury. *J Burn Care Rehabil*. 2005;26:331-340.
56. Jensenius JS. A detailed analysis of recent lightning deaths in the United States. 23rd International Lightning Detection Conference, 2014. Available at: www.vaisala.com/Vaisala%20Documens/Scientific%20papers.
57. Roeder WP. Lightning has fallen to third leading source of US storm deaths. National Weather Association annual meeting, 2012. Available at: www.nwas.org/meetings/nwa2012/extendedabstract/NWA2012_P2.29_Roeder.pdf.
58. Cooper MA, Holle RL. Mechanisms of lightning injury should affect lightning safety messages. 3rd International Lightning Meteorology Conference, Orlando, Florida, 2010.

59. Ritenour AE, Morton MJ, McManus JG, et al. Lighting injury: a review. *Burns*. 2008;34:585-594.
60. Lightning-associated injuries and deaths among military personnel–United States, 1998–2001. *MMWR Morb Mortal Wkly Rep*. 2002;51:859-862.
61. Billock RM, Chounthirath T, Smith GA. Pediatric firework-related injuries presenting to United States emergency departments, 1990–2014. *Clin Pediatr (Phila)*. 2017;56(6):535-544.
62. McFarland LV, Harris JR, Kobayashi JM, et al. Risk factors for fireworks-related injury in Washington state. *JAMA*. 1984;251:3251-3254.
63. Berger LR, Kalishman S, Rivara FP. Injuries from fireworks. *Pediatrics*. 1985;75:877-882.
64. Karamanoukian RL, Kilani M, Lozano D, et al. Pediatric burns with snap-cap fireworks. *J Burns Care Res*. 2006;27:218-220.
65. Peck MD. Epidemiology of burns throughout the world. Part II: intentional burns in adults. *Burns*. 2012;38:630-637.
66. Varley J, Pilcher D, Butt W, et al. Self-harm is an independent predictor of mortality in trauma and burns patients admitted to the ICU. *Injury*. 2012;43:1562-1565.
67. Modjarrad K, McGwin G, Cross JM, et al. The descriptive epidemiology of intentional burns in the United States: an analysis of the National Burn Repository. *Burns*. 2007;33:828-832.
68. Sonneborn CK, Vanstraelen TM. A retrospective study of self-inflicted burns. *Gen Hosp Psychiatry*. 1992;14:404-407.
69. Kaufman MS, Graham CC, Lezotte D, et al. Burns as a result of assault: associated risk factors, injury characteristics, and outcomes. *J Burns Care Res*. 2007;28:21-28.
70. Krob MJ, Johnson A, Jordan MH. Burned-and-battered adults. *J Burn Care Rehabil*. 1986;7:529-531.
71. O'Neill JA Jr, Meacham WF, Griffin PP, et al. Patterns of injury in the battered child syndrome. *J Trauma*. 1973;13:332-339.
72. Hodgman EI, Pastorek RA, Saeman MR, et al. *Burns*. 2016;42:1121-1127.
73. Elder abuse: what can be done? Select Committee on Aging, U.S. House of Representatives, Washington DC, Government Printing Office, 1991.
74. Bird PE, Harrington DT, Barillo DJ, et al. Elder abuse: a call to action. *J Burn Care Rehabil*. 1998;19:522-527.
75. Rinder CS. Fire safety in the operating room. *Curr Opin Anesthesiol*. 2008;21:790-795.
76. Mehta SP, Bhananker SM, Posner KL, et al. Operating room fires: a closed claims analysis. *Anesthesiology*. 2013;118:1133-1139.
77. Sadove RC, Furgasen TG. Major thermal burn as a result of intraoperative heating blanket use. *J Burn Care Rehabil*. 1992;13:443-445.
78. Leon-Villapalos J, Kaniorou-Larai M, Dziewulski P. Full thickness abdominal burn following magnetic resonance-guided focused ultrasound therapy. *Burns*. 2005;31:1054-1055.
79. Nicholson B, Dhindsa H. Helicopter transport in regionalized burn care: one program's perspective. *Air Med J*. 2016;35:355-359.
80. Cassidy TJ, Edgar DW, Phillips M, et al. Transfer time to a specialist burn service and influence on burn mortality in Australia and New Zealand: a multicenter hospital based retrospective cohort study. *Burns*. 2015;41:735-741.
81. Renz EM, Cancio LC, Barillo DJ, et al. Long-range transport of war-related casualties. *J Trauma*. 2008;64:S136-S144.
82. Jordan MH, Hollowed KA, Turner DG, et al. The Pentagon attack of September 11, 2001: a burn center's experience. *J Burn Care Rehabil*. 2005;26:109-116.
83. Yurt RW, Bessey PQ, Bauer GJ, et al. A regional burn center's response to a disaster: September 11, 2001 and the days beyond. *J Burn Care Rehabil*. 2005;26:117-124.
84. Yang CC, Shih CL. A coordinated emergency response: colour dust explosion at a 2015 concert in Taiwan. *Am J Public Health*. 2016;106:1582-1585.
85. Kennedy PJ, Haertsch PA, Maitz PK. The Bali Burn Disaster: implications and lessons learned. *J Burn Care Rehabil*. 2005;26:125-131.
86. Harrington DT, Biffl WL, Cioffi WG. The Station Nightclub fire. *J Burn Care Rehabil*. 2005;26:141-143.
87. Cairns BA, Stiffler A, Price F, et al. Managing a combined burn trauma disaster in the post-Nine/Eleven world: lessons learned from the 2003 West Pharmaceutical plant explosion. *J Burn Care Rehabil*. 2005;26:144-150.
88. Petinaux B, Valenta AL, Deatley C, et al. District of Columbia Emergency Healthcare Coalition burn mass casualty plan: development to exercise date. *J Burn Care Rehabil*. 2017;38:e299-e305.
89. Holmes T, ed. *A System of Surgery, Theoretical and Practical*. Vol. I. London: J W Parker & Son; 1860:723.
90. Deleted at revises
91. Berkow SG. Method of estimating extensiveness of lesions (burns and scalds) based on surface area proportions. *Arch Health*. 1924;8:138-148.
92. Bull JP, Squire JR. A study of mortality in a burns unit: standards for the evaluation of alternative methods of treatment. *Ann Surg*. 1949;130:160-173.
93. Bull JP, Fisher AJ. A study of mortality in a burns unit: a revised estimate. *Ann Surg*. 1954;139:269-274.
94. Schwartz MS, Soroff HS, Reiss E, et al An evaluation of the mortality and the relative severity of second and third-degree injuries in burns. Research Report Nr. 12–56. In: *Research reports*. US Army Surgical Research Unit, Fort Sam Houston, TX; 1956.
95. Moreau AR, Westfall PH, Cancio LC, et al. Development and validation of an age-risk score for mortality prediction after thermal injury. *J Trauma*. 2005;58(5):967-972.

4 Prevention of Burn Injuries

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Introduction

Prevention is the cure for the epidemic disease of injury.[1] Burns are one of the most devastating of all injuries and a major global public health issue. Treatment of burn injuries has historically received more focus than burn prevention, but this perspective is starting to shift. Burn centers and other partners in burn prevention efforts face a number of challenges including scarce resources, legislative delays, and the need to develop high-quality research methodology to further define the ideal ways to educate and promote safety. Despite these challenges, the potential impact of burn injury prevention efforts is now being recognized and examined on a larger scale.

Injury Prevention Models

The science of injury prevention emerged in the middle of the 20th century. Injuries became recognized as avoidable events resulting from a combination of adverse environmental conditions, equipment, behavior, and personal risk factors, rather than unpredictable accidents.[2] William Haddon developed a system, known as the Haddon Matrix, to apply the principles of public health to the problem of road traffic safety.[3] Since its introduction, it has been used as a means of developing ideas to prevent injury of all types. The matrix enables analysis of the contributing factors of the injury in relationship to the phases of the injury event. The contributing factors studied are:

a. The host or injured person,
b. The agent or vehicle,
c. The physical environment,
d. The social environment.

The identified phases of an injury event are:

a. Pre-event: preventing the causative agent from reaching the susceptible host.
b. Event: includes transfer of the energy to the victim. Prevention efforts in this phase operate to reduce or completely prevent the injury.
c. Post-event: determines the outcome once the injury has occurred. This includes anything that limits ongoing damage or repairs the damage. This phase determines the ultimate outcome.[4]

The resulting matrix provides a tool to identify strategies and priorities for injury prevention, areas of needed research, and how to best allocate resources (Table 4.1). Haddon further described 10 general strategies for injury prevention and control (Box 4.1). Both of these models can and should be applied to burn prevention because they highlight that society is capable of reducing injury and can do so at more than one stage of an injury event.

Public health is the effort organized by society to protect, promote, and restore the people's health. The public health model of injury prevention and control is divided into:

- surveillance,
- interdisciplinary education and prevention programs,
- environmental modifications,
- regulatory action, and
- support of clinical interventions.[2]

Prevention strategies are commonly described as either passive or active. Passive or environmental intervention is a strategy that provides protection against injury and requires little to no cooperation or action from the individual at risk.[2] Examples of passive burn prevention strategies include building codes requiring smoke alarms, sprinkler installation, and factory-adjusted water heater temperature. Active prevention measures are voluntary, and they emphasize education to encourage people to modify unsafe behavior. Examples are home fire drill plans and wearing goggles and gloves when handling toxic chemicals. Passive prevention is more effective because active prevention can be a very difficult strategy to maintain, especially over a long period of time[5] (Fig. 4.1).

Identified prevention strategies can also be classified as primary, secondary, and tertiary, and these are similar to the Haddon Matrix phases of injury. Primary prevention is preventing the event from ever occurring. Secondary prevention includes reducing the severity of injury via acute care of the injury. Tertiary prevention concentrates on preventing or reducing disability.[6]

Burn Intervention Strategy

Prevention science has turned attention away from individual blame and the attitude that injuries are random "accidents" and toward the view that sociopolitical involvement is necessary.[7] All burn injuries should be viewed as preventable. Prevention programs should target high-risk groups and also be implemented with patience, persistence, and precision.[5] The current approaches to burn prevention will be discussed in the framework of the five E's of Injury Prevention: Epidemiology, Engineering, Enforcement, Education, and Evaluation (Fig. 4.2).[8]

- Epidemiology: identify the demographics and situations involved with burn injuries.
- Engineering: focuses on modification of the physical environment. Examples include fire-resistant

Table 4.1 The Haddon Matrix for Burn Control

Agent or Vector	Host	Environment	Physical	Social
Pre-event	Fire-safe cigarette	Control seizure	Nonslip tub surface	Legislation—factory preset water heater thermostats
Event	Sprinklers, smoke detectors	Flame-retardant cloths	Fire escapes	Fire drill education
Post-event	Water	First aid antibiotics	EMS	Emergency and rehabilitation services

Matrix adapted from Haddon W. Advances in the epidemiology of injuries as a basis for public policy. *Public Health Rep.* 1980;95:411–421.

Box 4.1 General Strategies for Burn Control

Prevent creation of the hazard (stop producing firecrackers)
Reduce amount of hazard (reduce chemical concentration in commercial products)
Prevent release of the hazard (child-resistant butane lighters)
Modify rate or spatial distribution of the hazard (vapor-ignition-resistant water heaters)
Separate release of the hazard in time or space (small spouts for hot water faucet)
Place barrier between the hazard and the host (install fence around electrical transformers, fire screen)
Modify nature of the hazard (use low conductors of heat)
Increase resistance of host to hazard (treat seizure disorder)
Begin to counter damage already done by hazard (first aid, rapid transport, and resuscitation)
Stabilization, repair/rehabilitation of host (provide acute care; burn center and rehabilitation)

From Haddon W. Advances in the epidemiology of injuries as a basis for public policy. Public Health Rep. *1980;95:411–421.*

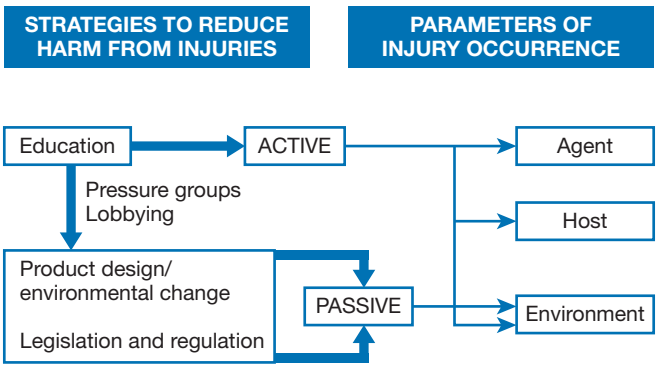

Fig. 4.1 Strategies to reduce harm from injury. (From Atiyeh BS, Costagliola M, Hayek SN. Burn prevention mechanisms and outcomes: pitfalls, failures and successes. *Burns* 2009;35(2):181-193.)

upholstery and bedding, child-resistant multipurpose lighters, and insulated electric wire.
- Enforcement: influences behavior with laws, building codes, and regulations. Examples include requiring fire escapes and sprinklers/smoke alarms in motels, hotels, and homes.
- Education: influences behavior through knowledge and reasoning. Examples include fire safety education programs, public television programs.
- Evaluation: assessment of the impact of a prevention strategy and areas of success or reasons for failure.

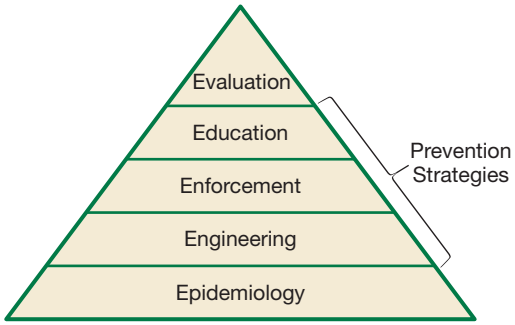

Fig. 4.2 The five 'E's of injury prevention. (From Judkins DG. Fifteen tips for success in injury prevention. *J Trauma Nurs.* 2009;16(4):184–193.)

Epidemiology

Prevention program planning begins with an assessment identifying the scope of the problem, the mechanisms of injury, and the populations at risk. With this information strategic designing and implementation can be directed at reducing the risk of injury or death. Epidemiologic data specific to burn injuries are accessible through multiple sources including the National Burn Repository, state and local health departments, and reports from the National Fire Protection Association (NFPA).[9]

OVERVIEW OF BURN INJURIES IN THE UNITED STATES

In the United States in 2014, the leading causes of injury deaths, in order of magnitude, were motor vehicle collisions, falls, drowning, and fire/burns.[10] This same year, fire departments responded to an estimated 1,298,000 fires, which is an increase of 4.7% from the previous year.[11] The American Burn Association estimates that, in 2016, there were 486,000 burn injuries that received medical treatment and 3275 fatalities due to fire or smoke inhalation. This represents a death due to fire every 2 hours and 41 minutes.[12] Approximately 40,000 people were hospitalized because of a burn injury. More than 60% of the acute hospitalizations for burn injury were admitted to the 128 burn centers in the United States. These centers average more than 200 admissions annually, while the other 4500 U.S. acute care hospitals average less than three burn admissions per year. In addition to the human cost, fires in 2014 in the United States resulted in $11.6 billion in property loss.[11]

COMMON MECHANISMS OF INJURY

The most common mechanisms of burns leading to admission to a burn center in 2015 were fire/flame (43%), scald (34%), contact (9%), electrical (4%), and chemical (3%). The most common places of these injuries were in the home (73%), at work (8%), on the street/highway (5%), and in recreational areas (5%).[12] The most common fire incident that firefighters were called for was outside fires, followed by structure fires and vehicle fires.[12]

House fires are by far the leading cause of fire deaths. In 2014, residential fires represented 83% of fatalities. The leading cause of home fires from 2007 to 2011 was cooking equipment, whereas the largest share of home fire deaths was caused by smoking materials.[13] Heating equipment was the second leading cause of home fires, deaths, and injuries. Sixty-four percent of the people killed and 51% of people injured in home fires were somehow involved in the ignition, such as leaving cooking unattended or a space heater or candle close to something flammable. About one-third (36%) of home fire deaths occurred while the victim was trying to escape and another third (34%) while the victim was sleeping. Only 3% of fire fatalities occurred while the person was engaged in fire control, but 35% of nonfatal injuries were sustained trying to control the fire. Smoke inhalation causes a larger share of deaths and injuries than do burns. From 2007 to 2011, 48% of fire deaths were due to smoke inhalation alone, 24% were due to both burns and smoke inhalation, and 28% were due to burns alone.[13]

HIGH-RISK POPULATIONS

Identifying susceptible population groups and significant risk factors is crucial in planning prevention strategies.[14] Studies conducted in both industrialized and developing nations have found similar risk factors including the extremes of age, low income, lack of education, unemployment, large families, single parents, illiteracy, low maternal education, substandard living conditions, not owning a home, not having a telephone, and overcrowding.[15–17] Prevention should aim at modifying these risk factors and targeting these vulnerable populations.[5,15,16,18,19]

In regards to age as a risk factor, infants and toddlers under the age of 4 years suffer a disproportionally higher number of burns.[18,20–22] The 2015 National Burn Repository Annual Report reveals that the most frequent cause of burn injuries in children under 5 is scalding.[23] In the United States, fires and burns were the third leading cause of unintentional injury death in 2006 for kids 1–9 years of age.[6] The incidence of burns decreases at the age of 4 years and starts to increase again after the age of 15, a phenomenon thought to be due to more exposure to hazards, risk-taking and experimentation, and initiation of employment during adolescence.[24] Children are also at risk for intentional burn injuries, which account for an estimated 10% of all abuse cases.[25] These victims are typically less than 2 years of age, and the most frequent mechanism of nonaccidental burn is a scald from immersion into hot water.

People over the age of 60 also represent a disproportionally higher percentage of hospitalizations due to burns.[26,27] This is attributed to slowed behavioral responses, mental and physical disabilities, isolation, and difficulty in accessing help. From 2007 to 2011, adults older than 65 were more than 2.4 times as likely as the general population to die in fires. For adults over 85, this increased to 3.6 times as likely.[13] A review from a U.S. burn center between 1990 and 1994 found that the most common cause of death for elderly women with burns was from cooking-relating injuries resulting in ignition of clothing.[28]

The risk of home fire death or injury in the United States also varies by race and socioeconomic status. African Americans were approximately twice as likely to be killed or injured in home fires as the overall population. The home fire death rate for African-American children under 15 years was four times higher than the rate for white children of the same age. This disturbing pattern also holds true for older African Americans over the age of 65 who had a home fire death rate three times as high as their white counterparts.[13]

Differences in fire incidence can also be seen regionally in the United States. The Northeast and the Midwest had the highest fire incident rate per thousand people at 4.6 and 4.4, respectively. The Midwest had the highest civilian death rate per million population at 12.5. Smaller communities have more fire incidents and deaths per capital, perhaps due to more limited access to fire departments and burn care centers. Communities of fewer than 2500 people had a fire rate of 10.3 events per thousand population and 19.8 deaths per million population, while communities with 10,000 or more had a rate of about 3 events per thousand population and about 8 deaths per million population.[11]

Continued epidemiological assessment of burn injuries at the national level is critical for purposes such as planning federal legislation efforts, providing statistics for public awareness campaigns, and helping learners understand the scope of the problem when providing burn prevention education. Knowledge of the state of burn injuries nationwide also provides a baseline for epidemiologic assessment at the local level. Burn centers and other safety advocates passionate about burn prevention often start local programs with limited time, staff, and funds. To maximize resources, careful planning begins with first identifying a burn injury, population, and mechanism of injury to be the focus of the local prevention strategy. Local epidemiologic data can be obtained through a burn center's registry program. Some local statistics may also be obtained through the state or city fire marshal's office.

Computerized mapping systems, or geographic information systems (GIS), have emerged over the past two decades as a potentially powerful epidemiological assessment tool for injury prevention. Using GIS, data can be geocoded by location and analyzed for spatial relationships between factors such as socioeconomic status, race, and injury rates.[29] In 2003, Williams et al. identified zip codes in St. Louis that had the highest frequencies of pediatric burn injuries and then used GIS to pinpoint specific block areas that were at the highest risk.[30] More recently, researchers from the University of Louisville School of Nursing and the Department of Geography and Geosciences partnered up to create a fire risk model using GIS. Primary maps of data for seven identified risk factors were combined using an overlaying technique to create a summation map (Fig. 4.3). A fire incidence map was also created (Fig. 4.4). Analysis showed a strong positive correlation between the high-risk

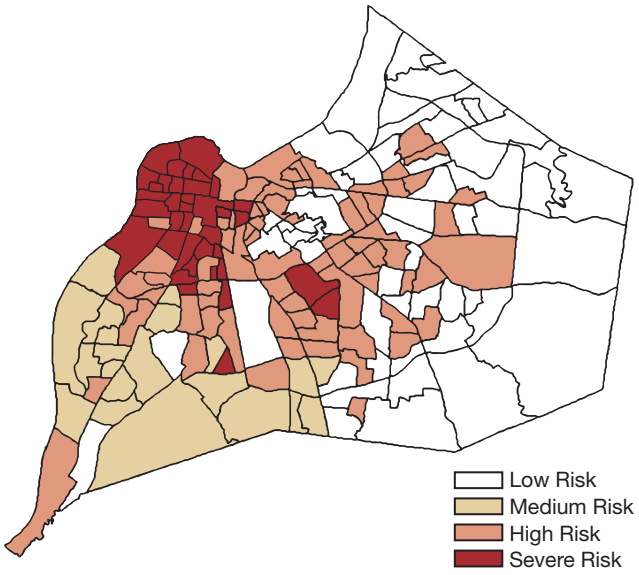

Fig. 4.3 The summed risk scores were separated into risk categories ranging from low to severe risk. The map shows each census tract's risk category based on a color gradient, where darker shading represents higher risk. (From Lehna C, Speller A, Hanchette C, Fahey E, Coty M-B. Development of a fire risk model to identify areas of increased potential for fire occurrences. *J Burn Care Res*. 2016;37(1):12–19.)

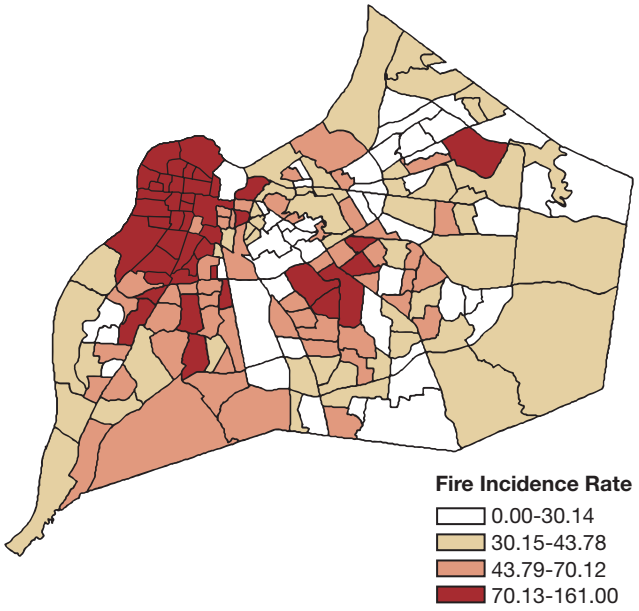

Fig. 4.4 The fire incidence rate for each census tract is shown with darker shading representing higher fire incidence rates. (From Lehna C, Speller A, Hanchette C, Fahey E, Coty M-B. Development of a fire risk model to identify areas of increased potential for fire occurrences. *J Burn Care Res*. 2016;37(1):12–19.)

areas on both the risk factor and fire incidence maps and identified census tracts that were potentially at the highest risk of experiencing fires (Fig. 4.5).[31] Prevention strategies can then be designed to target etiologies and population characteristics or behaviors that are specific to those areas. The use of GIS is an exciting example of how thoughtful epidemiological assessment could lead to the focused use of limited resources with the potential to have the greatest impact.[29]

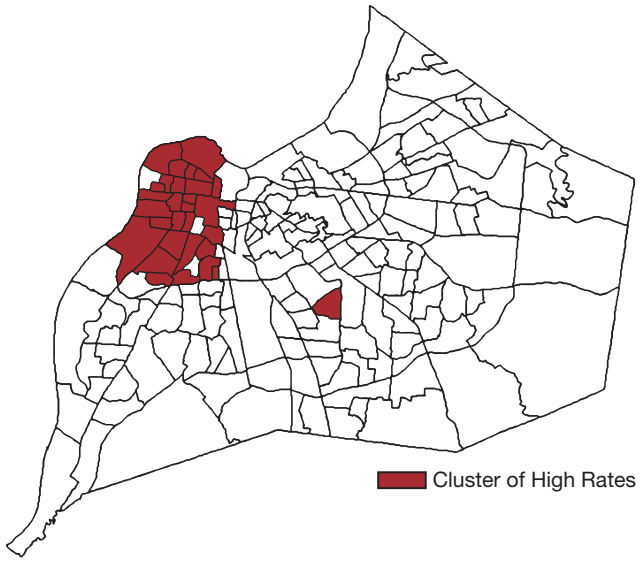

Fig. 4.5 Clusters of significantly high fire incidence rates are shown in shading. (From Lehna C, Speller A, Hanchette C, Fahey E, Coty M-B. Development of a fire risk model to identify areas of increased potential for fire occurrences. *J Burn Care Res*. 2016;37(1):12–19.)

Engineering and Enforcement

In several areas of burn prevention efforts, the manipulation of products or the physical environment (engineering) is closely linked with legislative efforts (enforcement). Engineering and enforcement strategies often require more resources and government involvement, but they are thought to be more effective than passive effort.[5] Smoke alarms, fire sprinklers, fabric flammability standards, fire-safe cigarettes, and water temperature controls are historical examples that may provide insight as the burn community examines where to focus resources in the future.

SMOKE ALARMS

Smoke alarms act as an early warning of fire, alerting residents of the need to exit a house or building. Fatalities from house fires decreased by almost half after the rise in popularity of smoke detectors in the 1980s and 1990s. This decline in home fire deaths is largely attributed to the widespread adoption of smoke alarms, although other notable changes during this time period included child-resistant lighters and flame-resistant upholsteries.[32] It has been reported that 96% to 97% of households now have at least one smoke alarm installed, leaving an estimated 5 million homes still unprotected. Households with no smoke alarms are twice as likely to experience a home fire fatality than are those with a working smoke alarm.[33] Most states have laws requiring smoke alarm installation for specific conditions such as new buildings, tenant buildings, and multiple family dwellings.[32] Some community-based efforts at providing and installing smoke alarms have been successful in reducing the risk of fire-related deaths and injury.

Operation Installation (OI), a Dallas-based community smoke alarm program, is an excellent example of how a partnership between community organizations can reduce risk of harm and death from fires. The program was designed, implemented, and evaluated through a collaboration of the Injury Prevention Center of Greater Dallas, the Dallas Fire Rescue Department, and the Dallas chapter of the American Red Cross. From 2001 to 2011, OI installed lithium-powered smoke alarms in 8134 homes located in high-risk areas. The incidence of house fire-related deaths and injuries in the program houses was then compared to the 24,346 nonprogram houses in the same census tracts, with an average of 5.2 years of follow-up. The adjusted analysis revealed that the incidence of house fire-related deaths and injuries in the OI houses was 68% lower.[34] This risk of fire-related injury or death in the OI houses was shown to begin increasing again at around 5 years after installation.[34] Ten years after installation, OI performed an evaluation on 198 smoke alarms and found that although 108 were still present, only 44 were still functioning. Most of the nonfunctioning smoke alarms had the battery removed or had been disconnected, revealing a potential area for targeted education and an indication that tamperproof smoke alarms could be useful.[35]

FIRE SPRINKLERS

Fire sprinklers are highly effective at reducing property damage and deaths from fires when present and working. From 2007 to 2011, only 10% of structure fires reported that fire sprinklers were present. Although most fire deaths and burn injuries occur in the home, only 6% of the structure fires with sprinklers present were houses. Having fire sprinklers installed in the home was shown to reduce the death rate per fire by 82%.[36] Despite this significant reduction in harm, only California and Maryland have currently passed statewide legislation requiring residential fire sprinklers in all new-construction one- and two-family homes. An example of using economic incentive as a complementary burn and fire prevention strategy is the reduction in home owner's insurance offered to some policy holders who install fire sprinklers in their home. One review concluded that the average discount in the United States for this safety feature is 7%.[37] While laws exist requiring the installation of automatic fire sprinklers in new nonresidential buildings, retrofitting older high-rise buildings is costly and not currently mandatory. In September 2015, the Fire Sprinkler Incentive Act was introduced into Congress. This legislation would strengthen the tax incentives for building owners by allowing 100% expensing of the cost of the automatic fire sprinkler system and a 15-year depreciation recovery.[38]

FABRIC FLAMMABILITY

Inspired by a series of injuries and deaths related to rayon-pile fabrics, the U.S. government formally recognized the risks of flammable clothing with the passage of the Flammability Fabrics Act in 1953.[39] This was the beginning of a passive prevention strategy to prevent burn injuries and deaths from clothing catching on fire. Although flammability standards were developed and standardized, there has been little evolution of these standards over the years. Between 1997 and 2006, there were still an average of 4300 burn injuries annually related to the ignition of clothing, and almost all of the garments involved were within the minimum clothing flammability standards. Despite the expansion of the initial legislation beyond clothing to other textiles (e.g., carpets, mattresses, upholstered furniture, tents, curtains, sleeping bags), it is estimated that 50% of fire deaths in the United States involved the ignition of materials included in the Flammable Fabrics Act.[40] The only notable evolution of these early efforts has occurred with children's sleepwear. In the 1970s, regulations were introduced that required children's clothing from size 0 to 14 be able to self-extinguish. The introduction of flame-resistant sleepwear demonstrated a significant decrease in the incidence of burn injuries and deaths related to children's pajamas in the 1970s and 1980s. It is believed that parents began to substitute other clothing as sleepwear due to limited flame-resistant pajama choices and also a desire for nontreated cotton fabrics. In 1996, restrictions were relaxed to allow exemptions for sleepwear for children 9 months and under and also for any tight-fitting sleepwear of any size. It is thought that tight-fitting clothing decreases the risk of the garment coming into contact with an ignition source and may also slow the burn of the material due to less oxygen between the clothing and the skin.[39] There have been no other major legislative or industry-driven efforts to improve the safety of fabrics offered to consumers, place additional warning labels, or educate the public regarding the flammability of fabrics. This is concerning because the number of clothing-related injuries and deaths has remained steady for decades. With 74% of burn injuries from clothing ignition related to daywear garments, and 75% of deaths in those 65 years and older, there is clear potential for growth in the area of both passive and active prevention strategies in this area.[40] Public understanding of the risks of flammable clothing and knowledge of current regulations is thought to be low.[41]

FIRE-SAFE CIGARETTES

Home fires originating from smoking materials comprise only 5% of all fires reported annually in the United States but are the leading cause of fire fatalities in the home.[42,43] An estimated two-thirds of deaths related to smoking involved the ignition of furniture upholstery or mattresses and bedding.[43] The idea of "fire-safe" or reduced ignition propensity (RIP) cigarettes was first proposed in the 1920s as a way to reduce the number of forest fires and was later recognized as a potential way to reduce the number of burn injuries and deaths related to smoking materials.[44] Design factors such as the circumference of the cigarette, type of paper used, and presence of a filter or accelerant can all influence the rate of burn. Assisted by legislative efforts addressing production and testing in the 1980s and 1990s, it was shown that slow-burning or self-extinguishing cigarettes could be produced without a large economic impact on manufacturers or a change in taste for consumers.[44] After years of failed bills attempting to require tobacco companies to produce safer cigarettes and a decade of stalled efforts to standardize testing for RIP cigarettes, legislation finally began to gain traction in 2003. By 2011, all 50

states had passed laws making RIP cigarettes mandatory (a cigarette must burn out 75% of the time when not in active use). In 2013, the National Fire Protection Agency released a report crediting this legislative effort with an astounding 30% reduction in smoking-material fire deaths from 2003 to 2011.[43] Although the long-term decrease in smoking-related fires seen over the past few decades is likely related to fewer people smoking, the decline in the smoking rate during the 2003 to 2011 time period was only 4%, leading researchers to believe that fire-safe cigarettes can be credited for this decrease in incidence.[43] Although the engineering to produce safer cigarettes was identified years ago, implementation did not happen until legislative enforcement occurred.

WATER TEMPERATURE REGULATIONS

According to the 2015 National Burn Repository Annual Report, 34% of burn admissions reported from 2005 to 2014 were scald injuries.[23] Most scald injuries are related to cooking or hot liquids in the kitchen, mechanisms that are often related to behavior and can be difficult to prevent with engineering or enforcement strategies. Estimates for the amount of burn injuries related to hot water from a tap vary from 12% to 25%.[45] There is an opportunity to prevent scald burns related to tap water with passive engineering and enforcement strategies. An animal study was performed to identify how long exposure to water at different temperatures took to result in a partial-thickness burn. If the temperature of the water was 140°F (60°C), it took only 3 seconds of exposure to result in a burn. When the water was decreased to 120°F (49°C), it took 10 minutes to cause significant thermal injury to the skin.[46] Historical efforts to reduce water temperature in facilities and homes include regulating the temperature setting of hot water heaters and requiring the instillation of antiscald devices at taps.[47] It was demonstrated in Washington state in the 1980s that requiring newly installed home hot water heaters to be set at 120°F significantly lowered the mean household water temperature and reduced the incidence of tap water injuries.[48] Despite evidence that this strategy can be effective, no nationally recognized and enforced standard exists today. Almost all U.S. states have legislation related to water temperature, but many do not regulate water temperature in the home. Types of facilities that are often subject to state regulations commonly include schools, child care facilities, and nursing care facilities. Although some plumbing codes at the city or state levels also address water temperature, these also vary widely in source, regulation, and enforcement.[47]

FIREWORKS REGULATION

Injuries from fireworks are a problem in several countries because they are commonly used during national holidays and traditional festivals.[49] In the United States, the Fourth of July has more fires reported than on any other day of the year.[50] Fireworks often result in hand burns, but flame burns also occur when clothes catch fire. In an attempt to decrease fireworks-related injuries, the United States prohibits the sale of certain types of fireworks including reloadable shells, cherry bombs, M-80 salutes, firecrackers containing more than 2 g of powder, and firework building kits.[45] The impact of legislation suggests a reduction in the number of fireworks-related injuries. In the United Kingdom, the number of firework injuries fell from 707 in 2001 to 494 in 2005, presumably due to the creation of firework legislation during that time.[51] After the repeal of a law banning private consumer fireworks in Minnesota in 2002, there was a 100% increase in the number of annual fireworks-related injuries.[52]

Education

Education is an active prevention process that requires behavior modification from the targeted population. Public education programs aimed at reducing the incidence and severity of burn injuries in the United States can be implemented at the local, state, regional, or national level. At the national level, the American Burn Association (ABA) sponsors Burn Awareness Week annually, a public campaign to promote safe practices and prevent burn injuries. The ABA Burn Prevention Committee also recently partnered with Safe Kids Worldwide, the International Association of Fire Fighters Charitable Foundation Burn Fund, the Federation of Burn Foundations, and the International Association of Fire Chiefs to create the National Scald Prevention Campaign. The website flashsplash.org provides scald prevention resources for burn centers, the public, and the media. Many burn centers used these resources for local prevention activities during Burn Awareness Week 2016.[53] The National Fire Protection Association also sponsors a Fire Prevention Week with a special emphasis on one area of prevention each year. Social media is also a rapidly evolving and widely accessible platform that may present novel ways for burn prevention education. In 2013, there were 21 videos on YouTube with technically accurate information regarding prevention and first aid for pediatric burns.[54] Use of the Internet and social media is a potentially effective and easy to way to disseminate information and raise public awareness regarding burn prevention and treatment, although validation of the material by qualified providers will be a challenge.

Many burn centers are providing general burn prevention education to the community through health fairs, public gatherings, and community classes. Some centers have assessed their community, identified specific educational gaps, and chosen to provide focused education to a target population.

In New York City, researchers noted that burns were the third leading cause of injury-related death among seniors 65 years and older. When surveyed, less than 20% of local seniors had received any fire safety education within the last 5 years. A community-based initiative was designed to reach older adults at recreational centers in this area. After reviewing the common etiologies for this age group, a presentation that focused on fire safety and the prevention of scald burns was designed. Over the course of several months, the presentation was given at 64 senior centers to 2196 older adults. Almost three-quarters of seniors who participated in and evaluated the program reported that they had learned something new about fire and burn safety. Eighty-five percent of respondents also reported a high

likelihood of incorporating the new knowledge into their daily lives.[55]

Firefighters have also recently been the target of an active prevention strategy. Thousands of firefighters suffer smoke inhalation or burn injuries, with an average of 100 fatalities each year.[56] A national program, It Happened in Seconds, was developed by a multidisciplinary team of burn professionals and firefighters to provide better situational awareness, instruction on the appropriate use of personal protective gear, and other strategies for burn prevention while working. The program was first taught to a group of core trainers representing different regions across the United States. As a result, more than 9000 firefighters had been through the course as of 2015. The impact of this program on local and national rates of firefighter burn injuries and death will be monitored.[56]

In another example of targeted education in burn prevention, a burn center identified that Amish children were at particularly high risk for scald burns and injuries related to the ignition of clothing or highly flammable materials. A lack of fire and burn education in Amish schools was also noted. A tool designed to improve burn prevention knowledge in Amish children, a storyboard with magnets, was created in collaboration with an Amish community and pilot tested. A subsequent multicenter pre- and post-testing of 15 Amish schools across eight states demonstrated that the tool was highly successful in increasing burn prevention knowledge in Amish children in grades 1 through 8.[57]

Another education strategy that should not be overlooked is the use of burn center staff to teach burn prevention education not only to patients and their families, but also to the community at large when participating in outreach events or engaging on social media. It is reasonable for burn center staff members to incorporate prevention teaching into their daily practice when caring for patients, although it is possible that many frontline staff have never received formal injury prevention training.[1] A multicenter assessment of the fire safety and burn prevention knowledge of multidisciplinary burn team members was recently performed and analyzed. While many of the respondents reported confidence in their level of prevention knowledge, the average score on the assessment was only 61.5%, indicating the need to provide more accurate information to burn center staff.[1] It is recommended that burn prevention programs should be supported by the burn center team and not solely the responsibility of a designated educator. Hospitals should consider prevention education for burn center staff to prepare them to provide updated information on the major fire safety and burn prevention topics in a variety of situations. The ABA Burn Prevention Committee provides several ways to increase fire safety and burn prevention knowledge, including a newsletter, prevention tip sheets, and other resources on the ABA website, and prevention-focused sessions at the ABA Annual Meeting.[1]

Evaluation

The evaluation of prevention programs is critical in the shift from anecdotal practices to evidence-based strategies. Evaluation should be viewed as a continuous component of any prevention program, rather than a rigid process used only after program implementation. Evaluation of epidemiologic data provides the focus for prevention programs. Once the target etiology and population is identified, potential strategies for reducing the incidence of injury must then be examined. As discussed previously, Haddon's Matrix can be used to organize strategies by injury factors into pre-event, event, and post-event. Each area then becomes a potential target for prevention intervention, and practical strategies to impact each area should be considered. Each strategy can then be assessed for feasibility and sustainability. When designing the program, it is essential to create measurable objectives to be evaluated after implementation.[58] Although historically scientific evaluations of burn prevention efforts were not prevalent in the literature, recent reviews suggest this is beginning to change. Determining if prevention strategies are reducing the incidence of burn injuries can be challenging, especially at the local level. It is important to remember that decreasing incidence is not the only metric available for analysis. Intermediate outcomes, such as an increase in knowledge or a change in behavior, may also be evaluated.[8] While it might take years to analyze the impact of a scald prevention campaign on the incidence of scald injuries in a community, an increase in behaviors known to prevent scald burns, such as using the back burners of the stove and turning the pot handles when cooking with children present, could be more quickly and easily evaluated. An increase in knowledge regarding scald prevention could be evaluated with a pre- and post-test. It should be noted that an increase in burn prevention knowledge has not always correlated with a behavior change or decrease in burn incidence.[5]

Global Burn Prevention

Although the focus of this chapter was primarily the United States, the global incidence of fire and burn injuries in comparison is noteworthy. Worldwide in 2004, it was estimated that approximately 11 million people sought care for burn injury, which exceeds the combined incidence of HIV and tuberculosis. Approximately 90% of burns injuries as well as burn deaths occur in low- to middle-income countries, with the highest prevalence in the Western Pacific, Eastern Mediterranean, and Southeast Asia regions.[18] These impoverished areas often suffer from substandard living conditions, overcrowding, and illiteracy, which have been shown to be risk factors for burns. They also often lack the needed infrastructure to reduce the incidence and minimize the damage of burns. Access to burn care is also often very limited.[15,16,59] It costs about U.S.$1,000 per patient per day to provide adequate burn care in the developed world, which is clearly not possible for most developing nations.[60,61]

The common mechanisms of burns are also often different between the developed and developing worlds. In the developing world, the use of kerosene lamps and stoves is much more common and will likely continue for years to come. There is slow progress in providing electricity to homes in low-income countries, but millions of people still depend on kerosene for heat, light, and cooking.[62] A review of 11,196 burn admissions in New Delhi, India, in 2002

found that more than 80% of burns were due to flames, and 35% of these were attributed to malfunctioning kerosene stoves.[59] A similar study in Sri Lanka found that 41% of accidental burns requiring medical attention were due to flame from a kerosene bottle lamp.[63] Three approaches to prevention of kerosene lamp and stove burns have been discussed and include educational campaigns teaching safe use, use of safer oil, and the provision of an inexpensive and safer lamp to families. A kerosene educational program in low-income South Africa resulted in a significant increase in self-reported knowledge and safety practices, but there are no data showing if this affected kerosene burn injury incidence.[62] The use of safer oil, such as coconut and sesame oil, has not been adopted because these alternatives are too heavy to rise to the top of wicks and do not provide as much heat and light. There is an ongoing program in Sri Lanka to provide safe and inexpensive kerosene lamps to poor families. The lamp was designed by a surgeon in the region in 1992. He designed it to be compact and heavy to avoid tipping over, with two flat sides to prevent rolling if it does tip over. It also has a screw top lid to prevent fuel spillage and much stronger glass. More than 775,000 "safe bottle lamps" were distributed in Sri Lanka as of 2010, and this has been credited in the media with a significant reduction in burn injuries and fires, although no formalized data have been collection.[60]

The proportionally high incidence of burns in the developing world highlights the importance of primary burn prevention efforts in these regions.[64] The World Health Organization has developed a Burn Plan that is organized into seven main components corresponding to the challenges in global burn prevention and care (advocacy, policy, data and measurement, research, prevention, services, capacity building). Accurate data on the incidence and causes of burn injuries are scarce for many developing countries, and incomplete reporting of burn events results in an underestimate of the extent of this public health issue. This understandably makes the development and enactment of effective burn prevention strategies very difficult, but very essential.

Future

The relatively small size of the burn community and the sometimes large geographic distance between neighboring burn centers can make it challenging for burn center staff to share prevention ideas and resources. An emerging theme in injury prevention literature is an emphasis on partnerships within a community. It is acknowledged that fire prevention and burn prevention efforts are often closely linked. Burn centers participating in prevention strategies can partner with local fire departments for joint projects and assist each other with efforts toward a common goal: reducing injuries and deaths from fire and flame. Other potential partners for burn center prevention programs include local and national safety associations and child advocacy organizations. Although difficult to evaluate, it has been noted that characteristics such as inclusivity, enthusiasm, and cultural competence among prevention program leaders can increase the success of the program.[65]

Burn injuries and deaths are a world health problem that represents a major global challenge. Coordination of prevention strategies on both national and international levels is necessary. Passive prevention programs are most effective but can be slow to implement and heavy on resources. Active prevention can be tedious and requires significant organizational support. Both measures should be utilized and are not mutually exclusive. Evaluation of the success of prevention efforts is also of utmost importance, although this can be quite difficult. Despite the many challenges, burns should be viewed as preventable, and efforts to decrease their incidence and severity should be continued at all levels. Prevention is an area of focus where creative and enthusiastic leaders have the opportunity to grow this movement by implementing innovative strategies, designing thoughtful evaluations, and sharing the results to move the science of burn injury prevention forward.

Complete references available online
www.expertconsult.inkling.com

References

1. Klas KS, Smith SJ, Matherly AF, et al. Multicenter assessment of burn team injury prevention knowledge. *J Burn Care Res*. 2015;36(3):434-439.
2. Barss PSG, Barker S. *Injury Prevention: An International Perspective Epidemiology, Surveillance, and Policy*. New York: Oxford University Press; 1998.
3. Haddon W Jr. Advances in the epidemiology of injuries as a basis for public policy. *Public Health Rep*. 1980;95(5):411-421.
4. Haddon W Jr. The changing approach to the epidemiology, prevention, and amelioration of trauma: the transition to approaches etiologically rather than descriptively based. *American Journal of Public Health and the Nations Health*. 1968;58(8):1431-1438.
5. Atiyeh BS, Costagliola M, Hayek SN. Burn prevention mechanisms and outcomes: pitfalls, failures and successes. *Burns*. 2009;35(2):181-1893.
6. Peden MM. *World Report on Child Injury Prevention*. New York: World Health Organization; 2008.
7. McKinlay JB. The promotion of health through planned sociopolitical change: challenges for research and policy. *Soc Sci Med*. 1993;36(2):109-117.
8. Judkins DG. Fifteen tips for success in injury prevention. *J Trauma Nurs*. 2009;16(4):184-193.
9. American Burn Association. Database summary description: possible sources for obtaining burn data; 2015. www.ameriburn.org/Preven/Database%20Summary%20Burn%20Data%20Sources%20Final.pdf.
10. Centers for Disease Control and Prevention (CDC). Ten leading causes of injury deaths by age group highlighting unintentional injury deaths in the U.S.; 2014. www.cdc.gov/injury/wisqars/leadingcauses.html.
11. Haynes H Fire loss in the U.S. during 2014. Quincy, MA: National Fire Protection Association; 2014.
12. American Burn Association. Burn incidence and treatment in the United State: 2016; 2016. www.ameriburn.org/resources_factsheet.php.
13. Ahrens M Characteristics of home fire victims. National Fire Protection Agency; 2014. www.nfpa.org/~/media/Files/Research/NFPA%20reports/Victim%20Patterns/oshomevictims.pdf.
14. Aldemir M, Kara IH, Girgin S, Guloglu C. Factors affecting mortality and epidemiological data in patients hospitalised with burns in Diyarbakir, Turkey. *S Afr J Surg*. 2005;43(4):159-162.
15. Delgado J, Ramirez-Cardich ME, Gilman RH, et al. Risk factors for burns in children: crowding, poverty, and poor maternal education. *Inj Prev*. 2002;8(1):38-41.
16. Edelman LS. Social and economic factors associated with the risk of burn injury. *Burns*. 2007;33(8):958-965.
17. Shai D. Income, housing, and fire injuries: a census tract analysis. *Public Health Rep*. 2006;121(2):149-154.
18. Forjuoh SN. Burns in low- and middle-income countries: a review of available literature on descriptive epidemiology, risk factors, treatment, and prevention. *Burns*. 2006;32(5):529-537.
19. Parbhoo A, Louw QA, Grimmer-Somers K. Burn prevention programs for children in developing countries require urgent attention: a targeted literature review. *Burns*. 2010;36(2):164-175.
20. Rossi LA, Braga EC, Barruffini RC, Carvalho EC. Childhood burn injuries: circumstances of occurrences and their prevention in Ribeirao Preto, Brazil. *Burns*. 1998;24(5):416-419.
21. Zhu ZX, Yang H, Meng FZ. The epidemiology of childhood burns in Jiamusi, China. *Burns*. 1988;14(5):394-396.
22. Learmonth AM. Domestic child burn and scald accidents (analysis of data from 4 Indian burn units). *J Indian Med Assoc*. 1979;73(2):43-47.
23. American Burn Association. 2015 National Burn Repository report of data 2005–2014. Chicago, IL: American Burn Association; 2015.
24. Murray CJ, Lopez AD. Measuring the global burden of disease. *N Engl J Med*. 2013;369(5):448-457.
25. Pressel DM. Evaluation of physical abuse in children. *Am Fam Physician*. 2000;61(10):3057-3064.
26. Edgar DW, Homer L, Phillips M, et al. The influence of advancing age on quality of life and rate of recovery after treatment for burn. *Burns*. 2013;39(6):1067-1072.
27. Mabrouk A, Maher A, Nasser S. An epidemiologic study of elderly burn patients in Ain Shams University Burn Unit, Cairo, Egypt. *Burns*. 2003;29(7):687-690.
28. Ryan CM, Thorpe W, Mullin P, et al. A persistent fire hazard for older adults: cooking-related clothing ignition. *J Am Geriatr Soc*. 1997;45(10):1283-1285.
29. Edelman LS. Using geographic information systems in injury research. *J Nurs Scholarsh*. 2007;39(4):306-311.
30. Williams KG, Schootman M, Quayle KS, Struthers J, Jaffe DM. Geographic variation of pediatric burn injuries in a metropolitan area. *Acad Emerg Med*. 2003;10(7):743-752.
31. Lehna C, Speller A, Hanchette C, Fahey E, Coty M-B. Development of a fire risk model to identify areas of increased potential for fire occurrences. *J Burn Care Res*. 2016;37(1):12-19.
32. Peck MD. Structure fires, smoke production, and smoke alarms. *J Burn Care Res*. 2011;32(5):511-518.
33. Ahrens M Smoke alarms in U.S. home fires. Quincy, MA: National Fire Protection Association; 2015.
34. Istre GR, McCoy MA, Moore BJ, et al. Preventing deaths and injuries from house fires: an outcome evaluation of a community-based smoke alarm installation programme. *Inj Prev*. 2014;20(2):97-102.
35. McCoy MA, Roper C, Campa E, et al. How long do smoke alarms function? A cross-sectional follow-up survey of a smoke alarm installation programme. *Inj Prev*. 2014;20(2):103-107.
36. Hall JR Jr. U.S. experience with sprinklers. Quincy, MA: National Fire Protection Association; 2013.
37. FPR Foundation FPR. Home fire sprinkler cost assessment. National Fire Protection Agency; 2008.
38. National Fire Safety Association. Senate: fire sprinkler incentive act is filed in 114th congress. www.nfsa.org/?page=Legislation.
39. Cusick JM, Grant EJ, Kucan JO. Children's sleepwear: relaxation of the Consumer Product Safety Commission's Flammability Standards. *J Burn Care Res*. 1997;18(5):469-476.
40. Hoebel JF, Damant GH, Spivak SM, Berlin GN. Clothing-related burn casualties: an overlooked problem? *Fire Technol*. 2009;46(3):629-649.
41. Frattaroli S, Spivak SM, Pollack KM, et al. Clothing flammability and burn injuries: public opinion concerning an overlooked, preventable public health problem. *J Burn Care Res*. 2016;37(3):e196-204.
42. Ahrens M *Home* Structure fires. Quincy, MA: National Fire Protection Association; 2013.
43. Hall JR Jr. The smoking-material fire problem. National Fire Protection Association; 2013.
44. Barillo DJ, Brigham PA, Kayden DA, Heck RT, McManus AT. The fire-safe cigarette: a burn prevention tool. *J Burn Care Res*. 2000;21(2):164-170.
45. Liao CC, Rossignol AM. Landmarks in burn prevention. *Burns*. 2000;26(5):422-434.
46. Moritz AR, Henriques FC. Studies of thermal injury: II. The relative importance of time and surface temperature in the causation of cutaneous burns. *Am J Pathol*. 1947;23(5):695-720.
47. Peck M, Chang Brewer A, Pressman M, Blank E. Mickalide A. Hot tap water legislation in the United States. *J Burn Care Res*. 2010;31(6):918-925.
48. Erdmann TC, Feldman KW, Rivara FP, Heimbach DM, Wall HA. Tap water burn prevention: the effect of legislation. *Pediatrics*. 1991;88(3):572-577.
49. Al-Qattan MM, Al-Zahrani K. A review of burns related to traditions, social habits, religious activities, festivals and traditional medical practices. *Burns*. 2009;35(4):476-481.
50. Injuries associated with homemade fireworks: selected states, 1993–2004. *MMWR Morb Mortal Wkly Rep*. 2004;53(25):562-563.
51. Edwin AF, Cubison TC, Pape SA. The impact of recent legislation on paediatric fireworks injuries in the Newcastle upon Tyne region. *Burns*. 2008;34(7):953-964.
52. Roesler JS, Day H. Sparklers, smoke bombs, and snakes, oh my! Effect of legislation on fireworks-related injuries in Minnesota, 1999–2005. *Minn Med*. 2007;90(7):46-47.
53. Campaign NSP. It can happen in a flash with a splash. International Association of Fire Fighters; 2015. http://flashsplash.org/about-us/.
54. Oomman A, Sarwar U, Javed M, Hemington-Gorse S. YouTube as a potential online source of information in the prevention and management of paediatric burn injuries. *Burns*. 2013;39(8):1652.
55. Leahy NE, Sessler KA, Baggott K, et al. Engaging older adults in burn prevention education: results of a community-based urban initiative. *J Burn Care Res*. 2012;33(3):e142-e147.
56. Kahn SA, Held JM, Hollowed KA, Woods J, Holmes JHI. "It Happened in Seconds" firefighter burn prevention program: evaluation of a "train the trainer" course. *J Burn Care Res*. 2016;37(1):e33-e36.

57. Rieman MT, Kagan RJ. Multicenter testing of a burn prevention teaching tool for Amish children. *J Burn Care Res*. 2013;34(1):58-64.
58. World Health Organization. *Burn Prevention: Success Stories and Lessons Learned*. Geneva, Switzerland: World Health Organization; 2011.
59. Ahuja RB, Bhattacharya S. Burns in the developing world and burn disasters. *Br Med J*. 2004;329(7463):447-449.
60. Lau YS. An insight into burns in a developing country: a Sri Lankan experience. *Public Health*. 2006;120(10):958-965.
61. Hsiao M, Tsai B, Uk P, et al. "What do kids know": a survey of 420 Grade 5 students in Cambodia on their knowledge of burn prevention and first-aid treatment. *Burns*. 2007;33(3):347-351.
62. Schwebel DC, Swart D, Simpson J, Hobe P, Hui SK. An intervention to reduce kerosene-related burns and poisonings in low-income South African communities. *Health Psychol*. 2009;28(4):493-500.
63. Laloe V. Epidemiology and mortality of burns in a general hospital of Eastern Sri Lanka. *Burns*. 2002;28(8):778-781.
64. McLoughlin E. A simple guide to burn prevention. International Society for Burn Injuries in collaboration with the World Health Organization. *Burns*. 1995;21(3):226-229.
65. Mallonee S, Fowler C, Istre GR. Bridging the gap between research and practice: a continuing challenge. *Inj Prev*. 2006;12(6):357-359.

5 Burn Management in Disasters and Humanitarian Crises

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Introduction

Mass casualty events and disasters are marked by a period of mismatch (disproportion) between supply and demand. Rescue organizations must work to reduce the duration of this period of mismatch. During the acute phase, actions follow the principles of *disaster medicine*: The goal is to save as many lives as possible even if it means postponing care for an individual patient. After the mismatch between supply and demand has been addressed, the principles of *individual medicine* can be restored. One goal in mass casualty care is to minimize the period of time it takes to restore care to the individual medicine paradigm. This period's length depends on such structural aspects as the existence and validity of a disaster plan, a regard for disaster capacity in health planning, and the educational level of medical services. These facts are often neglected in disaster planning, from the political aspect of planning and from the practical aspect of disaster capacity.

Ideally, treatment should be based on the state of the art in medical science. During a disaster, treatment with the "best available means" may weaken the quality of care for individuals. Therefore, in mass casualties and disasters, the infrastructure of a country or region may be unable to cope with a higher number of victims of special trauma types while maintaining the state of the art. When it is predictable that the state of the art cannot be maintained in a jurisdiction because of dwindling resources, help from other jurisdictions must be planned and coordinated—the time for international cooperation has come! Such instances include mass casualties with burn injuries. Resources available for specialized treatment are limited, but the demands of state-of-the-art treatment are high, meaning that even a small number of victims from one accident can push an area's or country's burn treatment system to its limits.

The purpose of this chapter is to introduce concepts of disaster medicine as applied to burn patients. A glossary of disaster medicine terms is provided. Examples of major burn disasters and the lessons learned are described. Phases in the typical response to a disaster are summarized. Special aspects of emergency care during a disaster are discussed. The role of communication in disaster response is detailed. The strategic approach to matching burn resources and patients is considered. Finally, the special case of humanitarian crisis response is discussed. Every disaster we have studied is somewhat different. There is, however, a common theme running through all of them: Prior planning and realistic training are essential to success.

Definitions

A shared language is critical for the process of planning for and responding to a disaster. The following provides a basic vocabulary for burn mass casualty and disaster response.

Mass casualty event: an emergency in which there is a greater number of victims than can be accommodated by the rescue forces and their supplies.[1] Infrastructure in the affected area is intact. With force mobilization, the crisis can be mastered. The period of mismatch between supply and demand is short. The goal is to reestablish treatment according to principles of individual medicine as quickly as possible and without transferring the supply–demand mismatch from the scene to hospitals. The challenge to save as many lives as possible, even disregarding the medical needs of an individual, stands in contrast to the paradigms of individual medicine in which any individual life claims the maximum medical effort. The procedure for this challenge is selection of patients—triage, based on urgency of medical procedures, chance of success, and distribution among the available qualified treatment centers (see later discussion).

Disaster: an event in which infrastructure is at least partly destroyed or degraded and that cannot be handled by regional rescue means alone. The first goal is to reestablish the minimal level of infrastructure required to provide basic medical care. (This is different from mass burns treatment in a resource-poor country, where infrastructure never existed.) One way to treat burns successfully in a disaster is to bring infrastructure, staff, and materials to the area to treat burns. Another is to move victims to a place with existing infrastructure. The maximum treatment possible locally is determined by the degree of infrastructure and resources in, or brought to, the disaster area.

Although mass casualty events remain in the purview of local rescue organizations, disasters are for regional or national authorities. This means different ways of handling the situation and different funding resources.

Mass burn casualty disaster: defined by the American Burn Association (ABA) as "any catastrophic event in

which the number of burn victims exceeds the capacity of the local burn center to provide optimal burn care."[2] Capacity includes the availability of burn beds, burn surgeons, burn nurses, other support staff, operating rooms, equipment, supplies, and related resources. This definition is inapplicable where, as in Germany, a central burn-bed bureau always organizes the distribution of burn victims; the definition supposes a very different degree of preparedness in these countries.

Triage: the process of sorting individual patients into categories according to priority of treatment. An example of triage categories is delayed, immediate, minimal, and expectant (DIME). Several factors influence triage decisions; these include available resources, number of patients, the severity of injury of each patient, and the timeframe during which the injuries must be addressed. Triage is not a one-time event, but it should be repeated throughout the mass casualty event (see later).

Basic capacity: the normal number of patients who can be treated, based on the availability of burn beds, burn surgeons, burn nurses, other support staff, operating rooms, equipment, supplies, and related resources

Capacity utilization: the degree of utilization of burn beds in a center over a certain time. This should be expressed as use of intensive-care burn beds and other beds. The average value over a year gives an overview of a burn center's disaster capacity.

Actual capacity: the number of burn patients that a center can admit on an actual day. It varies daily, can depend on the season, and is likely to fluctuate with seasonal or accidental presence or absence of severe patients.

Surge capacity: the increased capacity available in mass casualties and disasters. In burns, it is defined by the ABA as the capacity to handle, in a disaster, 50% more than the normal maximum number of burn patients.[3] Surge capacity must be developed and maintained, requiring action by health systems. Surge capacity must include continued medical care for all other patients. Elective medical and surgical care can be postponed temporarily to maintain surge capacity. When capacity is breached, patients must be transferred safely to other treatment facilities.

Sustained capacity: the maximum capacity that a burn center can sustain over a longer time without lowering treatment quality.

Burn capacity of a health system: the total capacity of burns that can be treated in a national health system. This capacity should be known; it should take into account the various requirements of burn treatment, such as the number of victims needing intensive care. The average capacity utilization over the year is part of resource planning for a health system.

Time to establish surge capacity: how much time a burn center needs to rise to maximum surge capacity. A good parameter is the number of complete burn teams available at various hours. This number is highly important in a hospital's organization of care.

National Disaster Medical System (NDMS): manages a country's national medical system in disasters. In the United States, the NDMS is a function of the Federal Emergency Management Agency (FEMA) under the Department of Homeland Security. It acts as a partner of the U.S. Department of Health and Human Services (HHS), the Department of Defense (DoD), and the Department of Veterans Affairs (VA).[3] Other countries' structures are comparable. The U.S. NDMS has three functions: (1) medical response at the disaster site, (2) transport of patients to unaffected areas, and (3) definitive medical care in unaffected areas.

Burn specialty team (BST) or burn assessment team (BAT): a special form of disaster medical team that provides expertise in burns. In the United States, a BST consists of 15 burn-experienced medical and nonmedical staff. These teams do not exist in many countries. Such teams can be formed only when burn experts are numerous enough and not already engaged in other aspects of disaster response.

Technical relief: the general "civil defense" functions required to support disaster response. In Germany, these functions are provided by the Bundesanstalt Technisches Hilfswerk and include lighting, debris removal, search and rescue, flood mitigation, electricity, water supply, sewage disposal, catering, command center support, communications, logistics, equipment repair, and transportation of supplies. In the United States, these functions are provided by FEMA or by equivalent agencies at the state and local levels.

The Historical Record

Even with the best preparation, a disaster remains a disaster for a certain period; the goal is to minimize that period. Although retrospectively correcting problems is impossible, lessons learned from the past should be applied to the future. Recurring themes that appear in the following case studies include the following:

- Communication problems
- Need to send major burn patients to burn centers
- Need for central incident command post
- Movement of patients to hospitals by private vehicles
- Importance of control of traffic leaving the disaster area
- Lack of coordination of patient evacuation from the scene
- Value of retriage out of the disaster area to other burn centers
- Infection control problems; multidrug-resistant organisms
- Lack of experience in burns by nonburn providers
- Need for psychological support of providers
- Value of international teamwork

TERRORIST ATTACKS

New York City—September 11, 2001

In New York, two hijacked airliners were flown directly into the Twin Towers of the World Trade Center. Although many were injured or killed, few survivors had severe burns.[4] The victims were sent mainly to two burn centers, although more centers were easily reachable.[5] Nineteen were seen at New York Presbyterian Hospital; there, the victims' average

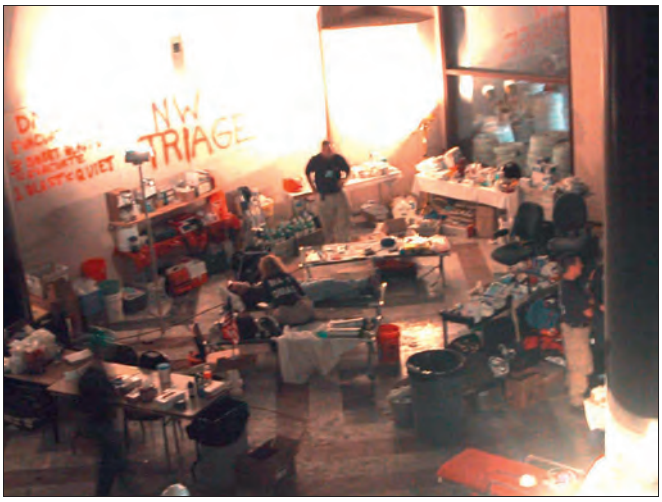

Fig. 5.1 New York, New York, 2001. Triage station set up by Burn Specialty Team 1 from Boston, Massachusetts. (Courtesy of Robert L. Sheridan, MD. Reprinted with permission from Sheridan R, Barillo D, Herndon D, et al. Burn specialty teams. *J Burn Care Rehabil* 2005;26:170-173.)

age was 44 years, and the burn size averaged 52.7%.[6] In total, 39 burns were reported by nine hospitals; 27 patients were admitted. Although enough burn beds within 1 hour's transport were available, only 26% of burned patients were triaged first to burn centers. Two thirds of burn injuries were ultimately treated in a burn center. The usual portion of burn victims triaged to burn centers in New York City in a year is 75.2%.[6] BST-1 from Boston, Massachusetts, responded to this event within hours (Fig. 5.1).

Kuta, Bali, Indonesia—October 12, 2002

A suicide bomber detonated a backpack bomb in a nightclub. People fled to the outside, where a car bomb exploded. There were 202 deaths and an additional 209 injured. The Australian Defence Force (ADF) initiated Operation Bali Assist, the largest Australian aeromedical evacuation since the Vietnam War.[7] An aeromedical staging facility (ASF) was prepared in a Bali airport hangar, whence 5 C-130 planes flew 61 Australian patients to Royal Darwin Hospital (RDH). Of the 61 patients, 28 had major injuries (Injury Severity Score >16). At RDH, 55 escharotomies were performed, along with 43 other surgical procedures. Three patients had been intubated in Bali; 12 more were intubated at RDH. Within 36 hours after first admission to RDH and 62 hours after the bombing, 48 patients were evacuated to burn centers. There were no "walking wounded." BATs were used for initial care at RDH.[8]

Eleven patients were transferred to Concord Repatriation General Hospital.[5] Burn injuries ranged from 15% to 85% total body surface area (TBSA), mostly full-thickness burns. All patients showed injuries from both the first and second blasts. There were complications from infections with *Acinetobacter baumannii* and *Pseudomonas aeruginosa* and from fragment injuries. Many ophthalmic injuries occurred, some being detected only later.

Royal Darwin Hospital received its first information about the incident from a patient who had been treated in Bali and then fled to Australia. The hospital learned nothing of the number of patients or the severity of injuries before the first wave of patients arrived.[9] Palmer et al[9] describe a need for improvement mainly in military–civilian communication. Communication in the hospital also was problematic: Mobile phones had no reception, there was no time to read electronic texts, and land lines were not mobile. ADF provided satellite phones to the medical staff for communication between the hospital in Bali and ADF.

Madrid, Spain—March 11, 2004

Bomb attacks on four commuter trains killed 191 and injured 2051 of 6000 persons present. Thirteen bomb bags each contained 10 kg of dynamite plus fragments. Three bombs failed to explode. Of the 191 dead, 175 died instantly, and 16 died later. It was not known that unexploded bombs remained on the trains while ambulance staff worked. Ambulance staff worked without coordination and were oblivious to overall medical priorities. Patients with only minor injuries were transported. Ambulances ran out of all medical supplies. No joint field medical command post was set up.

Patients were taken to 15 hospitals in Madrid and two field hospitals, ranging from 5 to 312 patients each.[10] Communication problems in hospitals[11] and among organizations arose. Only 33% of patients were transported in ambulances under medical control; 67% found their way to hospitals without triage and medical or organizational control. Most went to the nearest hospital, which received patients with both serious and minor injuries.[12] Of 312 patients taken to Gregorio Marañón University General Hospital, 45 had burns. The most common injuries were tympanic perforation (in 41%), chest injury (40%), fragment injury (36%), extremity fracture (18%), eye injury (16%), head injury (12%), abdominal injury (5%), and amputation (5%).

London, England—July 7, 2005

Four bombs in the transit system killed 56 (53 at the scene) and wounded 775.[13] Train bombs exploded in three locations; the fourth bomb exploded on a double-decker bus. The number of explosion sites was initially unclear because passengers left the subway at various exits. Triage was performed; 55 patients were classified as severely wounded (P1 and P2). Communication was difficult: All but one mobile-telephone network failed; radio communication between the scenes and ambulance control was very difficult. The fire brigade established an inner cordon and ascertained that there were no signs of chemical substances threatening the rescuers, but the presence or absence of more bombs was not confirmed before rescue work began. Patients mainly in triage groups 1 and 2 were transported to six university hospitals after minimal triage and treatment.[14]

INDOOR FIRES

Gothenburg, Sweden—October 30, 1998

Fire in an overcrowded discothèque during a Halloween party killed 61 teenagers at the scene; 2 died later; 235 were wounded (Fig. 5.2). Initial information was poor, resulting in incorrect alerts. There was no triage officer at the scene. Hospital disaster plans in some cases were unknown or not implemented. Preexisting disaster plans had the same

Fig. 5.2 Pope Air Force Base, North Carolina, 1994. Airport fire trucks extinguish a burning aircraft at the scene of the crash. Rescue efforts were aided by combat medics who were preparing to participate in parachute operations. (Reprinted with permission from the *Fayetteville Observer Times*.)

personnel simultaneously performing conflicting roles. Within 2 hours, 150 patients were admitted to four Swedish hospitals. Thirty-one patients presented with significant burn injuries; 11 patients were transferred secondarily to other burn centers in and outside Sweden.[15]

Despite the initial chaos at the scene, there were timely escharotomies and triage in the hospitals before transfer to burn centers. Inhalation injuries were diagnosed in 158; 54 of them were treated simply with suction and expectorants. In 51 of 61 deaths, carbon monoxide (CO) was the cause. Eleven patients were transferred secondarily to burn centers in four other cities, one in Norway.[16] All 11 had second- or third-degree burns of more than 20% of the TBSA.

Volendam, the Netherlands—January 1, 2001

A fire at a New Year's Eve party killed 8 and injured 203 of 350 present.[17] An early error in directing emergency traffic caused transportation chaos. Emergency-services tents were insufficiently staffed, and tent placement was problematic. In all, 241 patients went to hospitals: 110 by ambulance, 18 by bus, and 113 by self-referral to the nearest hospital.[18] Of 182 admitted, 112 went to intensive care units (ICUs). Nineteen hospitals provided initial care. The closest hospital, receiving 73 patients, was overwhelmed.

After primary treatment in the hospitals, burn specialists did tertiary triage, distributing patients to hospitals and burn centers in and outside the Netherlands. Burn center criteria were adapted on the basis of both burn extent and inhalation injury: The indications for burn center treatment were greater than 30% TBSA burn with inhalation injury.

Warwick, Rhode Island—February 20, 2003

Fire at The Station, a nightclub, killed 100 and injured 215 of 439 present. The building totally collapsed within 30 minutes. Rhode Island Hospital (RIH) first became aware of this incident from breaking news on television;[19] shortly after, RIH got official notification that 200–300 burn victims were expected. A triage site was established. Sixteen area hospitals evaluated 215 patients. Patients admitted to RIH numbered 47. TBSA averaged 18.8%. There were 33 burns of less than 20% TBSA, 12 with TBSA of 21–40%, and 2 of greater than 40% TBSA. Of 32 patients presenting with inhalation injuries, 28 required intubation; 12 needed escharotomies; and in just 6 weeks, 184 bronchoscopies were necessary.[20] Retrospective analysis called for improvement in communication with the disaster scene and in specific instructions for patient transport.[20]

Buenos Aires, Argentina—December 30, 2004

Fire at the overcrowded República Cromañón nightclub killed 194 and injured 714 of 3000 present.[21] CO and hydrogen cyanide poisoning were the main causes of death. At the scene, 46 ambulances and 8 fire crews sent the victims to the 8 closest hospitals, which were overwhelmed by critically ill patients within 2 hours. In Buenos Aires city, 38 hospitals were engaged and another 5 elsewhere in Buenos Aires province.

Ramos et al describes the experience of Argerich Hospital,[21] to which 74 patients were taken. All had inhalation injuries. There were no severe burn injuries. Eighteen patients (24%) were pronounced dead on arrival. Twenty-five showed respiratory insufficiency and reduced level of consciousness and were intubated. Initially, 22 patients were sent to the ICU; the 14 sent to the operating room for mechanical ventilation were transferred to other hospitals in Buenos Aires Province within 48 hours.

Kiss Nightclub Fire, Santa Maria, Rio Grande do Sul, Brazil—January 27, 2013

In this fire, 242 people were killed, and more than 630 others were wounded because of the use of fireworks. Firefighters had to create a hole in the outer wall to help people to escape. From the estimated 1200–1300 people present in the disco, 169 were hospitalized because of inhalation injuries and burns.[22] The extent of the disaster was not communicated to the response workers. Triage was hindered by crowded bystanders and victims. The military police had to hinder relatives from entering the disaster site that was filled with smoke and toxic gases. Many of them were in critical conditions, emergency departments (EDs) of 5 hospitals, and ICUs of 6 hospitals, and all of the emergency units were crowded. Fifty-four patients had to be transported by helicopters and ground transport to hospitals in Porto Alegre and Caxias do Sul and Cachoera do Sul and Canoas. Transport was supervised and coordinated by a Brazilian Air Force officer and the Brazilian government corporation responsible for operating the main commercial airports. The main issues were with command and control at the incident scene and the absence of a disaster plan.[23]

Colectiv Nightclub Fire, Bucharest, Romania—October 30, 2015[24]

Fire in the nightclub caused by fireworks during a show killed 26 on the spot, 38 died in hospitals, and 184 were injured. About 200–400 people present in the club were engulfed in a stampede when they realized there was fire. The fire started at 22:30, first and emergency call was sent over 112. The first ambulances arrived 12 minutes later. A field hospital was set up. Resuscitation of the unconscious

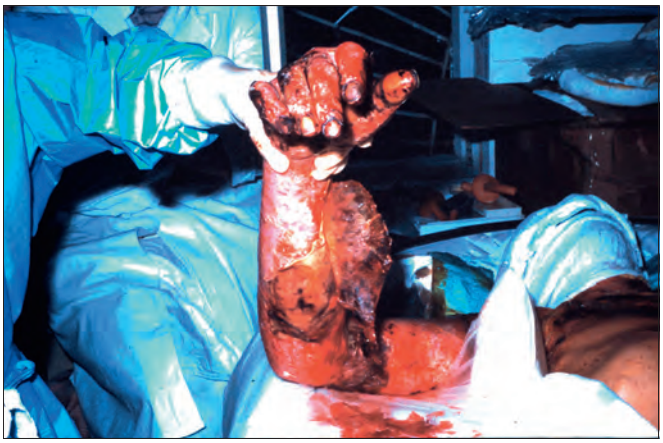

Fig. 5.3 Ufa, Russia, 1989. Invasive Gram-negative burn wound infection may be particularly common after a disaster. (Photo courtesy of U.S. Army.)

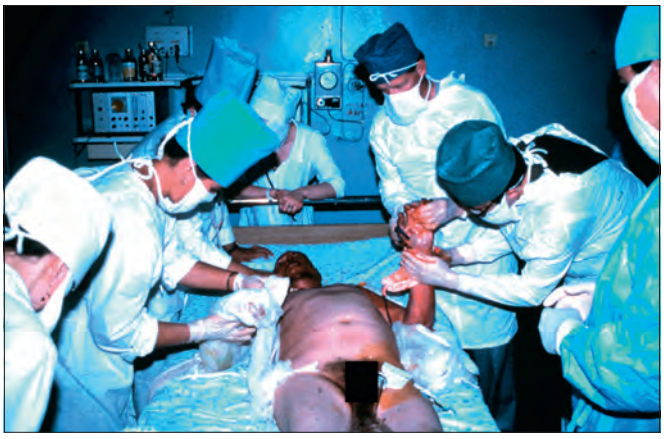

Fig. 5.4 Ufa, Russia, 1989: U.S. and Russian teams perform burn wound care. (Photo courtesy of U.S. Army.)

was tried; the effect was not described.[19] At 23:30, the police isolated a perimeter of several streets around the night club. Seventy-five special vehicles of the Inspectorate for Emergency Situations and 57 SMURD trucks and ambulances were in place. A total of 500 emergency service personal were mobilized. Victims accessed hospitals driven by bystanders, taxis, and ambulances. Twelve hospitals received between 57 and 15 victims each, and some had to be redistributed to other hospitals because of overburdening. Ventilation devices had to be moved from other hospitals to the places they were needed. After 1 week, victims were distributed to burn centers in Israel, The Netherlands, Belgium, Austria, the United Kingdom, Norway, Germany, and France. Patients died during or immediately after the transport because of the severity of their injuries.[24] In Bucharest, enzymatic debridement was used to reduce the logistic challenge. There were problems in identifying 29 of 146 hospitalized victims because of the severity of their burns. On March 14, 2016, the last victim treated in a Romanian hospital died.

TRANSPORTATION CRASHES

Alcanar, Spain—July 11, 1978

A tanker truck carrying liquefied flammable gas exploded beside the Los Alfaques campground, killing 102 at the scene and injuring 288; eventually, the dead totaled 215 (Fig. 5.3).[25,26] The burning tanker divided the scene into two parts. The 58 patients transported north to Barcelona received adequate care before transfer. The 82 patients taken south to Valencia received minimal treatment before and during transport. Both Valencia and Barcelona had state-of-the-art burn centers. There was no significant difference in age or the extent and depth of burns between these two groups. After the first 4 days, Barcelona's survival rate was 93%, and Valencia's was 45%. Ultimately, the mortality rate did not differ.

Lyce Diyarbakir, Turkey—July 21, 2014[27]

A driver of a liquid petroleum gas tanker lost control over the vehicle and caused an over roll followed by a boiling liquid expanding vapor explosion after 15 minutes. Sixty-nine patients were admitted mainly to Dicle University Faculty of Medicine and Diyarbakir Training and Research Hospital, including 62 male and 7 female patients. The average TBSA was 51 ± 32%, including 4 patients with minor burns (<2%), 9 with moderate burns (2–10%), and 56 with severe burns (>10%). In 75%, fasciotomies had to be performed. Twenty-seven (48%) required endotracheal intubation, and 13 (23%) needed tracheostomy. A total of 76% of the patients with severe burns had to be transferred to a burn ICU. Forty-seven (68%) of the patients were distributed to 14 different locations. The overall mortality rate was 49%. The length of hospital stay was 19.4 ± 19.8 days for the survivors and 6.4 ± 4.2 days for those who died.

Ramstein, West Germany—August 28, 1988

Aircraft collisions and crashes during an air show killed 70 and injured more than 1000 of 300,000 present (Fig. 5.4). Three pilots and 67 spectators died; 346 others had serious injuries. Cooperation was hindered by medical systems that were not adapted to each other. On day 1, 12 hospitals were treating the injured; on day 2, 28; and on day 3, 74.[28]

Outpatients numbered 213; 146 were admitted as inpatients; 84 others were transferred to ICUs. There were 112 with mechanical injuries only; 263 had isolated burn injuries; 68 had both mechanical and thermal injuries.[28] Patients with burns of less than 20% TBSA numbered 209 (79.5% of 263). Patients with TBSA of 20–49% numbered 37; 3 of them died. Six of 9 patients with TBSA of 50–70% died. Another 8 patients, with TBSA greater than 70%, died. Of the 68 patients with combined injuries, 55 had TBSA less than 20%. Three of the 9 with TBSA of 20–40% died. No patient with combined injuries and TBSA burns greater than 40% survived.

The burn center at Ludwigshafen received 28 victims. The existing emergency plan was activated; overstaffing occurred on the first day. Initial care in the burn unit was provided in the normal way, not according to emergency plans. Experienced burn teams evaluated the patients. The disaster plan worked, but incomplete initial documentation greatly increased the next days' workload. During

treatment, there were no problems with the expanded nursing staff. Qualified medics who worked double shifts for weeks were exhausted. Heavy use of burn beds caused cross-infection problems. The senior surgeon on duty on day 1 concluded that patients should have been transferred to other burn units, where free beds were available.[28]

Kerosene caused difficulties in respiration and in function of patients' kidneys, livers, and central nervous systems. Evaluating cyclic carbohydrates in the blood soon after the incident may be important for prognosis.[29]

Pope Air Force Base, North Carolina—March 23, 1994

Two planes collided in the air, attempting to land on the same runway. The C-130E was able to land; the F-16D, whose crew ejected, slid into a parked, fully fueled C-141 cargo plane with a crew aboard (see Fig. 5.2). Five hundred paratroopers, waiting 50–70 feet from the plane, were sprayed with a fireball of burning aviation fuel, with flying debris, and with the F-16's 20-mm ammunition, which began cooking off from the heat.[30] Fifteen to 30 minutes after the incident, casualties arrived at Womack Army Medical Center (WAMC), a 155-bed hospital 5 minutes away. Fifty-one patients were treated and released; of 55 admitted, 25 went to ICUs. Six patients needing urgent surgery were sent to nearby hospitals. Seven patients were sent to the closest civilian burn center, Jaycee Burn Center at the University of North Carolina at Chapel Hill.[31]

One U.S. Army Burn Flight Team arrived 4 hours after the accident and another after 9 hours. Escharotomies were reevaluated; some had to be repeated. Resuscitation was guided by urine output, but fluid amounts initially were not documented. Use of the Parkland formula (4 mL/kg/TBSA), rather than the modified Brooke formula (2 mL/kg/TBSA), along with untrained personnel's overestimation of TBSA, contributed to overresuscitation. Forty-one patients were transferred to the U.S. Army Institute of Surgical Research (USAISR) Burn Center for treatment, of whom 13 required mechanical ventilation. Patients assessed as having nonsurvivable injuries stayed at WAMC.

Points from Mozingo et al's[31] review include the following:

- Initially, patients with the largest burn sizes were transferred to a nearby civilian burn center. Most of them later died. This sapped resources in the burn center with little impact on outcome.
- Use of different resuscitation formulas caused difficulties.
- Patients with obviously lethal injuries were not transported. This did not meet expectations of the referring hospital (WAMC).
- Several burn victims remained at WAMC without burn specialists because all the burn specialists were needed at the USAISR.
- There was a lack of burn experience and training at WAMC. Knowledge deficits were noted in techniques (e.g., escharotomy).
- Training of nonsurgical staff in Advanced Trauma Life Support (ATLS) and Advanced Burn Life Support (ABLS) was needed because the surgical staff was busy doing emergency procedures.

EXPLOSIONS

San Juanico, Mexico—November 19, 1984[32]

An 11,000-m^3 mixture of propane and butane exploded in San Juan Ixhuatepec (population, 40,000), causing one of the most severe explosion disasters in history and registering 5 on the Richter scale. In a 25-acre (10-hectare; 100,000-m^2) area, 7000 persons needed medical help and 2000 required hospitalization, with 625 severe thermal injuries. Thirty-three hospitals were involved, with transportation by 363 ambulances and helicopters. Sixty thousand people were evacuated. About 23,000 needed help with smaller injuries, lodging, and food.

The magnitude of the event meant that during the first hour, total chaos reigned, and rescue work was unguided. Secondary explosions, heat from fire, and debris forced rescuers into temporary retreat to avoid risking more lives. Private vehicles fleeing the disaster zone obstructed relief and evacuation traffic. After triage and initial care, victims were distributed to 33 hospitals, most of them in Mexico City. Within 3 days, burn patients had been distributed to 12 hospitals with good burn facilities. After 5 days, only 300 of the 625 burn patients were still in burn units: 140 had died, and 185 had been sent to other hospitals. There were "rather few" very extensive and deep burns and very few who needed respirator care.

Centro Médico reported 37 severe burns admitted because of a silo explosion 3 days before and received 88 more burn patients from San Juanico. The facility mobilized additional staff and prepared additional beds near the burn unit. Only 2 of the 88 victims had airway injuries requiring tracheostomy and ventilation. This burn unit's usual capacity is 48 beds; the maximum number of patients simultaneously treated was 136. Fifteen patients died within 4 days, whose burns exceeded 60% TBSA.

Piper Alpha, North Sea—July 6, 1988[33]

An oil fire and gas explosion on an oil rig killed 167 and injured 189. Information about the event reached Aberdeen Royal Infirmary in Scotland by television. Sixty-three were rescued; of 22 who went to the hospital, 15 were admitted, 11 to the burn unit. There were severe thermal injuries from molten helmets on victims' heads. All patients had some degree of inhalation injury.

All patients were operated on within 72 hours. Operations were performed by two teams working in two areas simultaneously. The high number of dead took a grave toll on the medical and lay teams' psyches. Psychiatrists, psychologists, and social workers were engaged. The retrospective recommendation is to distribute patients among other units. News media were a problem, as was the administration's lack of awareness of the need to maintain the high staffing levels for a long time. Knowledge of basic burn procedures (e.g., escharotomies and the way to treat a burn) is important.

Bashkir Autonomous Soviet Socialist Republic—June 4, 1989

Two trains were passing a methane–propane pipeline when it exploded, killing 575 and injuring 623.[34] Intravenous (IV) fluid resuscitation was initiated for most patients. Those

with serious but potentially survivable injuries were then evacuated to Chelyabinsk, Sverdlovsk, and Ufa. Later, the military and Aeroflot took most of them to Gorky, Leningrad, and Moscow. Most had burns of 30–40% TBSA. Several international teams deployed to assist.[35] In Ufa, a team from Galveston, Texas, under Dr. David Herndon found four children with burns of 30–68% TBSA and 12 with moderate burn size (15–30% TBSA). The team began treatment in cooperation with Russian personnel; the earlier, conservative therapy was changed to an operative one, using dermatomes and meshers brought from Galveston. A U.S. Army team was deployed to treat adults in Ufa. The U.S. Army selected 28 patients for burn-wound excision and coverage. The team reported many infected wounds (see Fig. 5.3). A microbiological program was set up. Cross-infection between burn victims was common, mostly by multiresistant *Pseudomonas* and *Staphylococcus* spp. Local therapy was done with mafenide acetate and silver sulfadiazine (SSD) (see Fig. 5.4).[35] This effort was one of the very successful international joint operations in a burn disaster.[36]

Phases of Mass Casualty Events

CHAOS AND ALARM

Initially, information about the event is unavailable; even those involved often cannot verify the incident's dimensions and sometimes cannot even describe the location. False information leads to inaccurate alerts and is disastrous for all who then must cope with unexpected situations.[15,18] Questions to be answered include the exact time, place, and type of accident; the estimated number of casualties and expected pattern of injuries; hazards (e.g., contamination, toxic smoke); and the number of persons potentially exposed.

Immediately after the accident, victims often flee to the nearest hospitals, overcrowding them before any official alarm. This influences the execution of emergency plans because everyone is busy with arriving victims, and there may be no resources available to carry out those plans. Contaminated victims can bring severe risks to hospitals; this can cause a partial loss of medical resources.

ORGANIZATION

After verification, the incident command system and the in-field command post must be established and must coordinate the work of rescue, security, medical, and technical relief teams to enable working in the damaged area and to protect the teams and their work from hazards, violence, and distracting demands made by victims and their friends and relatives.

Medical care at the scene and in alerted hospitals should be established. First, the scene must be cleared of further hazards, or rescue workers must be outfitted for the risk. A cordon should be established to control victims' departure to hospitals and to prevent onlookers' and news media's interference in rescue work.

Traffic regulation must begin, and all teams must understand it: It must include movement and assembly of ambulances, fire trucks, and police cars; landing and take-off of helicopters; decontamination areas; areas for triage, treatment, and minor injuries; and a temporary morgue. Divide the scene into rescue areas, and make schedules for technical-support teams.

In this phase, cooperation among medical teams, fire brigades, police, and technical-relief teams is crucial. Local command, control, and communication (C3) structures must be established; they are the coordination hub for preclinical treatment. A central C3 structure coordinates preclinical and clinical treatment and transport and disseminates up-to-date information. At hospitals, disaster plans are implemented, and staff is called in.

SEARCH AND RESCUE

The first goal of search and rescue (SAR) is to bring victims to a safe casualty collection point (CCP) out of the way of imminent danger (hostile action or environmental hazards). In-field triage and tagging must occur at the CCP. This primary evaluation should take less than 30 seconds per patient and should be limited to life-threatening conditions.

TRIAGE AND FIRST AID

Triage is a process whereby patients are sorted according to treatment priority, the purpose of which is to do the greatest good for the greatest number. Several schemes exist to define levels of triage. The *Advanced Disaster Medical Response* course[37] is field oriented and outlines the following:

- Level 1 triage occurs at the point of injury.
- Level 2 triage occurs at the scene (or nearby) by the most experienced medical provider.
- Level 3 triage is performed to determine evacuation priorities.

The *Fundamental Disaster Management* course[37] is ICU oriented and describes the following levels of triage:

- Primary triage occurs at the scene.
- Secondary triage occurs upon arrival at the hospital.
- Tertiary triage occurs in the ICU.

Finally, the ABA approach is burn center oriented and defines the following:

- Primary triage is that occurring at the disaster scene or at the ED of the first receiving hospital.
- Secondary triage is the selection for transfer of burn patients from one burn center to another when surge capacity is reached.

Clearly, triage is not a one-time operation but has to be repeated at each step of the way. There are several different algorithms for triage. Paramedics may use simple triage and rapid treatment (START) in both emergency medicine and mass casualties. The sensitivity for START varies from 85%[38] to 62%.[39] Medic in-field triage is another approach. This is done in an established triage area by medics assisted by teams of helpers. It consists of a brief history (time of accident, mechanism of injury, condition, how the patient was found, primary measures taken, actual discomfort, pre-existing condition, medications, and allergies) and a quick head-to-toe examination:

Table 5.1 Triage Color Code and Urgency

Group	START	Medic Triage
1	Immediate	Immediate
2	Urgent	Urgent (2a and 2b)
3	Delayed	Delayed
4		Expectant
4	Expectant or dead	
No number, no color		Dead

- Physical examination—external bleeding; penetrating injuries; thermal burns; chemical burns; neurologic status; and investigation of head, spine, thorax, abdomen, pelvis, and extremities
- Vital signs, including respiration rate, pulse oximetry, and temperature
- Burn size is estimated by the rule of nines, and there is evaluation of suspected inhalation injury and of the need for intubation.

Triage classifies patients according to the following treatment urgency groups shown in Table 5.1. An easy-to-remember acronym is DIME, which stands for delayed, immediate, minimal, and expectant. The main factors to consider in burn patient triage are TBSA burn and age.

Emergency treatment at the scene is done in a treatment area by appropriately trained providers. Burns needing treatment for shock or intubation should be classified for urgent treatment. Because of the need to resuscitate as soon as possible, resuscitation should begin here!

In mass casualties, cardiopulmonary resuscitation (CPR) is not performed as it binds resources for mostly futile efforts for victims initially classified as dead (no ventilation after airway opened, no pulse). This is especially after rescue from indoor fires (because deadly CO poisoning can be assumed) and in the setting of massive trauma.[40]

Triage group 4 (in Austria, Germany, Switzerland, and some other countries) includes the unsalvageable, who deserve "expectant" treatment. This may be controversial because the duration of the disparity between supply and demand should be short and, when the period is over, this group's priority may change to 1 or 2. Group 4 needs staff at least for comfort care. Dead victims need neither staff nor transports in the acute phase.

If available, tags are attached to each patient. Tags are used not only to indicate triage category but also to provide each patient with a unique number. These tags facilitate victim identification and registration; tell about patients' history, medical treatment, injuries, urgency of treatment, and classification of injury; and specify the hospital for treatment. The tags must not be removed until all the following have occurred: hospital arrival, identifying the patient, and registering the tag number and treatment data.

INITIAL TRANSPORT

For burn patient transport from the scene to the hospital, ambulance heating should be maximized to avoid cooling the patients. Warming pads and extra blankets should be prepared and IV fluids warmed up. Ambulance doors should be kept closed to retain heat! The transport order must accord with urgency status determined in triage.

Transporting the dead steals resources from the living. The dead, and where they are found (important for identification[41]) should be registered; when they have to be removed, they should be taken to a temporary morgue.

One strategy for distributing patients from a mass casualty event is based on proximity to the scene and classifies hospitals as first, second, or third line. As much as possible, *first-line hospitals* (those closest to the scene) should be avoided. They will be overcrowded with people arriving as walking wounded or by private vehicles and will have been neither triaged nor registered.[3,16] *Second-line hospitals* are the main destinations for those in need of emergency treatment. *Third-line hospitals*, those far from the incident, are ideal for patients in triage group 3 ("delayed treatment," "walking wounded" with only minor burns). Mass transport means (e.g., buses) can be used.

BURN CENTER REFERRAL

Central incident command should already know the number of available burn beds and at least the number and locations of victims. Burn extent and severity, need for ventilator support, quality of treatment for shock, CO poisoning, and quality of escharotomies all must be evaluated with the goal of getting reliable data. BATs may play a role in this phase by gathering information from outlying hospitals and assisting in emergency care. With central collection and distribution of data, the best treatment option allowed by the resources available can be chosen for the patient. This can be supported by information technology (IT) solutions that enable central registration of burn cases.[42]

Depending on resource availability, burn patients are either distributed to burn centers with free resources or, when burn-center resources are limited, criteria for burn-center treatment must be established. These criteria should include burn size, age, and the need for ventilator support. The survival grid published by the ABA is recommended for this purpose.[2] Patients meeting these criteria are to be transported to burn units; the rest either stay in the primary hospital or are transferred to nonburn centers.

Whether to transport patients whose care has been classified as futile to burn centers must be decided in advance. They are a burden for the primary hospital in terms of workload, psychological effect, and legal aspects.[31] In burn centers, they tie up resources needed for treating patients who are likelier to survive. The pairing of two recommendations in the United States—to send any third-degree burn to a burn center and not to send to a burn center anyone with a severe, life-threatening, nonsurvivable burn—may produce conflict. At any rate, these patients, their relatives, and the staff caring for them need both psychosocial support and support from experienced burn personnel.

EVACUATION TO OTHER BURN CENTERS

Depending on the number of casualties and the available burn beds, it may be necessary to transfer patients out of the local burn center. There are three possible scenarios:

1. If the number of patients is within the local burn center's surge capacity, then the local burn center can do primary stabilization and treatment and afterwards can decide whether to distribute some patients to other burn centers.
2. If the number of patients exceeds the surge capacity of the local burn center but can be handled by the national system of burn centers, then initial care must occur in local trauma centers or burn centers. Dispersal of patients to national burn centers must come later.
3. If the number of victims exceeds national resources, international resources must be evaluated to determine which patients are to be treated in burn centers nationally and which could be evacuated internationally. This scenario can be facilitated by preexisting conventions and treaties.

SECONDARY TRANSPORT

During transport, the patient must be protected from bacterial contamination and from cooling. This requires special dressings and devices that prevent cooling. Klein and associates reported that the most common complications during air transport were loss of venous access and inability to secure an airway. Hypothermia below 35°C was reported in about 10%, mostly in patients with larger TBSA burns.[43]

TRANSPORT HOME

For patients whose treatment occurred far from their homes, transport to home hospitals should be arranged. Central disaster management must conduct a general survey of treatment centers to identify survivors and space available in the home area. Patients should be transported if they are stable and the situation in the home area is suitable. Transport funding must be obtained.

LONG-TERM FOLLOW-UP AND REHABILITATION

After treatment in a burn center, further care must be planned. Regular follow-ups, surgical interventions, rehabilitation, and psychosocial support must be initiated. These should be long-lasting measures to give the patient a point of care that she or he trusts.

Rehabilitation must be coordinated for all patients. The primary shortage in burn beds will be followed by a secondary shortage in rehabilitation centers. Follow-ups must be planned far into the future; projects should be established and funded. Care—physical, psychological, and social—should be given not only to the victims but also to their relatives.

DEBRIEFING

Debriefing is part of psychosocial preventive care in emergency response. Staff in mass casualties have a higher risk of illness than the average population. Contributing factors include the need to make triage decisions, bad information, lack of routine, lack of resources, inability to provide help, and contact with aggressive news media.[44,45] Debriefing allows those involved in the incident to overcome the event psychologically and to reflect on its effects. Optimally, it is conducted near the site of the event and begins within the first 24–72 hours. The preferred approach is one-on-one interviews and small-group sessions, after which the psychosocial specialist decides whether debriefing should be offered. It is suggested to contact people again after 4–6 weeks for reevaluation.[40]

The Critical Incident Stress Debriefing (CISD) system has three parts—preparation, attendance, and aftercare. CISD is offered by many institutions and organizations. Although minimum standards are rather clear, quality control is sometimes lacking.[40]

Emergency Care: Special Considerations in Disasters

FIRST AID

Bystanders, hurt and unhurt, give first aid according to their experience and training. Basic measures that can be performed by trained lay persons include the following:

- Stop bleeding.
- Open the airway.
- Extinguish fire on persons; cool wounds while preventing hypothermia.
- Prevent wound contamination.

In mass casualty events, clean polyethylene film (e.g., Saran wrap, a plastic wrap used for food) is suggested for protection of areas other than the face. This occlusive dressing prevents wound dehydration and evaporative heat loss. Care must be taken not to stop circulation or hinder ventilation.

FLUID RESUSCITATION

An approach to initial care of burn patients in EDs is provided in Tables 5.2 and 5.3. To simplify fluid resuscitation by nonburn providers, who possibly have to resuscitate a lot of patients at the same time, Chung et al[46] implemented a new formula known as the rule of 10 (for adult patients weighing between 40 and 80 kg):

- Estimate burn size to the nearest 10.
- % TBSA × 10 = Initial fluid rate in milliliters per hour.
- For every 10 kg above 80 kg, increase the rate by 100 milliliters per hour.

During the next hours, fluid administration should be adjusted to physiologic response. The target is a urinary output of 30–50 mL/h. The crystalloid infusion rate (e.g., lactated Ringer's solution [LRS]) is adjusted up and down by about 25% every hour or two to achieve this goal. The formula is *not* suitable for resuscitation of burned children (weighing <40 kg body weight); for children, a weight-based formula should be used along with a maintenance fluid.

Mass casualty events and disasters make it difficult to provide fluid resuscitation at the right time and in sufficient quantities. A 70-kg patient with a 40% TBSA burn, for example, needs approximately 6000 mL of LRS during the first 8 hours. Because supply is a bottleneck in disasters,

Table 5.2 Primary Assessment of Burns in Hospitals

- A—Airway
  - Intubation?
  - Tracheotomy
  - Inhalation
- B—Breathing
  - Pneumothorax
  - Escharotomy thorax
  - Remove necrotic plates from thorax
- C—Circulation
  - Resuscitation fluid
  - TBSA recalculated
  - Urine output
  - Core temperature
  - Hemorrhage
  - Escharotomy
- D—Disability
  - CO—Carboxyhemoglobin
  - Hydrogen cyanide
  - Shock
  - Trauma
- E—Environment
  - Additional injury
  - (Trauma CT scan)

CO, Carbon monoxide; *CT,* computed tomography; *TBSA,* total burn surface area.

Table 5.3 Important Items During Primary Hospital Assessment in Burns

VENTILATION

- **If ventilation is impaired:** Check the need for intubation, tracheotomy, or coniotomy.
- **If patient is intubated and ventilation is disturbed:** Check tubus position; exclude pneumothorax; consider thoracic escharotomies and fasciotomies.
- **Check for inhalation injury and aspiration:** Bronchoscopy may be needed.
- **If carboxyhemoglobin is high:** Oxygen appliance is needed.

CIRCULATION

- If perfusion of extremities is disturbed or pressure is high: Check the need for escharotomy and fasciotomy.
- Recalculate TBSA.
- Recalculate fluid requirement: Present corrected fluid amount.
- If blood pressure is disturbed: Correct fluid administration. Other medication? Additional injuries?

ORGAN PERFUSION

- Check urine output.
- Core temperature: Warm up.

OTHER INJURIES

- Is other medical treatment (besides burn treatment) necessary? Complete the diagnosis and give treatment according to urgency.

LOCAL TREATMENT

- Clean; apply disinfectants: Take primary swabs.

NUTRITION

- Nasogastric or nasoenteric tube in intubated patients.

TBSA, Total burn surface area.

facility with how to resuscitate patients using fluids other than LRS may be important.

ORAL RESUSCITATION

Since the development of IV resuscitation formulas in the early 1950s, oral resuscitation in major burns (>15–20% TBSA) has been underused. This mainly reflects concerns about disturbed gastric emptying and impaired peristalsis after the burn injury, exacerbated by the side effects of opioid analgesics. In the early 1970s, Monafo resuscitated a small group of adults and children with burns of 22–95% TBSA using a 600-mOsm/L hypertonic oral solution.[47] In the 1990s, experience with early enteral feeding[48] demonstrated that, if feeding is begun no more than 2 hours postburn, the gastrointestinal effects are favorable, and even major burns could be managed with enteral, rather than parenteral, feeding.

Today, the main focus is on the World Health Organization's oral resuscitation solution (ORS). It is a small packet containing glucose, sodium, potassium, chloride, and buffer, with a slightly hypertonic osmolarity of 331 mmol/L when dissolved in water. It was first developed to treat the massive loss of volume and electrolytes in cholera, dysentery, and so on. With a feeding catheter placed in the intestine of 40% TBSA burned anesthetized pigs, Thomas et al demonstrated resuscitation with the WHO ORS according to the Parkland formula.[49] Michell et al reported similar results.[50] El-Sonbaty reported good results using WHO ORS for oral resuscitation of children with burns of 10–20% TBSA.[51] More research into both the ideal enteral fluid and the quantities to administer is necessary. But in early burn resuscitation in disasters with IV fluid shortages, there may be a role for oral rehydration solutions, such as the WHO ORS or one of the following:[52,53]

- 5.5 g of salt as undissolved tablets swallowed with 1 L of water
- 1 L of water with 1 tsp of salt (or 1/2 tsp of salt and 1/2 of baking soda) and 8 tsp of sugar
- 1 L of LR with 8 tsp of sugar.

The importance of beginning fluid resuscitation (orally, enterally, or intravenously) as early as possible must be emphasized.

AIRWAY MANAGEMENT

In burn disasters, oxygen and ventilators often are scarce, increasing the importance of correctly assessing which patients need oxygen or intubation.

OXYGEN

In disasters, oxygen (O_2) requirements rise rapidly. Delivering small bottles of liquid O_2 is logistically difficult; the available capacity is strained by the weight, space, and the need to refill bottles. Even hospitals' large bulk liquid-oxygen systems may be damaged or inaccessible. In such cases, alternatives must be implemented as soon as possible. Portable bulk systems (1000–5000 L of liquid oxygen) or mobile cylinder banks are helpful, but are often unavailable in disasters.

Two other options are portable oxygen generators (POGs) and nonportable oxygen generators, often used in military field hospitals. If electrical power is present, oxygen generators can deliver oxygen with a concentration of 93% or more. They can be connected to patients or ventilators. With a booster system to provide enough pressure, oxygen generators can be used to refill oxygen tanks.

For safe work with diminished resources, there are several requirements: organizing a sufficient supply, ensuring the right connections between the systems, rechecking different systems during exercises, and evaluating actual oxygen needs to minimize wasted gas.[54]

ANESTHESIA

In disasters with few fully equipped anesthesia workstations, relatively stable patients without threatened airways or inhalation injuries and no major surgery of thorax or abdomen can be managed safely with (1) ketamine, (2) ketamine and midazolam, or (3) ketamine and low-dose propofol.[55] Ketamine preserves spontaneous ventilation; airway reflexes are mostly intact. The drug induces dissociative anesthesia and is a potent analgesic. Increasing central sympathetic tone helps stabilize hemodynamics. It is a bronchodilator but increases mucus production. It therefore may require concomitant administration of glycopyrrolate or atropine. To avoid dysphoria and hallucinations, it can be combined with midazolam (0.03–0.15 mg/kg) or low-dose propofol (0.25–0.5 mg/kg). As a racemate, ketamine has a loading dose of 0.25–1 mg/kg IV or 0.5–2 mg/kg intramuscularly for analgesia; the anesthetic dose is 0.75–3 mg/kg IV. S (+) ketamine, with less psychomimetic effect, can be administered at half the dose of the racemate. The effect lasts 5–15 minutes.

Acute surgery of wounds on upper and lower limbs and reduction of open fractures can be done under peripheral single-shot regional anesthetic techniques if the region where the block must be performed is clean and not burned. The same can be done with smaller burns on the extremities.

The availability of ventilators and anesthesia machines depends on the scale of disaster. If field hospitals are required, providers must be familiar with the equipment available therein. First-line field anesthesia machines are draw-over systems. They are used in the forward deployed medical units in the army but also in civil units like the German Red Cross "ziviles Feldlazarett." Their main advantage is their extremely low weight (5 lb or 2.3 kg). For ventilation in a controlled mode, however, they have to be connected to a ventilator. Another disadvantage is their failure to meet American Society of Anesthesiologists (ASA) safety standards. Therefore, training with the devices is difficult and requires connection to the safety and monitoring systems of standard anesthesia machines.

Recently, field-deployable versions of standard anesthesia machines were developed and introduced. They are of a robust and lightweight design, are able to operate under extreme temperatures, have extended battery capacities, require little maintenance, and are able to ventilate in different modern ventilation modes. The same applies to some modern transport ventilators, which are easy to transport and able to replace a heavy ICU ventilator.

BLOOD

Few publications describe the responsiveness and efficacy of transfusion services in catastrophes and disasters. Blood supply is mentioned as scarce in the first and prolonged phases of disaster response.[12] But the 9/11 terror experience showed that an uncoordinated surge in blood donation may generate, several weeks later, an unusual drop in the supply.[56] Managing blood in disasters and catastrophes is therefore a tricky matter.[57]

Hospital blood banks possess a certain inventory, which usually is not more than the amount of blood products needed for 2–3 normal days, including additional units for major trauma. Burn disasters immediately deplete the available stocks and lead to urgent requests to the local blood center. Triaging mass casualties, especially in burn disasters, results in the dissemination of patients to different trauma centers, so that multiple hospital blood banks are involved. High-volume and high-priority requests concentrate in a spiraling sequence in one blood center, which is greatly strained to coordinate the distribution to its hospital blood banks.

Supplies are usually sufficient to meet the urgent first requests, but many blood centers hold an average of blood products to meet the regular demand of 1 week or less. Burn disasters are characterized by the urgent need for platelet products and erythrocyte concentrates in the early phase. A blood center's stocks may be depleted within hours—platelets first and then erythrocyte concentrates. Plasma products are usually available even in bigger disasters.

Deliveries from other blood centers and national coordination may help to mitigate the center's own insufficiency. More often, a blood center acts without information about the disaster and the estimated need for blood products. Communication between emergency services and blood centers is rare.

WOUND CARE AND ESCHAROTOMIES

Whereas courses such as ABLS emphasize early transfer of individual patients to a burn center, where debridement of wounds and escharotomies (if needed) are done by the burn experts, this may not be possible in a mass casualty event. Initial wound debridement should be thorough and aggressive and should use a surgical antiseptic such as chlorhexidine gluconate solution. After debridement, the patient should be prescribed a topical antimicrobial. SSD (Silvadene, Flamazine) has the advantage of widespread availability and familiarity. Mafenide acetate (Sulfamylon; Mylan Institutional, Rockford, IL) has the advantage of deep penetration into eschar. A silver-impregnated dressing (Silverlon; Argentum Medical, Geneva, IL; others) is a less labor-intensive option than the creams. For mass casualty situations, SSD with cerium nitrate (Flammacerium; Alliance Pharma, Chippenham, United Kingdom) is an attractive option based on the concept that the resulting eschar may permit a delay in excision with diminished ill effect.[58] An enzymatic debriding agent, NexoBrid (MediWound Ltd, Yavne, Israel), is under evaluation as a topical alternative to surgical wound debridement, which would be useful in mass casualty events.

Communication

Communication is an essential component of successful disaster response and a component that frequently

malfunctions during a crisis. Hospitals and burn centers often learn first of an incident through the media or other unofficial channels.[19] Victims arriving on their own sometimes give the first information.[9] News media also can be faster than the designed information structure sometimes video is a better source of information than mere words. When patients arrive tagged or telling certain stories, it indicates a mass casualty event. Measures to establish hospital preparedness should be taken, including checking supplies and the local situation and not allowing staff to go home after shifts until the situation is cleared.

Crisis communication is the exchange of information among public authorities, organizations, news media, and affected individuals and groups—before, during, and after a crisis.[59]

MEANS OF COMMUNICATION

In disasters and mass casualties, many factors increase the need for communication—and communication resources are limited. Sequential failure of various communication methods was described in many disasters such as Enschede,[60,61] London, and Madrid.[10,11] Communication problems are reported in almost all mass casualties and disasters.

Cellular Telephone

Cellular networks usually are overwhelmed because victims, news media, relatives, friends, and others all quickly begin dialing to or from cell phones. This leads to breakdown within minutes. Cell phones should not be used near explosive devices;[62] a 50-ft (15.2-m) safety radius is suggested. People trying to use cell phones may be endangered by security forces, who know that cell phones can be used to trigger bombs. In case of suspected bombs, cell phones can be jammed by security forces.[63] Amateur videos, often shot on cell phones, are important in mass casualties for reconstructions and intelligence.

Conventional Telephone

In most hospitals, the number of incoming and outgoing landlines is limited. A manual switchboard, as opposed to automatic switching, can become overloaded very quickly. For alerting staff, an alarm server with call-center function makes sense.

Voice over Internet Protocol

Voice over Internet Protocol (VoIP) permits conference calls. For security reasons, public VoIP systems are usually disabled in hospital IT systems.

Two-Way Radio

Reception and transmission can be poor or nonexistent indoors and underground (e.g., 9/11, London). In hospitals, the number of persons who can talk at the same place and time over one circuit can be limited, causing problems when an area includes many persons exchanging information.

Trunked Radio System

Such systems use computer control to allow almost unlimited talk groups with only a few channels. Relief units use trunked radio systems (TRSs) for intra- and interorganizational communication. In Europe, TRSs are being established for emergency organizations.

Satellite Telephone

Satellite phones are independent of local infrastructure and can be helpful in cases of uncertain or overloaded infrastructure. However, even a call made from a satellite phone will not go through if the telephone system at the receiving end is not functioning.

Internet

Internet communication is an option only if connections are intact.[64] The Internet can be helpful in building up information structures for victims' relatives and to provide information to large audiences.

Electronic News Media

These are important in disasters, especially when locales must be evacuated and when staff are needed. News reports sometimes constitute burn centers' first information source about incidents before the official alarm arrives.

COMMUNICATION WITH NEWS MEDIA

News media shape the public face of the disaster. Information should originate from a desire to be as correct and as complete as possible.[59] Training in crisis communication should be given. The central incident command should appoint spokespersons to provide regular, scheduled press conferences and bulletins. The press should be kept away from victims and their relatives. The hunt for headlines does not stop at the hospital door.

When spokespersons start their work, they should express first their concern about the situation and their condolences to those who have lost loved ones; they should provide assurance that everything possible is being done to help.

Methods of supplying information to the media include websites, press releases, press conferences, and radio and television interviews.

The media want people for interviews and photos. This should be kept in mind and prepared for, with forethought given to what aspects can be discussed without causing problems. The following is a list of things to avoid when interacting with the press:[59]

- Guessing; presenting your own theories; communicating falsehoods
- Becoming upset or angry
- Using jargon
- Discussing classified information
- Saying, "No comment"
- Speaking about issues outside your area of expertise.

Communication with the media should be done in an environment outfitted for information transfer by media and away from patient treatment areas.

COMMUNICATION WITH RELATIVES AND FRIENDS

Centers should be established at hospitals for friends and relatives to gather in private. Crisis counselors and communication tools (e.g., telephones) should be available here.

Access to this area should be restricted to identified relatives and friends. Information here should be exact, honest, and never speculative. A contact person for relatives and friends should be nominated. Relatives coming to visit their badly injured loved ones should be given psychosocial help and should be supported by the offer of guest rooms and continuous, fact-based information. Patients and relatives should be protected from news media, which often constitute a big problem in this phase.

Strategies for Distribution of Patients and Resources

Fundamental to disaster planning and response are strategies for admitting burn patients, for redistributing burn patients away from the disaster zone, and for bringing additional resources into the disaster zone. Strategies differ by country, depending on the resources available. A fundamental principle in any successful disaster strategy is that of a *tiered response*. This means that higher and higher tiers of support are brought into play as the magnitude of the event increases. Most mass casualty events are handled at the local level; regional, national, and then international resources are programmed as needed.

THE ROLE OF BURN CENTERS

Individual-medicine criteria for admitting to burn centers are rather extensive. For example, the German-Speaking Association for Burn Treatment (DGV) and the European Burns Association (EBA) have guidelines stating that burns in functionally or aesthetically important areas should be treated in burn centers regardless of their degree and extent. According to the ABA, all third-degree burns should be treated in burn centers. It may not be possible to follow these guidelines in mass casualties and disasters, at least not initially; the available burn beds must be filled by victims who will get the maximum survival advantage from burn center treatment.

In theory, admitting all burn patients to burn centers is reasonable in resource-rich jurisdictions, with many burn centers, many burn beds, and lots of staff. In reality, the availability of burn beds varies among nations. Usually it can be assumed that burn beds are in short supply and high demand. Even in the United States, many burn centers have fewer than 15 beds[65] and even fewer ICU beds.

The advantages of admitting all burn patients to burn centers are lost when the number of victims is so high that quality cannot be maintained. Burn center staff then get tied up treating many patients with non-life-threatening burns. Likewise, admitting only the most severely burned patients to burn centers is of little use, as demonstrated in the case of Pope Air Force Base. There, an influx of lethally injured patients monopolized the Jaycee Center's resources. Burn beds are scarce and so must be reserved for victims with the best chance of survival. The ABA published a benefit-to-resource ratio table to optimize this process.

Transferring patients elsewhere can be reasonable even for burn centers because surge capacity cannot be maintained indefinitely. "Medical vanity" should never be a reason to avoid transferring patients elsewhere. Workload above the normal capacity can cause complications, such as an infection control problem.[28]

THE ROLE OF TRAUMA CENTERS

Trauma centers will always be part of disaster response. Trauma centers, being much more numerous than burn centers, can cope more easily with initial treatment of an unknown number of casualties.[66] In special cases, patients with combination injuries (e.g., mechanical injuries) may benefit from transfer to a trauma unit.

Although initial care of burns is part of ATLS, many emergency doctors, trauma surgeons, and other medical personnel are not experienced in burns.[31] Trauma centers without burn units therefore need support from experts and seem to be the place where BATs can be most effective. BATs act as experts and can support other surgeons. Because they are busy not with details but with directing treatment by others, they are in a position to improve results. They also can help determine the extent and severity of burns for central data collection and for redistribution of patients to burn centers or other hospitals. This assumes that BATs are readily deployable on short notice.[3,8]

THE ROLE OF BURN-BED DATABASES

Burn-bed databases are a necessity for knowing quickly who should go where. These databases should include the different burn-bed types (adult or pediatric; ICU or ward). It takes too much time during an incident to ask each center individually how many beds are free for use; therefore, an online system is preferable.

At present, few data exist on the real availability of burn beds in case of disaster. Germany has the highest ratio of burn beds to population. In the Enschede fireworks explosion, Germany could offer 19 burn ICU beds of 127 for adults and 15 for children.[61] There are national burn-bed bureaus in Germany and the United Kingdom, and there are networking facilities for cooperation (e.g., the Mediterranean Burns Club).

THE ROLE OF INTERNATIONAL COOPERATION

Transfer of burn patients across international boundaries has worked well in some mass casualty events, particularly in Europe. The European Union has a "Community Mechanism for Civil Protection," which regulates disaster support among nations both in and outside the European Union. This process covers sending disaster-relief staff to countries with disasters, but it does not address transferring victims to other countries. There are exchange treaties between some countries, and there is actual cross-border hospital cooperation, but there is no general regulation thereof.

Humanitarian Crises

A humanitarian crisis is an event causing critical threats to health, safety, or human well-being, usually over a wide area. For burn injuries, armed conflicts and natural disasters are the likeliest forms. Natural disasters can not only be directly linked to fire (as in wildfires) but also cause burn

injuries through atypical use of energy: When people are not used to open fire but they need it because their electricity resource has failed, burn incidence rises. The same happens when people try to get electricity by throwing wires over power lines. After a severe storm, the increased use of internal-combustion emergency generators and internal-combustion power saws causes a higher rate of burn injuries and of burns related to burn accelerants.[67]

In disasters and humanitarian crises, medical treatment can often begin only after minimal infrastructure and order are reestablished. Where looting or political or religious rivalry occurs, medical work can be dangerous.[68] Therefore, cooperation with security forces, at least in the early stages, may be necessary.[69] Minimum requirements for work are shelter, safe water, food, and electricity.[70] One of the basic problems in medical aid work in disasters and low-resource countries is sterility: There usually is a high rate of infections with hepatitis and HIV, which must not be spread.[71] It may be helpful to conceptualize burn injuries during a humanitarian crisis as follows:

- Those that can be treated with minimal efforts (e.g., by clean dressings and available analgesics).
- Those that are not survivable without specialized care. Such specialized care must first be instituted.
- Those that cannot be treated successfully in this environment. Patients must be transported to facilities where successful treatment can be performed and is funded, or they are deemed futile, and "comfort care" should be provided.

To prepare medical systems for burn treatment during a humanitarian crisis, history provides data on what interventions are most likely to improve outcome at the lowest cost. At the end of World War II, only 50% of young adult patients survived burns of greater than 40% TBSA.[72] Stepwise improvements in survival were the result of the following advances:[73]

- Fluid resuscitation techniques
- Safe blood support
- Topical antibacterial treatment with mafenide acetate or silver-containing products
- Early excision and grafting; cadaver skin as a temporary skin substitute
- Enteral nutrition
- Improvements in mechanical ventilation and general critical care.

In other words, relatively low-cost interventions (e.g., prevention of invasive Gram-negative burn wound infection by use of topical antimicrobial burn creams and basic hygiene) are likely to have a greater impact than some of the higher cost, high-tech interventions.[74]

Conclusions

Recent events have raised worldwide awareness of burn disasters. Ongoing wars and terrorist attacks, along with several indoor fires, have shown that preparedness for such events is necessary.[75,76] No one is immune to such risks. The question is not whether such disasters will happen but when they will happen and how we can cope.

Preparedness requires plans, and it requires staff, stuff, and structure (the three Ss). Plans include international disaster plans, national disaster plans, coordinated disaster plans at the state level, and local disaster plans for locales and institutions. Structure is the national or international health system. Stuff is emergency supplies ready for disasters. Staff includes medical, paramedical, rescue, and technical-relief organizations. On the basis of these plans, legal preconditions must be established, and resources must be planned and funded. Both the planning and the execution require money, which is an investment in a society's future and security.

Burn societies can aid this procedure because they comprise the experts in these fields. Planning without the experts in burn treatment is futile, but working on their own, burn experts lack the resources to plan for mass casualties.

Disaster drills for hospitals and rescue organizations must be performed realistically. Education in burn treatment (e.g., Advanced Burn Life Support (ABLS), Emergency Management of Severe Burns (EMSB)) is essential for effective coping with mass casualties—not only for medical staff but also for hospital administrations. Burn surgeons are scarce in burn disasters, and surgeons are not the only personnel to be trained. We encourage readers to learn from the experiences described in this chapter; we hope that these experiences will motivate them to plan assiduously and to train diligently.

Complete references available online at
www.expertconsult.inkling.com

References

1. Weidringer JW, Weiss W, eds. *Aspekte zur Katastrophenmedizin und Definition ihrer Inhalte und Aufgaben. Katastroph*. Berlin: 2003:25-28.
2. ABA. Disaster Management and the ABA Plan. *J Burn Care Rehabil*. 2005;26(2):102-106.
3. Jordan MH, Mozingo DW, Gibran NS, Barillo DJ, Purdue GF. Plenary Session II: American Burn Association Disaster Readiness Plan. *J Burn Care Rehabil*. 2005;26(2):183-191.
4. Rapid assessment of injuries among survivors of the terrorist attack on the World Trade Center-New York City, September. *Mortal Wkly Rep*. 2002;51:1-5.
5. Kennedy PJ, Haertsch PA, Maitz PK. The Bali burn disaster: implications and lessons learned. *J Burn Care Rehabil*. 2005;26(2):125-131.
6. Yurt RW, Bessey PQ, Bauer GJ, et al. A regional burn center's response to a disaster: September 11, 2001, and the days beyond. *J Burn Care Rehabil*. 2005;26(2):117-124.
7. McLaughlin M Hospital staff looking back on Bali bombing aftermath. 2004. Available from: http://www.abc.net.au/7.30/content/2004/s1218623.htm. Accessed 30 May 2016. 0–12.
8. Greenwood JE, Pearce AP. Burns assessment team as part of burn disaster response. *Prehosp Disaster Med*. 2006;21(1):45-52.
9. Palmer DJ, Stephens D, Fisher DA, et al. The Bali bombing: the Royal Darwin Hospital response. *Med J Aust*. 2003;179(7):358-361.
10. Carresi AL. The 2004 Madrid train bombings: an analysis of prehospital management. *Disasters*. 2008;32(1):41-65.
11. Bolling R, Ehrlin Y, Forsberg R, et al. KAMEDO Report 90: terrorist attacks in Madrid, Spain, 2004. *Prehospital disaster Med Off J Natl Assoc EMS Physicians World Assoc Emerg Disaster Med Assoc with Acute Care Found*. 2004;22(3):252-257.
12. de Ceballos JPG, Turégano-Fuentes F, Perez-Diaz D, et al. 11 March 2004: The terrorist bomb explosions in Madrid, Spain – an analysis of the logistics, injuries sustained and clinical management of casualties treated at the closest hospital. *Crit Care*. 2005;9(1):104-111.
13. Aylwin CJ, König TC, Brennan NW, et al. Reduction in critical mortality in urban mass casualty incidents: analysis of triage, surge, and resource use after the London bombings on July 7, 2005. *Lancet (London, England)*. 2006;368(9554):2219-2225.
14. Hughes G. The London bombings of 7 July 2005: what is the main lesson? *Emerg Med J*. 2006;23(9):666.
15. Cassuto J, Tarnow P. The discotheque fire in Gothenburg 1998: A tragedy among teenagers. *Burns*. 2003;29(January 2001):405-416.
16. Gewalli F, Fogdestam I. Triage and initial treatment of burns in the Gothenburg fire disaster 1998. On-call plastic surgeons' experiences and lessons learned. *Scand J Plast Reconstr Surg Hand Surg*. 2003;37(3):134-139.
17. van Harten SM, Bierens JJLM, Welling L, et al. The Volendam fire: lessons learned from disaster research. *Prehosp Disaster Med*. 2006;21(5):303-309.
18. Alders C Investigators Report The New Years Eve fire in Volendam [Internet]. 2003. Available from: http://nationaalbrandweerdocumentatiecentrum.nl/rapporten/overige-rapporten/commissie-onderzoek-cafebrand/. Accessed 1 Jan 2016.
19. Digi24 R. Reanimieren und weinen [Internet]. 2015. Available from: http://www.digi24.ro/Stiri/Digi24/Actualitate/Stiri/Asistenta+de+la+Maternitatea+Bucur+printre+primii+salvatori+Era+. Accessed 5 Aug 2016.
20. Mahoney EJ, Harrington DT, Biffl WL, et al. Lessons Learned from a Nightclub Fire: Institutional Disaster Preparedness. *J Trauma Inj Infect Crit Care*. 2005;58(3):487-491.
21. Ramos G, Flageat G, Queiroz G, et al. Massive hospital admission of patients with respiratory failure resulting from smoke inhalation injury: the Cromagnon Republic Tragedy. *J Burn Care Res*. 1994;27(6):842-847.
22. Dal Ponte ST, Dornelles CFD, Arquilla B, Bloem C, Roblin P. Mass-casualty Response to the Kiss Nightclub in Santa Maria, Brazil. *Prehosp Disaster Med [Internet]*. 2015;30(1):93-96. Available from: http://www.journals.cambridge.org/abstract_S1049023X14001368. Accessed 21 Mar 2016.
23. Atiyeh B. Brazilian kiss nightclub disaster. *Ann Burns Fire Disasters [Internet]*. 2013;26(1):3-4. Accessed 21 Mar 2016.
24. Wikipedia F. Colectiv nightclub fire [Internet]. *Wikipedia*. 2015;Available from: https://en.wikipedia.org/wiki/Colectiv_nightclub_fire.
25. Baux S, Saizy R, Porte A, et al. The Los Alfaques disaster. *Ann Chir Plast*. 1981;26(2):185-187.
26. Banuelos Roda JA. Our Experience in the Treatment of a Great Number of Burns Due to Two Catastrophes. In: Zellner P-R, ed. *Die Versorgung des Brandverletzten im Katastrophenfall*. 1st ed. Darmstadt: Steinkopff; 1990:25-27.
27. Zengin Y, Dursun R, İçer M, et al. Fire disaster caused by LPG tanker explosion at Lice in Diyarbakır (Turkey): July 21, 2014. *Burns [Internet]*. 2015;41(6):1347-1352. Available from: http://www.sciencedirect.com/science/article/pii/S0305417915000406.
28. Steen M, Uhlemann PR, Zellner R. Die Versorgung der Opfer des Unglücks von Ramstein. In: Zellner PR, ed. *Die Versorgung des Brandverletzten im Katastrophenfall*. Steinkopff; 1990.
29. Steen M, Uhlemann PRH. Die Auswirkungen von Kerosin bei Großschadensereignissen mit Flugzeugbeteiligung. In: Zellner PR, ed. *Die Versorgung des Brandverletzten im Katastrophenfall*. Steinkopff; 1990:71-74.
30. Condon-Rall ME, Washington D, S U. Disaster on Green Ramp the Armys response. Disaster Green Ramp Armys response xvi 145 p C Cent Mil Hist Rep No. 1996;0–70.
31. Mozingo DW, Barillo DJ, Holcomb JB. The Pope Air Force Base Aircraft Crash and Burn Disaster. *J Burn Care Rehabil*. 2005;26(2):132-140.
32. Arturson G. The tragedy of San Juanico-the LPG disaster in history. *Burns*. 1987;87-102.
33. Rayner CRH. Offshore disaster on a fixed installation-The Piper Alpha Disaster on July 6th. In: Zellner R, ed. *Die Versorgung des Brandverletzten nim Katastrophenfall*. Steinkopff; 1990.
34. Wikipedia authors. Ufa Train disaster [Internet]. Available from: https://en.wikipedia.org/wiki/Ufa_train_disaster. Accessed 30 May 2016.
35. Herndon DN. A survey of the primary aid response to the Bashkir train-gas pipeline disaster. *Burns*. 1990;16(5):323-324.
36. Kulyapin AV, Sakhautdinov VG, Temerbulatov VM, Becker WK, Waymack JP. Bashkiria train-gas pipeline disaster: a history of the joint USSR/USA collaboration. *Burns*. 1990;16(5):339-342.
37. SM B, ed. *Advanced Disaster Medical Response: Manual for Providers*. Boston MA: Harvard Medical International Trauma and Disaster Institute; 2003.
38. Garner A, Lee A, Harrison K, Schultz CH. Comparative analysis of multiple-casualty incident triage algorithms. *Ann Emerg Med*. 2001;38(5):541-548.
39. Schenker JD, Goldstein S, Braun J, et al. Triage accuracy at a multiple casualty incident disaster drill: the Emergency Medical Service, Fire Department of New York City experience. *J Burn Care Res*. 2006;27(5):570-575.
40. Ortenwall P, Sager-Lund C, Nyström J, Martinell S. Disaster management lessons can be learned from the Gothenburg fire. *Lakartidningen*. 2000;97(13):1532-1539.
41. Prize N, Korn A. Disaster victim identification – a need to create zonewise scientific working groups Some drawbacks of the higher education system in India. *Curr Sci*. 2015;109(12):2173-2174.
42. Haller HL, Dirnberger J, Giretzlehner M, Rodemund C, Kamolz L. Understanding burns": research project BurnCase 3D–overcome the limits of existing methods in burns documentation. *Burns*. 2009;35(3):311-317.
43. Klein MB, Nathens AB, Emerson D, Heimbach DM, Gibran NS. An analysis of the long-distance transport of burn patients to a regional burn center. *J Burn Care Res*. 2003;28(1):49-55.
44. Helmerichs J, Luitz T, Lackner CK, Peter H, Schmidt J. Psychosoziale Notfallversorgung. In: Luitz T, Lackner CK, Peter HSJ, eds. *Medizinische Gefahrenabwehr*. 1st ed. München: Urban & Fischer; 2010.
45. Crisis Communications Handbook. In: Agency SEM, ed. *SEMA's Educational Series 2008:3*. Swedish Emergency Management Agency; 2008.
46. Chung KK, Wolf SE, Cancio LC, et al. Resuscitation of severely burned military casualties: fluid begets more fluid. *J Trauma [Internet]*. 2009.
47. Monafo WW. The treatment of burn shock by the intravenous and oral administration of hypertonic lactated saline solution. *J Trauma*. 1970;10(7):575-586.
48. Raff T, Hartmann B, Germann G. Early intragastric feeding of seriously burned and long-term ventilated patients: a review of 55 patients. *Burns*. 1997;23(1):19-25.
49. Bergwall S Thomas Quick : the Swedish serial killer who never was. 2012;1–9.
50. Michell MW, Oliveira HM, Kinsky MP, et al. Enteral resuscitation of burn shock using World Health Organization oral rehydration solution: a potential solution for mass casualty care. *J Burn Care Res*. 2006;27(6):819-825.

51. El-Sonbaty MA. Oral rehydration therapy in moderately burned children. *Ann Mediterranian Burn Club*. 1991;4:29-32.
52. Greenhalgh DG. Burn resuscitation: the results of the ISBI/ABA survey. *Burns [Internet]*. 2010;36(2):176-182. Accessed 10 Nov 2012.
53. Cancio LC, Kramer GC, Hoskins SL. Gastrointestinal fluid resuscitation of thermally injured patients. *J Burn Care Res*. 2006;27(5):561-569.
54. Swift D. *Oxygen delivery during a mass casualty incident. What a gas?* Vol. 2. SRC-G; 2010.
55. Ashraf M, Sheik I. Anesthetic management of mass casualties—what should be the drug of choice? *Pakistan Armed Force Med J*. 2006;4.
56. Sass RG. Toward a More Stable Blood Supply: Charitable Incentives, Donation Rates, and the Experience of September 11. *Am J Bioeth [Internet]*. 2013;13(6):38-45.
57. Erickson ML, Champion MH, Klein R, et al. Management of blood shortages in a tertiary care academic medical center: the Yale-New Haven Hospital frozen blood reserve. *Transfusion [Internet]*. 2008;48(10):2252-2263. Accessed 26 Jun 2017.
58. Rosenberg L, Krieger Y, Bogdanov-Berezovski A, et al. A novel rapid and selective enzymatic debridement agent for burn wound management: A multi-center RCT. *Burns [Internet]*. 2014;40(3):466-474.
59. Swedish Emergency Management Agency. Cris Communication Handbook. 2008.
60. van Walsum AD, Rödel SG, Klaase JM, Vierhout PA. Local and regional in-hospital trauma care following fireworks depot explosion in Enschede. *Ned Tijdschr Geneeskd*. 2001;145(48):2330-2335.
61. Woltering HP, Schneider BM. Great damage event of the Dutch Enschede on May 13th, 2000. *Unfallchirurg*. 2002;105(11):961-967.
62. Associated Press F. *Cell Phone Triggered Bombs*. Vol. 59207. SRC; 2003:6-11.
63. Netline: Cell Phone Blocking. http://www.netline.co.il/page/prisons_cell_phone_blocking.aspx. Accessed 2010.
64. Kabbo: Undersea Internet Cables damaged by Taiwan Earthquake. http://thetechjournal.com/off-topic/undersea-internet-cables-damaged-by-taiwan-earthquake.xhtml. Accessed 2010.
65. ABA. Burn Care Facilities [Internet]. 2017. Available from: http://c.ymcdn.com/sites/ameriburn.site-ym.com/resource/resmgr/bcrd/USBurnCareFacilities.pdf.
66. Rivara FP, Nathens AB, Jurkovich GJ, Maier RV. Do trauma centers have the capacity to respond to disasters? *J Trauma*. 2006;61(4):949-953.
67. Rainey S, Cruse CW, Smith JS, et al. The occurrence and seasonal variation of accelerant-related burn injuries in central Florida. *J Burn Care Res*. 2007;28(5):675-680.
68. Smith J: Mob justice in Haiti http://www.thestar.com/news/world/article/751792--haiti-street-justice-the-worst-in-people. Accessed 17 Jan 2010.
69. Greene RA: Aid workers heading to Haiti fear for their safety. http://edition.cnn.com/2010/WORLD/americas/01/14/haiti.aid.hurdles/index.html. Accessed 2010.
70. Le Saout E: Haiti earthquake: health priorities and challenges in large-scale disasters. http://www.icrc.org/web/eng/siteeng0.nsf/html/haiti-earthquake-interview-150110. Accessed 2010.
71. Fontham ETH. Infectious diseases and global cancer control. *CA Cancer J Clin*. 2009;59(1):5-7.
72. Saffle JR. Predicting outcomes of burns. *N Engl J Med*. 1998;338(6):387-388.
73. Janzekovic Z. A new concept in the early excision and immediate grafting of burns. *J Trauma*. 1970;2(12):1103-1117.
74. Young AW, Graves C, Kowalske KJ, et al. Guideline for Burn Care Under Austere Conditions. *J Burn Care Res [Internet]*. 2016;1.
75. Dai A, Carrougher GJ, Mandell SP, et al. Review of Recent Large-Scale Burn Disasters Worldwide in Comparison to Preparedness Guidelines. *J Burn Care Res [Internet]*. 2017;38(1):36-44. Accessed 7 Nov 2016.
76. Chim H, Yew WS, Song C. Managing burn victims of suicide bombing attacks: outcomes, lessons learnt, and changes made from three attacks in Indonesia. *Crit Care [Internet]*. 2007;11(1):R15.

6 Care of Outpatient Burns

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Introduction

Many small burn injuries can be treated in the outpatient clinic once it is determined that there are no other injuries, complicating medical problems, or suspicion of abuse. As with burn care in the hospital setting, the goals of outpatient burn care are to adequately heal wounds with minimal scarring or deformity, as well as reducing pain, the risk of infection, and impaired function. To achieve these, outpatient burn care encompasses wound management, rehabilitation, and psychosocial support.

Outpatient burn care extends to follow-up treatment of patients with larger burns following discharge. Care for these patients is similar, with evaluation for proper wound healing and monitoring for areas that may need surgical revision, along with ongoing physical and psychosocial therapy and scar control management.

Who Can Be Managed as an Outpatient?

Patients should be carefully evaluated to determine whether outpatient management of the burn would be sufficient for the course of medical treatment. Careful medical history and physical examination will help to guide decision-making whether the patient should be admitted or can be treated as an outpatient. Important factors to note include the extent and depth of burn injury, cause of the burn, associated trauma, and premorbid diseases. Patients who require intravenous fluid resuscitation should be treated in the hospital, as should those in whom it will be difficult to properly manage pain as an outpatient. However, once resuscitated and pain controlled with oral pain medication, subsequent treatment may be performed in the community setting depending upon the severity of the burn injury. The American Burn Association (ABA) provides guidelines to assist in identifying patients who should be referred for treatment at a burn center, and this will be discussed in more detail later (Table 6.1).

PERCENT OF THE BURN

The ABA recommends referral to a dedicated burn center for all patients with greater than 10% total body surface area (TBSA) burn.[1] The TBSA may be estimated by using the Wallace "rule-of-nines"(2), or the "rule-of-palm," which estimates the body surface area involvement by using the size of the patient's palm and fingers, with the thumb extended and all fingers adducted, as a guide to estimate approximately 1% of the TBSA for that patient. The rule-of-palm is useful especially in children who, because of their body proportions, do not follow the rule-of-nines. A more accurate method of estimating burn size is the Lund-Browder chart.[1] It is important to note that hand size may overestimate the size of the burn,[2] and both the rule-of-nines and Lund-Browder chart may have significant error when estimating the burn size of obese patients.[3,4] Therefore, it is important to understand that these methods of determining burn involvement are not exact and to know the limits of your facility and staff.

DEPTH OF THE BURN

The depth of the burn injury is important to note during the evaluation of the patient because it is recommended that any patient with a third-degree burn be referred to a burn center due to the additional care needed. First-degree burns and third-degree, full-thickness burns are relatively easy to identify at the time of presentation. First-degree burns, like sunburns, only involve the epidermis and are dry, painful, and do not blister. Third-degree burns involve the epidermis, dermis, and the subcutaneous tissues. These wounds can appear black, white, or leathery, and they will not blanch to the touch or be sensate or painful (Fig. 6.1). It is still possible to elicit pain because manipulation of a full-thickness burn may stimulate the edges of the burn, which is inflamed and sensate. Second-degree burns can be divided into superficial partial-thickness and deep partial-thickness injuries. The difference between these two can be subtle during the initial evaluation. All partial-thickness burns will be painful and moist and can have blisters (Fig. 6.2). However superficial wounds will have clear fluid in blisters, and deeper wounds may have bloody fluid with late presentation. Superficial wounds will also blanch to pressure as opposed to deeper wounds. Occasionally wounds that appear perfused with ruptured blisters that initially appear to be superficial may progress to a more severe injury due to thrombosis of the small blood vessels in the wound, leading to the wound becoming a deeper injury.[5,6] Superficial partial-thickness wounds will heal within 3 weeks, while deep partial-thickness wounds may take longer to heal or require excision and grafting.

Burn injuries can be divided into three zones (Fig. 6.3). At the point of greatest damage is the zone of coagulation, in which there is irreversible tissue damage. Surrounding this is the zone of stasis, an area of the wound that can potentially necrose with inadequate treatment or heal if the area is properly perfused. Should the patient be underresuscitated, this region of the burn wound may progress to become part of the zone of coagulation. The third zone, at the edge of the burn injury, is the zone of hyperemia, which will likely heal with treatment if the region maintains perfusion and infection is not involved.[7]

Table 6.1 American Burn Association Burn Center Referral Criteria.

BURN INJURIES THAT SHOULD BE REFERRED TO A BURN CENTER INCLUDE:

1. Partial thickness burns greater than 10% total body surface area (TBSA)
2. Burns that involve the face, hands, feet, genitalia, perineum, or major joints
3. Third-degree burns in any age group
4. Electrical burns, including lightning injury
5. Chemical burns
6. Inhalation injury
7. Burn injury in patients with preexisting medical disorders that could complicate management, prolong recovery, or affect mortality
8. Any patient with burns and concomitant trauma (such as fractures) in which the burn injury poses the greatest risk of morbidity or mortality. In such cases, if the trauma poses the greater immediate risk, the patient may be initially stabilized in a trauma center before being transferred to a burn unit. Physician judgment will be necessary in such situations and should be in concert with the regional medical control plan and triage protocols.
9. Burned children in hospitals without qualified personnel or equipment for the care of children
10. Burn injury in patients who will require special social, emotional, or rehabilitative intervention

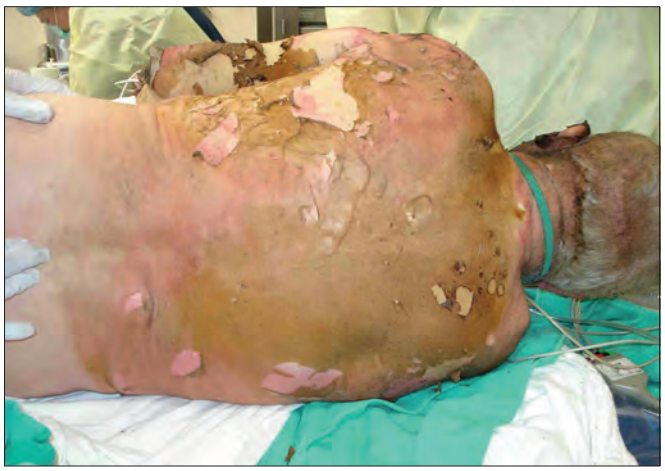

Fig. 6.1 Third-degree burn. Note the leathery appearance of this burn.

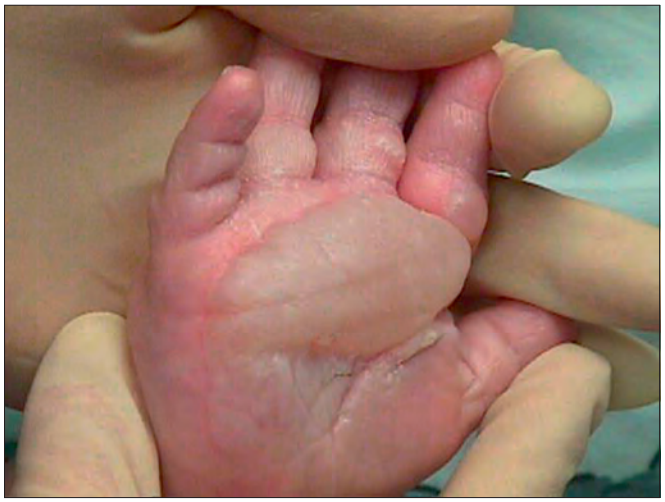

Fig. 6.2 Second-degree burn.

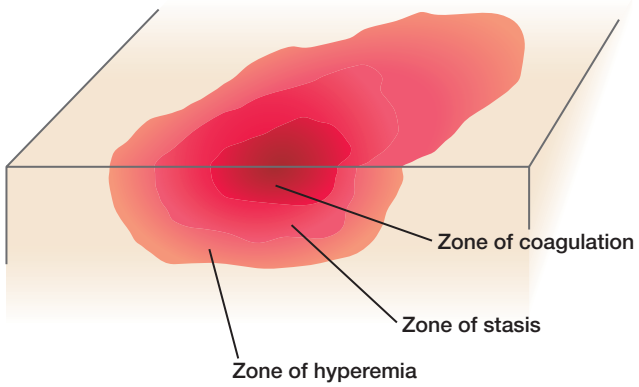

Fig. 6.3 Zones of injury.

DISTRIBUTION OF THE BURN

According to ABA guidelines, burns involving the hands, feet, face, genitalia, and perineum, and those that cross major joints should also be treated in a burn center.[8] Lasting damage to these areas can have a severe impact on patient outcomes. Impairments to the hands can affect grip and can therefore have deleterious effects upon the ability to work or handle activities of daily living. Burns of the feet or those that cross joints can severely limit mobility, while burns to the face can impair vision and the ability to eat, as well as having an emotional impact due to altered appearance. Finally burns to the genitalia and perineum can restrict patient autonomy, hindering urinary and sexual function or the ability to defecate. While burns to these areas may not necessitate specific inpatient treatment, they should be treated at a burn center with the proper resources to handle the special reconstructive and rehabilitative needs of these patients.

Special consideration should be given to burns that are completely circumferential around a part of the body, such as a limb or the trunk. Due to the tissues beneath the wound becoming edematous, circumferential wounds can cause increased pressure, resulting in compartment syndrome and leading to ischemia.[9] The classic symptoms are the five "P's" which are pain, pallor, paresthesia, pulselessness, and paralysis. The physician should have a high index of suspicion for compartment syndrome, which necessitates inpatient treatment.

INJURING AGENT

Electricity

Fatal cardiac dysrhythmias are a major risk following electrical injury; therefore all patients with electrical injuries should have an electrocardiogram (ECG) performed, and all meet the criteria for referral to a burn center. Injuries due to low voltages are usually smaller, therefore, these patients, as long as no ECG abnormalities are present and no loss of consciousness occurred, can be treated as an outpatient should there be no other indication for admission.[10] The presence of dysrhythmia, ECG abnormalities, or a history of loss of consciousness is grounds for admission to the hospital for monitoring. A common means of injury from

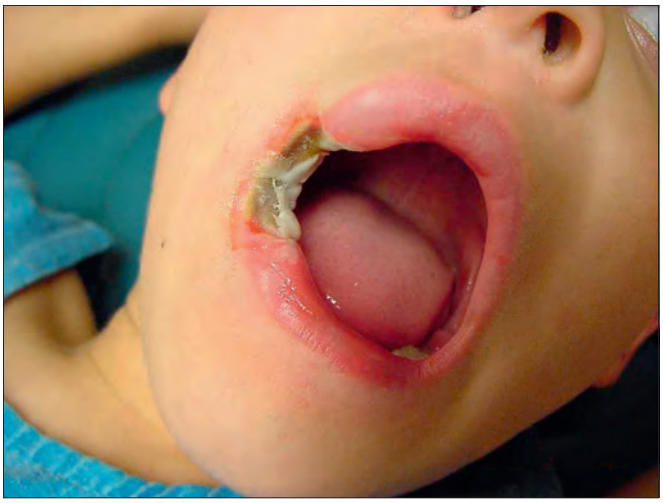

Fig. 6.4 Labial burn.

low-voltage energy sources is that of children sucking on a defective electrical cord, resulting in damage to the lips, tongue, gums, or dentition. Such patients may need admission because oral intake may be hindered. Such injuries to the mouth are at risk of resulting in rupture of either the superior or inferior labial arteries, especially from days 4 through 7 post burn (Fig. 6.4). If treating as an outpatient, the caregiver should be educated on this risk and instructed in proper first aid, which consists of pinching the labial commissure between the index finger and thumb.

All patients exposed to high-voltage electricity should be referred to a burn center due to increased deep-tissue injury and subsequent increased amputation rates, organ failure, and mortality as compared to patients with comparable TBSA thermal burns.[10]

Chemicals

While not caused by thermal injury, chemical burns are treated by burn surgeons, and chemical injury is one of the criteria for referral to a burn center. Initial management of a patient with a chemical injury involves brushing off dry chemicals and copious flushing of areas affected by wet chemicals.[11,12] The author recommends flushing until the patient is pain-free, and, with alkaline exposure, until the skin pH is 7, which is the pH of water. The normal skin pH is around 5, but once the pH has reached 7 further injury seems unlikely. As with thermal injuries, prompt irrigation of chemical injuries results in decreased full-thickness injury as well as shorter hospital stays.[13] Irrigation of the chemical burn may need to continue in excess of 1 hour.[14] In the author's experience, it often takes longer in alkaline exposures to reach a pH of 7.

Specific considerations need to be made depending on the causative substance. Phenol compounds do not flush well with water, so polyethylene glycol or vegetable oil followed by water lavage may be used. Water needs to be avoided if metallic sodium or potassium is suspected because the resultant exothermic chemical reaction may worsen the burn injury. Hydrofluoric acid injuries are treated with calcium following water lavage, and a calcium gel can be used to cover the injury. Some recommend that the tissues should be injected with calcium gluconate to alleviate pain as well as prevent tissue necrosis.[15] The author uses intra-arterial calcium gluconate, slowly injecting into the artery supplying the affected part until the patient is pain-free. This may have to be repeated in a few hours. Dermal exposure to hydrofluoric acid results in the absorption of the dissociated fluoride anion and subsequent insoluble salt formation by binding with calcium and magnesium. The patient may then develop hypocalcemia and hypomagnesemia accompanied by hyperkalemia due to potassium efflux from cells. Hypocalcemia is the main cause of death following hydrofluoric acid poisoning via the induction of fatal dysrhythmias. As little as 1% TBSA exposure to 50% concentration hydrofluoric acid or 5% TBSA exposure to any concentration is enough to result in potentially fatal hypocalcemia.[16] Identification of the chemical and communication with local poison control centers is recommended if needed. After the appropriate removal of the causative chemical, treatment is the same as for any other wound.

RESPIRATORY COMPLICATIONS

Inhalation injury is one of the criteria for referral to a burn center, and the physician must have a high index of suspicion concerning inhalation injury and carbon monoxide poisoning based on the circumstances surrounding the burn injury because there may be little to no exterior sign of injury.[17,18] The sequelae of both of these complications may not be initially present and may develop over time. Of note, airway obstruction may occur following burns of the oropharynx, face, or neck as the tissues of the upper airway become edematous.[19] Therefore, observation is warranted if there is any suspicion of inhalation injury.

ASSOCIATED TRAUMA

Due to the often accidental nature of burn injuries, there is frequently concomitant trauma at the time of presentation. Assessment should be made whether the associated trauma or the burn injury is of greater threat to the patient's morbidity or mortality, with the decision of the need for direct admission or stabilization and referral to a burn center made at the discretion of the treating physician.[8]

COMORBID DISORDERS

A comprehensive medical history of the burned patient should be performed to identify those with preexisting medical conditions that would complicate the ability to properly care for the patient in a community setting or have an impact on recovery, morbidity, and mortality.

The stress of the burn may exacerbate previous medical conditions such as diabetes mellitus, asthma, or coronary artery disease.

SOCIAL CIRCUMSTANCES

Proper outpatient management of burns requires that there are sufficient resources available to care for the wound and provide for proper follow-up care. Such resources

include either persons, such as family members or visiting nurses, who can assist with dressing changes, as well as the ability to easily access medical care and receive proper rehabilitation and psychosocial services. Should these resources be unavailable to the patient in the community setting, referral to a burn center should be considered.

Of serious concern when considering the social circumstances surrounding the patient is the possibility that the injury was nonaccidental. If there is any suspicion that the injury to the patient was intentional, admission to the hospital and notification of the proper agencies is warranted for their protection (Figs. 6.5 and 6.6).

HOSPITAL RESOURCES

Available resources should be taken into account in the decision-making process. Pediatric burn patients should be treated at hospitals with qualified personnel and equipment to treat children.

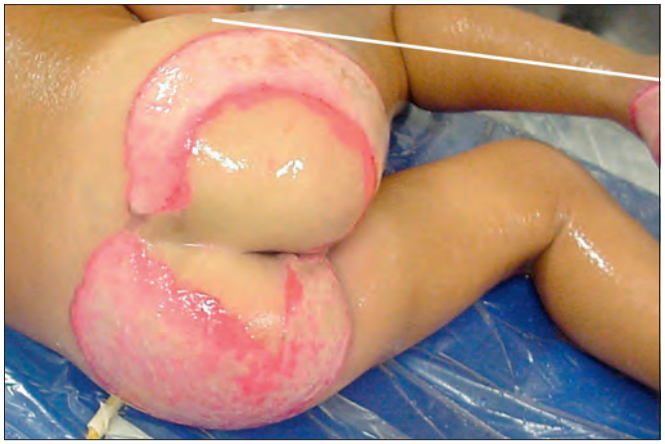

Fig. 6.5 Nonaccidental scald burn. Note the area that is not burned on this child. She was held down in a tub of hot water. The area of the buttocks that is not burned was in contact with the bottom of the tub and the heat had dissipated, thus not burning the child.

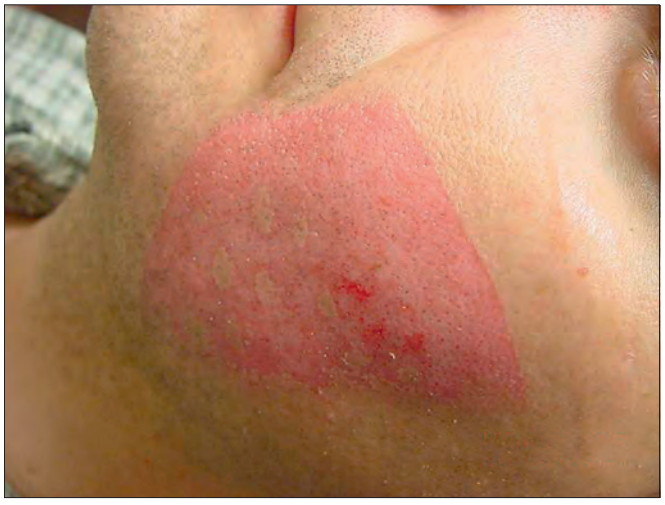

Fig. 6.6 Nonaccidental contact burn. This burn was caused by a clothes iron; note the triangular shape.

Management of Minor Burns

COOLING THE BURN

First aid for burn wounds should begin with removing clothing from the burned area and subsequently cooling the wound with cool, running tap water or saline.[20–22] The burn wound should be cooled as close to the time of injury as possible because damage continues while the tissue remains above 44°C.[23] A study by Rajan et al. has shown that even cooling initiated 60 min following burn injury will still have a beneficial effect on burn wound outcomes.[24] Excessive cooling, such as through the use of ice, may actually result in a deeper wound when compared to uncooled burn wounds in an animal model.[25]

Cooling is also important in the first aid of thermal injuries because cooling stabilizes mast cells in the skin, resulting in decreased histamine release and subsequent reduced edema of the burn wound. The application of cool, moist compresses can also be effective in relieving the pain associated with partial-thickness burns.[26–29] While patients with large surface area involvement may experience hypothermia if too aggressively cooled, patients who are eligible to be treated as an outpatient, with a smaller TBSA, should have little risk of this occurring. It is still prudent to monitor the patient's core temperature during active cooling.

A limit to the surface area that is cooled is arbitrary, but a practical limit is about 10% of the TBSA. A recent study concluded that 20 min was the optimal time to cool a burn.[30]

PAIN CONTROL

First-line treatment for pain in the emergency setting is usually narcotics. Intravenous doses of morphine can be given incrementally to titrate for the desired effect. Other pain relief options include acetaminophen with codeine, oxycodone, or similar analgesics that can be used individually or in combination. However due to growing concerns about the overuse of opioids and the risk of addiction and overdose, the physician may consider the use of medications such as acetaminophen or nonsteroidal antiinflammatories (NSAIDs), especially in smaller burns that are more appropriate for outpatient management. Partial-thickness wounds are the most painful burn wounds because the injury leaves the wound without epidermis. The pain is severe initially, but will partially subside in the following hours. During dressing changes or physical activity when the wound is manipulated, pain will again be exacerbated. Wounds with eschar will not be painful unless the eschar is removed or separated, exposing the viable tissue beneath.[31] Therefore additional analgesia may be required during physical activity and dressing changes. Should oral medication be unable to control the patient's pain, the patient should be admitted for adequate pain management. For additional information on management of pain in the burn patient, see Chapter 63.

BLISTERS

There is no clear consensus on the management of blisters, and therefore treatment depends on the experience of the

burn care team. Options for blister management include leaving the blister intact,[32] removing the blistered skin during the initial wound care,[33] removing the blister at a later time,[34] or aspirating the fluid from the blister.[32] Laboratory studies suggest that blister fluid may have detrimental effects via suppression of immunologic responses and inhibited fibrinolysis.[33] Others advocate that the blister can be left intact to serve as a biological wound dressing, with spontaneous resorption of the blister fluid beginning within 1 week. The devitalized skin from a ruptured blister can also be left in place in a similar fashion to serve as a dressing. The author removes blisters that are felt likely to rupture on their own and leaves the others intact, but covers them with an antimicrobial dressing.

CLEANSING THE WOUND

For thermal injuries, cleansing of the burn would should be performed using room temperature to tepid (100°F) sterile water or normal saline with a mild soap. In injuries involving tar or asphalt, cooling should be performed first, and the solidified tar or asphalt should be removed through the use of a solvent. Solvents with affinity for the substance to be removed should be used. One such product is Medi-Sol Adhesive Remover, a nontoxic, nonirritating, citrus-based Category I Medical Device solvent approved by the U.S. Food and Drug Administration (FDA), which has been shown to be effective in the removal of both tar and asphalt.[35] Other options include using polysorbates (a class of emulsifiers), which can be used on their own or in conjunction with topical antibiotics, and topical antibiotics in petroleum jelly. However these options may require multiple applications to be effective.[36,37] The author prefers the use of mineral oil because it is inexpensive and works well without causing additional skin irritation.[38]

TOPICAL AGENTS

Antibacterial agents are used to prevent burn wound infections.[39] Prophylactic use of topical agents such as these have not shown benefit in preventing infections or septicemia versus other dressing options, such as petrolatum-impregnated gauze[40,41]; however the author recommends that these substances should be used when the physician has suspicion that an infection is present. Should topical antimicrobial agents be warranted, there are several options available. A popular agent used in the treatment of burn wounds is 1% silver sulfadiazine, which has antiseptic properties due to the presence of silver, but also results in delayed wound healing.[42,43] This delay in wound healing has been shown to be alleviated through the co-administration of nystatin or aloe vera in an animal model.[44] Use of silver sulfadiazine should be discontinued once reepithelialization is noted because the agent impairs epithelialization. If the wound is covered with eschar, however, silver sulfadiazine may be used with few side effects. Care must be taken that the patient is not allergic to sulfa products or that the patient is not pregnant, nursing, or an infant under 2 months of age due to the risk of kernicterus.

Combinations of antibiotics in ointments have been of increasing interest because there have been no noted effects on wound healing in these medications. Examples include triple-antibiotic ointment (containing neomycin, bacitracin zinc, and polymyxin B sulfate) and Polysporin (containing polymyxin B sulfate and bacitracin zinc), which both have coverage against gram-positive cocci and some aerobic gram-negative bacilli. When using these compounds, small superficial pustules may form on uninjured or healed skin due to yeast. Discontinuation of the compound will clear these pustules. When compared to petrolatum-impregnated gauze alone, the addition of a topical antibiotic ointment may decrease odors. For partial-thickness facial burns, bacitracin can be applied several times a day without a secondary dressing, making it less likely the patient will attract unwanted attention from strangers.

DRESSING THE WOUND

There are few comparative studies concerning available wound dressing options therefore individual preference and comfort will be the determining factors in which option is selected. Wound dressings primarily serve to protect the wound from the outside environment, decrease pain, absorb drainage, and provide a moist environment to promote wound healing. Whatever dressing is used, as long as these qualities are met, the wound should properly heal. As Ambroise Paré said, "*Je le pansai, Dieu le guérit*" ("I treated him, but God healed him").[45]

Management of first-degree wounds may include the use of emollients or light dressings if needed. Follow-up care should monitor how the wound is healing.

Second-degree wounds can be managed with daily washing of the wound, along with the use of emollients and dressings that are changed daily. Alternatively these wounds can be covered with a polyurethane foam dressing, biologic dressing (discussed later), a silver-impregnated dressing, alginate dressing, or a 3% bismuth tribromophenate and USP petrolatum gauze. These allow for longer intervals between dressing changes and outpatient visits, and they are helpful in areas that require long travel times for patients to be seen in the outpatient setting. As with first-degree wounds, follow-up care of second-degree burns should monitor the progression of wound healing. Third-degree wounds, if small, will heal by epithelial ingrowth and contraction. However most will require referral for surgical intervention.

Patients should be seen at follow-up within several days in order to examine the progression of wound healing. The follow-up visit also serves to confirm the patient's adherence to wound care instructions and provides the opportunity to ensure the proper resources are available to the patient to provide an adequate environment for proper healing. Should any concerns arise, changes to the treatment plan, including types of dressing or frequency of visits, may be needed to optimize care. Otherwise, weekly intervals of follow-up visits provide adequate wound observation.

SYNTHETIC WOUND DRESSINGS

Synthetic wound dressings are popular in the treatment of superficial, partial-thickness burn wounds because they reduce pain, reduce healing time, and cost less than their biologic alternatives. There are many products in this category, with the following discussion representing a small

selection of what is available. Choice of dressing is at the discretion of the provider based on personal preference and experience.

Mepitel

Mepitel is a wound contact dressing that adheres to dry skin but not to the wound bed. After application, it can be left in place for up to 2 weeks. Secondary dressings may be placed on top of the Mepitel. These secondary dressings may then be changed when necessary, leaving the Mepitel in place and not disturbing the wound bed.[46] In a comparison with silver sulfadiazine, Mepitel has been shown to decrease healing times in pediatric burn patients.[47]

Mepilex AG

Mepilex AG is a synthetic wound dressing commonly used in the treatment of partial-thickness burn wounds. It is composed of three layers, with a silicone layer facing the wound, an absorbant polyurethane foam layer, and a protective waterproof film to keep the wound environment moist while allowing gases to permeate the dressing.[48] The foam layer in this dressing contains silver sulfate, providing antimicrobial action. After cleansing of the wound, the dressing is cut to size and applied onto the burn wound, followed by wrapping with gauze and elastic bandages to hold the dressing in place. Follow-up visits for dressing changes can be scheduled for every 3–7 days. In a recent randomized study comparing Mepilex AG with silver sulfadiazine, it was shown that a significantly higher number of burn wounds treated with Mepilex AG had healed after 1 week, although overall healing rates were similar.[48] In the same study, patients with Mepilex AG reported less pain associated with dressing changes.

Acticoat

Acticoat is a dressing composed of three layers, with an inner layer of rayon/polyester and outer layers of polyethylene coated with elemental silver. This silver is ionized into its bactericidal form when the dressing is moistened. The dressing can be left in place longer, requiring dressing changes every 3–7 days depending on which form of Acticoat is chosen. The dressing must be kept moist to be active. Studies suggest that Acticoat may reduce healing time when compared with silver sulfadiazine.[49,50]

TheraBond 3D

TheraBond 3D is a woven, silver-impregnated fabric with a perforated wound contact surface. The dressing is designed to allow fluid and exudate from the wound to be transferred through the dressing to an absorbent, secondary dressing. This dressing can be left in place for up to 14 days.[51]

Silverlon

Silverlon is a silver-nylon dressing that has been used extensively in the treatment of burn wounds in the military.[52] Similar to other listed wound dressings, Silverlon may be left in place for 3–7 days between dressing changes.

Suprathel

Suprathel is a newer synthetic burn wound dressing consisting of a thin, porous membrane composed of polylactic acid. The porous nature of the membrane prevents the accumulation of excess wound exudate. When applied to the wound surface, Suprathel becomes translucent, allowing for the wound to be visually inspected for healing and infection without removal of the dressing. The dressing is applied to the burn wound after débridement and is left in place without changing because it will detach on its own as reepithelialization occurs. Petroleum gauze is placed on top of the Suprathel, which is then held in place by gauze and elastic bandages. During follow-up visits, everything except the Suprathel and petroleum gauze may be removed and changed to allow inspection of the wound. In unpublished data from our institution comparing Suprathel with Mepilex AG, Suprathel was shown to be a safe alternative wound dressing with similar healing time; however it has significant advantages, such as reduced pain and decreased wound bed disturbance due to the ability to leave the dressing in place. These results are similar to those reported in comparison with other wound dressings.[53–56]

Hydrocolloid Dressings

Hydrocolloid dressings are composed of cross-linked matrix gelatin, pectin, and carboxymethyl-cellulose and can be formulated in wafers, pastes, or powders. They adhere to the burn wound on their own and provide a moist environment by trapping water in the matrix, thereby promoting wound healing. Compared with 1% silver sulfadiazine, these dressings show improvements in wound healing and reductions in pain and number of dressing changes.[57,58] Such dressings can be used for small partial-thickness burns and can be left in place for several days.

SYNTHETIC TISSUE-ENGINEERED WOUND DRESSINGS

Biobrane

Biobrane is a biosynthetic skin consisting of an outer silicone membrane and an inner nylon mesh bonded with porcine dermal collagen. This dressing allows gases to permeate it, but not liquids or bacteria.[59] This helps to keep the burn wound moist to improve healing, but care must be taken to not cover infected wounds or those with eschar or debris. The wound must also have sensation and appropriate capillary blanching and refill; thus, its use for partial-thickness wounds. When used in this manner, compared to 1% silver sulfadiazine, Biobrane resulted in decreased pain, reduced pain medication requirements, and decreased healing time.[42,60] At the time of writing, Biobrane is not currently available in the United States, but the manufacturer indicates that it, or a newer product called PermeaDerm, will be available shortly.

After cleansing the wound, Biobrane is applied so that it overlaps itself and is fixed to the surrounding unburned skin with sterile strips of tape or with drops of cyanoacrylate adhesive. Then the wound is dressed and splints applied if the wound crosses a joint to prevent shearing. Within a day, the Biobrane should be adherent to the wound surface, although any loose sections can be trimmed and new Biobrane applied. At follow-up, sterile fluid accumulating underneath the Biobrane can be aspirated and purulent fluid drained by opening the Biobrane. After reepithelialization, the Biobrane can be removed gently.

BIOLOGIC WOUND DRESSINGS

Allogenic Amnion

Allogenic amnion is a biologic wound dressing composed of the innermost fetal amniotic membranes whose first reported use was in 1910,[61,62] although its use as a temporary burn wound covering was first described in 1952.[63] Following donor screening, the amniotic membrane is harvested during caesarian section, and the donor tissue is screened for transmissible diseases.[62,64] For additional information on the harvesting of amnion, see Chapter 14. Amnion can be used in the treatment in partial-thickness burns, where it has been shown to promote wound healing, relieve pain, reduce scar formation, and reduce burn wound infections.[62,63,65–70] It can also be used as a temporary dressing to protect a clean, excised wound prior to skin grafting.[71]

Xenograft

In the treatment of partial-thickness burns, porcine xenograft reduces pain and decreases hypertrophic scarring.[72,73] It has been shown to be as effective as either human allograft or human fibroblast-derived temporary skin substitute, with the advantage of being more cost-effective.[74] The application is the same as discussed in the section on Biobrane.

Allograft

The authors do not recommend the use of allograft in small burn wounds, such as those that would be treated in an outpatient setting, due to high cost and limited supply. The application and use is the same as for xenograft, just discussed.

ELEVATION OF THE BURNED PART

Edema is one of the main sources of pain following burn injury, therefore reduction of this edema is an effective method of pain control. Injured extremities may be kept immobile by the patient in an effort to reduce discomfort, but this may result in exacerbation of edema and therefore pain. To relieve edema, injured parts should be placed slightly above the level of the heart. Regular exercise and physical therapy are also important factors in reducing edema. Should edema persist for longer than 3 days in patients with small burns, the likely culprit is immobilization and dependent positioning.

INFECTION AND USE OF SYSTEMIC ANTIBIOTICS

The use of prophylactic topical or systemic antibiotics has not been shown to decrease the incidence of burn wound infections, sepsis, or mortality[40,75] and should therefore only be used when there is clinical suspicion for infection. Although the risk of developing sepsis is quite low in patients who are able to be treated in the outpatient setting, patients should be instructed in the warning signs for infection before discharge. Patients should be advised to contact the physician should they experience temperatures higher than 38°C, malaise, increasing pain, erythema, foul odor, or anorexia.

Wounds should be examined both at follow-up by the physician and by those performing dressing changes in the outpatient setting to monitor for changes in the appearance. Early discolorations are likely to occur in the first few days following injury after injured blood vessels thrombose and wound perfusion is decreased. Discolorations, including black or gray spots, are suspicious for infection, and patients should be admitted and wound biopsies and microbiological studies performed for proper treatment of the infection.[76]

VACCINATIONS

All burn wounds are susceptible to tetanus infection.[77] If the patient has not received a dose of tetanus toxoid within the past 5 years, then tetanus immunization should be administered. For patients who have received less than three doses or have unknown immunization status, both tetanus toxoid and tetanus immune globulin can be given.[78]

INSTRUCTIONS AND FOLLOW-UP CARE

Before discharge from emergency care, patients should be instructed in proper techniques for wound care, positioning, and physical therapy. Warning signs of infection should also be described, and patients should be instructed about whom to contact for appropriate medical care if signs of infection occur. Finally physicians should ensure that patients have adequate pain medication and wound dressings.

DEFINITIVE WOUND CLOSURE

The goal for wound closure is to have all burn wounds healed within 1 month, which is easily attainable by the outpatient with smaller burns. Burn wounds that heal spontaneously within 3 weeks will have better outcomes, such as improved elasticity and reduced risk of hypertrophic scarring or pigmentation changes. Poorly healing wounds that take longer, however, have increased risk of scarring[79] or pigmentation alterations. In addition, wounds that take a very long time to heal spontaneously may have unstable epithelium. Careful attention should be paid to the rate of wound healing during follow-up appointments because wounds that are healing slowly may have improved outcomes with excision of necrotic and granulation tissue with subsequent grafting.[80–82] At 10 days after burn injury, partial-thickness wounds without necrotic tissue that show evidence of squamous reepithelialization should heal within the month. Reepithelialization can be recognized by small opalescent islands of epithelium scattered across the wound. If these features are not seen, the partial-thickness wound may be a deeper injury that would benefit from surgery. The author tells patients, "If your burn heals in less than 2 weeks, it is better off without an operation. If it takes more than 3 weeks, it is better off with an operation."

PRURITUS

Itching is a common sequela of healing burn wounds and may persist after the wound has healed. Pruritus causes significant distress in burn patients, and resultant scratching may result in reopened wounds. Pruritus is more common in children, most frequently affects the lower extremities compared to the upper extremities, and rarely involves the

face.[83] Environmental triggers may bring on or exacerbate pruritus, including heat, physical activity, or stress. For most patients, the pruritus is worst immediately following wound healing and diminishes after healing is complete, sometimes lasting up to 18 months. In those with persistent itching, one should consider an ongoing psychosocial trigger.

Pruritus is a primary sensory modality that has multiple causative factors, such as the increased synthesis of histamine in burn wounds, as well as bradykinin and endopeptides.[84–86] Management of itching may include antihistamines, cool compresses, or lotions as needed. Most commonly, the initial treatment is diphenhydramine hydrochloride,[83] which also provides mild sedation that may be of benefit. Other antihistamines, such as cyproheptadine or hydroxyzine hydrochloride, may also be used as the physician feels appropriate. Analgesics may alter the perception of itching, and combinations of the two medications may be considered. Environmental treatments may include air conditioning, cool compresses, and loose fitting, soft cotton clothing. Other options include aloe vera, which is antiinflammatory and antimicrobial,[87] or skin moisturizing creams that are free of alcohol. Penicillin may even be used in the management of pruritus; Phillips and Robson[88] noted in a study of post-burn hypertrophic scars that these scars were more frequently colonized with β-hemolytic streptococcus, *Staphylococcus aureus*, and *S. epidermidis.* Because inflammation is a major source of pruritus, 250 mg of oral penicillin was given twice daily along with topical aloe vera to reduce itching. For further information on the treatment of pruritus in burns, see Chapter 63.

TRAUMATIC BLISTERS IN REEPITHELIALIZED WOUNDS

During reepithelialization, the thin epithelium may be easily damaged by itching or trauma brought about by, for example, movement, resulting in traumatic blisters that may rupture. As healing progresses, this epithelium will strengthen and traumatic blisters will stop occurring. Ruptured blisters can be left exposed to form a crust, or a light dressing may be applied.

REHABILITATIVE PHYSICAL CARE

Prior to discharge, plans for rehabilitative care should be made for the patient to ensure that there is access to this necessary part of burn treatment. Although burns treated in the community tend to be of smaller area, rehabilitation should still be utilized to preserve and restore both strength and function in the burned area.[89] The patient should also be instructed in range of motion and strength exercises to perform on his or her own.

Strength, range of motion, and function should be continually assessed at follow-up visits, and if there are compliance issues or worsening function, referral for physical and occupational therapy may be warranted. Depending on the location of the burn injury, supervised therapy might be indicated initially, such as in burns that cross joints or those that involve the hands or feet. When treating those with burns of the face, speech pathologists may need to be referred. Just as with patients treated in the hospital, outpatients should be monitored for hypertrophic scarring and contractures, as surgical intervention may be required.[89]

Outpatient Treatment of Moderate and Major Burns

Some patients with larger burns may be treated with outpatient care later in the course of their treatment.[90] Physicians may opt for this course due to the advantages of decreased costs and increased physical and emotional comfort for the patient, along with decreased exposure to drug-resistant organisms. Outpatient treatment may be appropriate for patients when intravenous fluid resuscitation has been completed, the patient is able to receive adequate nutrition enterally, pain is controlled, and there is no present wound or systemic infection. Should these conditions be met, the physician may opt to complete wound care and physical and occupational therapy in the ambulatory setting.

Conclusion

This chapter discussed the options for outpatient management of the burn patient. Depending on the expertise of the treating physician and the resources of the facility, some or all the options may be available. If the patient fails to meet criteria for referral to a burn center and does not require admission for another reason, outpatient management is appropriate, following these recommendations for immediate treatment:

- Wash the wound with soap and water.
- Dress with an appropriate dressing, as discussed earlier.
- Place the wound in Xeroform with a secondary dressing; having the patient follow-up in 24–48 hours is reasonable.
- If the Xeroform is adherent, it can be left in place and trimmed as it lifts off; if not, an alternate dressing should be considered.
- Another option is to use a silver-impregnated dressing.
- Depending on the dressing selected, the patient may follow-up in 3–7 days.
- If resources are available, daily to twice-daily wound cleansing and dressing changes may be utilized with follow-up in 1–3 days.
- Burns that do not heal in 2 weeks should be referred to a designated burn center for evaluation.

Complete references available online at www.expertconsult.inkling.com

References

1. Lund CC, Browder NC. The estimation of areas of burns. *Surg Gynecol Obstet*. 1944;79:352-358.
2. Rossiter ND, Chapman P, Haywood IA. How big is a hand? *Burns*. 1996;22(3):230-231.
3. Neaman KC, Andres LA, McClure AM, et al. A new method for estimation of involved BSAs for obese and normal-weight patients with burn injury. *J Burn Care Res*. 2011;32(3):421-428.
4. Livingston EH, Lee S. Percentage of burned body surface area determination in obese and nonobese patients. *J Surg Res*. 2000;91(2):106-210.
5. Gatti JE, LaRossa D, Silverman DG, Hartford CE. Evaluation of the burn wound with perfusion fluorometry. *J Trauma*. 1983;23(3):202-206.
6. deCamara DL, Raine TJ, London MD, Robson MC, Heggers JP. Progression of thermal injury: a morphologic study. *Plast Reconstr Surg*. 1982;69(3):491-499.
7. Hettiaratchy S, Dziewulski P. ABC of burns: pathophysiology and types of burns. *BMJ*. 2004;328(7453):1427-1429.
8. American Burn Association/American College of S. Guidelines for the operation of burn centers. *J Burn Care Res*. 2007;28(1):134-141.
9. Waymack JP, Pruitt BA Jr. Burn wound care. *Adv Surg*. 1990;23:261-389.
10. Arnoldo B, Klein M, Gibran NS. Practice guidelines for the management of electrical injuries. *J Burn Care Res*. 2006;27(4):439-447.
11. Curreri PW, Asch MJ, Pruitt BA. The treatment of chemical burns: specialized diagnostic, therapeutic, and prognostic considerations. *J Trauma*. 1970;10(8):634-642.
12. van Rensburg L. An experimental study of chemical burns. *S Afr Med J*. 1962;36:754-759.
13. Leonard LG, Scheulen JJ, Munster AM. Chemical burns: effect of prompt first aid. *J Trauma*. 1982;22(5):420-423.
14. Gruber RP, Laub DR, Vistnes LM. The effect of hydrotherapy on the clinical course and pH of experimental cutaneous chemical burns. *Plast Reconstr Surg*. 1975;55(2):200-204.
15. Dibbell DG, Iverson RE, Jones W, Laub DR, Madison MS. Hydrofluoric acid burns of the hand. *J Bone Joint Surg Am*. 1970;52(5):931-936.
16. Dalamaga M, Karmaniolas K, Nikolaidou A, Papadavid E. Hypocalcemia, hypomagnesemia, and hypokalemia following hydrofluoric acid chemical injury. *J Burn Care Res*. 2008;29(3):541-543.
17. Heimbach DM, Waeckerle JF. Inhalation injuries. *Ann Emerg Med*. 1988;17(12):1316-1320.
18. Thompson PB, Herndon DN, Traber DL, Abston S. Effect on mortality of inhalation injury. *J Trauma*. 1986;26(2):163-165.
19. McManus WF, Pruitt BA Jr. Thermal injuries. In: Mattox KL, Moore EE, Feliciano DV, eds. *Trauma*. Norwalk, CT: Appleton & Lange; 1988:675-689.
20. Blomgren I, Eriksson E, Bagge U. The effect of different cooling temperatures and immersion fluids on post-burn oedema and survival of the partially scalded hairy mouse ear. *Burns Incl Therm Inj*. 1985;11(3):161-165.
21. Jandera V, Hudson DA, de Wet PM, Innes PM, Rode H. Cooling the burn wound: evaluation of different modalites. *Burns*. 2000;26(3):265-270.
22. Saranto JR, Rubayi S, Zawacki BE. Blisters, cooling, antithromboxanes, and healing in experimental zone-of-stasis burns. *J Trauma*. 1983;23(10):927-933.
23. Moritz AR, Henriques FC. Studies of thermal injury: II. The relative importance of time and surface temperature in the causation of cutaneous burns. *Am J Pathol*. 1947;23(5):695-720.
24. Rajan V, Bartlett N, Harvey JG, et al. Delayed cooling of an acute scald contact burn injury in a porcine model: is it worthwhile? *J Burn Care Res*. 2009;30(4):729-734.
25. Sawada Y, Urushidate S, Yotsuyanagi T, Ishita K. Is prolonged and excessive cooling of a scalded wound effective? *Burns*. 1997;23(1):55-58.
26. King TC, Zimmerman JM. First-aid cooling of the fresh burn. *Surg Gynecol Obstet*. 1965;120:1271-1273.
27. Ofeigsson OJ. Water cooling: first-aid treatment for scalds and burns. *Surgery*. 1965;57:391-400.
28. Purdue GF, Layton TR, Copeland CE. Cold injury complicating burn therapy. *J Trauma*. 1985;25(2):167-168.
29. Pushkar NS, Sandorminsky BP. Cold treatment of burns. *Burns Incl Therm Inj*. 1982;9(2):101-110.
30. Wood FM, Phillips M, Jovic T, et al. Water first aid is beneficial in humans post-burn: evidence from a bi-national cohort study. *PLoS ONE*. 2016;11(1):e0147259.
31. Osgood PF, Szyfelbein SK. Management of burn pain in children. *Pediatr Clin North Am*. 1989;36(4):1001-1013.
32. Swain AH, Azadian BS, Wakeley CJ, Shakespeare PG. Management of blisters in minor burns. *Br Med J (Clin Res Ed)*. 1987;295(6591):181.
33. Rockwell WB, Ehrlich HP. Should burn blister fluid be evacuated? *J Burn Care Rehabil*. 1990;11(1):93-95.
34. Demling RH, LaLonde C. Burn trauma. In: Blaisdell FW, Trunkey DD, eds. *Trauma Management*. IV. New York: Thieme Medical; 1989:55-56.
35. Stratta RJ, Saffle JR, Kravitz M, Warden GD. Management of tar and asphalt injuries. *Am J Surg*. 1983;146(6):766-769.
36. Ashbell TS, Crawford HH, Adamson JE, Horton CE. Tar and grease removal from injured parts. *Plast Reconstr Surg*. 1967;40(4):330-331.
37. Demling RH, Buerstatte WR, Perea A. Management of hot tar burns. *J Trauma*. 1980;20(3):242.
38. Carta T, Gawaziuk J, Liu S, Logsetty S. Use of mineral oil Fleet enema for the removal of a large tar burn: a case report. *Burns*. 2015;41(2):e11-e14.
39. Hartford CE. The bequests of Moncrief and Moyer: an appraisal of topical therapy of burns – 1981 American Burn Association Presidential Address. *J Trauma*. 1981;21(10):827-834.
40. Barajas-Nava LA, Lopez-Alcalde J, Roque i Figuls M, Sola I, Bonfill Cosp X. Antibiotic prophylaxis for preventing burn wound infection. *Cochrane Database Syst Rev*. 2013;(6):CD008738.
41. Heinrich JJ, Brand DA, Cuono CB. The role of topical treatment as a determinant of infection in outpatient burns. *J Burn Care Rehabil*. 1988;9(3):253-257.
42. Barret JP, Dziewulski P, Ramzy PI, et al. Biobrane versus 1% silver sulfadiazine in second-degree pediatric burns. *Plast Reconstr Surg*. 2000;105(1):62-65.
43. Hansbrough JF, Achauer B, Dawson J, et al. Wound healing in partial-thickness burn wounds treated with collagenase ointment versus silver sulfadiazine cream. *J Burn Care Rehabil*. 1995;16(3 Pt 1):241-247.
44. Muller MJ, Hollyoak MA, Moaveni Z, et al. Retardation of wound healing by silver sulfadiazine is reversed by aloe vera and nystatin. *Burns*. 2003;29(8):834-836.
45. Hernigou P. Ambroise Paré's life (1510–1590): part I. *Int Orthop*. 2013;37(3):543-547.
46. White R, Morris C. Mepitel: a non-adherent wound dressing with Safetac technology. *Br J Nurs*. 2009;18(1):58-64.
47. Bugmann P, Taylor S, Gyger D, et al. A silicone-coated nylon dressing reduces healing time in burned paediatric patients in comparison with standard sulfadiazine treatment: a prospective randomized trial. *Burns*. 1998;24(7):609-612.
48. Tang H, Lu G, Fu J, et al. An open, parallel, randomized, comparative, multicenter investigation evaluating the efficacy and tolerability of Mepilex Ag versus silver sulfadiazine in the treatment of deep partial-thickness burn injuries. *J Trauma Acute Care Surg*. 2015;78(5):1000-1007.
49. Huang Y, Li X, Liao Z, et al. A randomized comparative trial between Acticoat and SD-Ag in the treatment of residual burn wounds, including safety analysis. *Burns*. 2007;33(2):161-166.
50. Cuttle L, Naidu S, Mill J, et al. A retrospective cohort study of Acticoat versus Silvazine in a paediatric population. *Burns*. 2007;33(6):701-707.
51. Friedman SG. Use of a new antimicrobial dressing (TheraBond) on a non-healing wound. *Wounds*. 2011;23(2):E1-E3.
52. Barillo DJ, Pozza M, Margaret-Brandt M. A literature review of the military uses of silver-nylon dressings with emphasis on wartime operations. *Burns*. 2014;40(suppl 1):S24-S29.
53. Highton L, Wallace C, Shah M. Use of Suprathel® for partial thickness burns in children. *Burns*. 2013;39(1):136-141.
54. Rahmanian-Schwarz A, Beiderwieden A, Willkomm LM, et al. A clinical evaluation of Biobrane® and Suprathel® in acute burns and reconstructive surgery. *Burns*. 2011;37(8):1343-1348.
55. Schwarze H, Kuntscher M, Uhlig C, et al. Suprathel, a new skin substitute, in the management of partial-thickness burn wounds: results of a clinical study. *Ann Plast Surg*. 2008;60(2):181-185.
56. Schwarze H, Kuntscher M, Uhlig C, et al. Suprathel, a new skin substitute, in the management of donor sites of split-thickness skin grafts: results of a clinical study. *Burns*. 2007;33(7):850-854.
57. Hermans MH. HydroColloid dressing (Duoderm) for the treatment of superficial and deep partial thickness burns. *Scand J Plast Reconstr Surg Hand Surg*. 1987;21(3):283-285.

58. Wyatt D, McGowan DN, Najarian MP. Comparison of a hydrocolloid dressing and silver sulfadiazine cream in the outpatient management of second-degree burns. *J Trauma*. 1990;30(7):857-865.
59. Tavis MJ, Thornton JW, Bartlett RH, Roth JC, Woodroof EA. A new composite skin prosthesis. *Burns*. 1980;7(2):123-130.
60. Gerding RL, Emerman CL, Effron D, et al. Outpatient management of partial-thickness burns: Biobrane versus 1% silver sulfadiazine. *Ann Emerg Med*. 1990;19(2):121-124.
61. Rejzek A, Weyer F, Eichberger R, Gebhart W. Physical changes of amniotic membranes through glycerolization for the use as an epidermal substitute. Light and electron microscopic studies. *Cell Tissue Bank*. 2001;2(2):95-102.
62. Kesting MR, Wolff KD, Hohlweg-Majert B, Steinstraesser L. The role of allogenic amniotic membrane in burn treatment. *J Burn Care Res*. 2008;29(6):907-916.
63. Maral T, Borman H, Arslan H, et al. Effectiveness of human amnion preserved long-term in glycerol as a temporary biological dressing. *Burns*. 1999;25(7):625-635.
64. *AATB Standards for Tissue Banking*. 14th ed. McLean, VA: American Association of Tissue Banks; 2016.
65. Branski LK, Herndon DN, Celis MM, et al. Amnion in the treatment of pediatric partial-thickness facial burns. *Burns*. 2008;34(3):393-399.
66. Ninman C, Shoemaker P. Human amniotic membranes for burns. *Am J Nurs*. 1975;75(9):1468-1469.
67. Quinby WC Jr, Hoover HC, Scheflan M, et al. Clinical trials of amniotic membranes in burn wound care. *Plast Reconstr Surg*. 1982;70(6):711-717.
68. Robson MC, Krizek TJ. The effect of human amniotic membranes on the bacteria population of infected rat burns. *Ann Surg*. 1973;177(2):144-149.
69. Robson MC, Krizek TJ, Koss N, Samburg JL. Amniotic membranes as a temporary wound dressing. *Surg Gynecol Obstet*. 1973;136(6):904-906.
70. Salisbury RE, Carnes R, McCarthy LR. Comparison of the bacterial clearing effects of different biologic dressings on granulating wounds following thermal injury. *Plast Reconstr Surg*. 1980;66(4):596-598.
71. Atiyeh BS, Hayek SN, Gunn SW. New technologies for burn wound closure and healing–review of the literature. *Burns*. 2005;31(8):944-956.
72. Bukovcan P, Koller J. Treatment of partial-thickness scalds by skin xenografts–a retrospective study of 109 cases in a three-year period. *Acta Chir Plast*. 2010;52(1):7-12.
73. Burkey B, Davis W 3rd, Glat PM. Porcine xenograft treatment of superficial partial-thickness burns in paediatric patients. *J Wound Care*. 2016;25(2):S10-S15.
74. Hermans MH. Porcine xenografts vs. (cryopreserved) allografts in the management of partial thickness burns: is there a clinical difference? *Burns*. 2014;40(3):408-415.
75. Durtschi MB, Orgain C, Counts GW, Heimbach DM. A prospective study of prophylactic penicillin in acutely burned hospitalized patients. *J Trauma*. 1982;22(1):11-14.
76. Pruitt BA Jr. The diagnosis and treatment of infection in the burn patient. *Burns Incl Therm Inj*. 1984;11(2):79-91.
77. Larkin JM, Moylan JA. Tetanus following a minor burn. *J Trauma*. 1975;15(6):546-548.
78. Ross SE. Prophylaxis against tetanus in wound management; 1995. Available from: https://www.facs.org/~/media/files/quality%20programs/trauma/publications/tetanus.ashx.
79. Deitch EA, Wheelahan TM, Rose MP, Clothier J, Cotter J. Hypertrophic burn scars: analysis of variables. *J Trauma*. 1983;23(10):895-898.
80. Burke JF, Bondoc CC, Quinby WC Jr, Remensnyder JP. Primary surgical management of the deeply burned hand. *J Trauma*. 1976;16(08):593-598.
81. Engrav LH, Heimbach DM, Reus JL, Harnar TJ, Marvin JA. Early excision and grafting vs. nonoperative treatment of burns of indeterminant depth: a randomized prospective study. *J Trauma*. 1983;23(11):1001-1004.
82. Janzekovic Z. A new concept in the early excision and immediate grafting of burns. *J Trauma*. 1970;10(12):1103-1108.
83. Bell L, McAdams T, Morgan R, et al. Pruritus in burns: a descriptive study. *J Burn Care Rehabil*. 1988;9(3):305-308.
84. Herndon JH Jr. Itching: the pathophysiology of pruritus. *Int J Dermatol*. 1975;14(7):465-484.
85. Kahlson G, Rosengren E. New approaches to the physiology of histamine. *Physiol Rev*. 1968;48(1):155-196.
86. Keele CA, Armstrong D. *Substances Producing Pain and Itch*. London: Edward Arnold Ttd; 1964:297-298.
87. Heimbach DM, Engrav LH, Marvin J. Minor burns: guidelines for successful outpatient management. *Postgrad Med*. 1981;69(5):22-26, 8–32.
88. Phillips LG, Robson MC. Pruritus in burns. Comments from Detroit Receiving Hospital, Detroit, Michigan. *J Burn Care Rehabil*. 1988;9(3):308-309.
89. Helm PA, Kevorkian CG, Lushbaugh M, et al. Burn injury: rehabilitation management in 1982. *Arch Phys Med Rehabil*. 1982;63(1):6-16.
90. Warden GD, Kravitz M, Schnebly A. The outpatient management of moderate and major thermal injury. *J Burn Care Rehabil*. 1981;2:159-160.

7 Prehospital Management, Transportation, and Emergency Care

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Introduction

Advances in trauma and burn management over the past three decades have resulted in improved survival and reduced morbidity from major burns. The cost of such care, however, is high; it requires conservation of resources such that only a limited number of burn intensive care units with the capabilities of caring for such labor-intensive patients can be found; hence, regional burn care has evolved. This regionalization has led to the need for effective prehospital management, transportation, and emergency care. Progress in the development of rapid, effective transport systems has resulted in marked improvement in the clinical course and survival for victims of thermal trauma.

For burn victims, there are usually two phases of transport. The first is the entry of the burn patient into the emergency medical system with treatment at the scene and transport to the initial care facility. The second phase is the assessment and stabilization of the patient at the initial care facility and transportation to the burn intensive care unit.[1] With this perspective in mind, this chapter reviews current principles of optimal prehospital management, transportation, and emergency care.

Prehospital Care

Immediate burn care by first responders is important and can vastly alter outcomes, and it can significantly limit burn progression and depth. The goal of prehospital care should be to ease the burning process as well as prevent further complications and secondary injuries from burn shock. Identifying burn patients appropriately for immediate transfer is an important step in reducing the morbidity and mortality.[2] Prior to any specific treatment, a patient must be removed from the source of injury and the burning process stopped. As the patient is removed from the injuring source, care must be taken so that a rescuer does not become another victim.[3] All caregivers should be aware of the possibility that they may be injured by contact with the patient or the patient's clothing. Universal precautions, including wearing gloves, gowns, masks, and protective eye wear, should be used whenever there is likely contact with blood or body fluids. Burning clothing should be removed as soon as possible to prevent further injury.[4] It has been shown that prompt removal of clothing after scald injuries may reduce postburn morbidity.[5] All rings, watches, jewelry, and belts should be removed because they can retain heat and produce a tourniquet-like effect with digital vascular ischemia.[5] If water is readily available, it should be poured directly on the burned area. Early cooling can reduce the depth of the burn and reduce pain, but cooling measures must be used with caution since a significant drop in body temperature may result in hypothermia with ventricular fibrillation or asystole.[6] Cold water treatment over large body surfaces has been shown to trigger clinically relevant hypothermia.[6] Ice or ice packs should never be used because they may cause further injury to the skin or produce hypothermia.

Initial management of chemical burns involves removing saturated clothing, brushing the skin if the agent is a powder, and irrigation with copious amounts of water, taking care not to spread chemical on burns to adjacent unburned areas. Irrigation with water should continue from the scene of the accident through emergency evaluation in the hospital. Efforts to neutralize chemicals are contraindicated due to the additional generation of heat, which would further contribute to tissue damage. A rescuer must be careful not to come in contact with the chemical (i.e., gloves, eye protectors, etc. should be worn).

Removal of a victim from an electrical current is best accomplished by turning off the current and by using a nonconductor to separate the victim from the source.[7]

Onsite Assessment of a Burned Patient

Assessment of a burned patient is divided into primary and secondary surveys. In the primary survey, immediate life-threatening conditions are quickly identified and treated. The primary survey is a rapid, systematic approach to identify life-threatening conditions. The secondary survey is a more thorough head-to-toe evaluation of the patient. Initial management of a burned patient should be the same as for any other trauma patient, with attention directed at airway, breathing, circulation, and cervical spine immobilization.

PRIMARY ASSESSMENT

Exposure to heated gases and smoke from the combustion of a variety of materials results in damage to the respiratory tract. Direct heat to the upper airways results in edema

formation, which may obstruct the airway. Initially, 100% humidified oxygen should be given to all patients when no obvious signs of respiratory distress are present. Upper airway obstruction may develop rapidly following injury, and the respiratory status must be continually monitored in order to assess the need for airway control and ventilator support. Progressive hoarseness is a sign of impending airway obstruction. Endotracheal intubation should be done early before edema obliterates the anatomy of the area. Intubation should be performed by the most experienced provider.[4,8]

The patient's chest should be exposed in order to adequately assess ventilatory exchange. Circumferential burns may restrict breathing and chest movement. Airway patency alone does not assure adequate ventilation. After an airway is established, breathing must be assessed in order to ensure adequate chest expansion. Impaired ventilation and poor oxygenation may be due to smoke inhalation or carbon monoxide intoxication. Endotracheal intubation is necessary for unconscious patients, for those in acute respiratory distress, or for patients with burns of the face or neck that may result in edema, which causes obstruction of the airway.[4,8] The nasal route is the recommended site of intubation. Assisted ventilation with 100% humidified oxygen is required for all intubated patients.

Blood pressure is not the most accurate method of monitoring a patient with a large burn because of the pathophysiologic changes that accompany such an injury. Blood pressure may be difficult to ascertain because of edema in the extremities. A pulse rate may be somewhat more helpful in monitoring the appropriateness of fluid resuscitation.[9]

If a burn victim was in an explosion or deceleration accident, there is the possibility of a spinal cord injury. Appropriate cervical spine stabilization must be accomplished by whatever means necessary, including a cervical collar to keep the head immobilized until the condition can be evaluated.

SECONDARY ASSESSMENT

After completing a primary assessment, a thorough head-to-toe evaluation of the patient is imperative.[10] A careful determination of trauma other than obvious burn wounds should be made. As long as no immediate life-threatening injury or hazard is present, a secondary examination can be performed before moving the patient; precautions such as cervical collars, backboards, and splints should be used.[11] Secondary assessment should examine the patient's past medical history, medications, allergies, and the mechanisms of injury. Any suspicion of nonaccidental injury should lead to immediate admission of a child to the hospital, irrespective of how trivial the burn injury is, and notification of social services.[12]

There should never be a delay in transporting burn victims to an emergency facility due to an inability to establish intravenous (IV) access. If the local/regional emergency medical system (EMS) protocol prescribes that an IV line is started, then that protocol should be followed. The American Burn Association recommends that if a patient is less than 60 min from a hospital, an IV is not essential and can be deferred until a patient is at the hospital. If an IV line is established, Ringer's lactate (LR) solution should be infused at the following rates:

- 14 years and older: 500 mL/h
- 6–13 years old: 250 mL/h
- 5 years and younger: 125 mL/h

Prehospital care of wounds is basic and simple because it requires only protection from the environment with an application of a clean dressing or sheet to cover the involved part. Covering wounds is the first step in diminishing pain. If it is approved for use by local/regional EMS, narcotics may be given for pain, but only intravenously in small doses and only enough to control pain.[13] It has been shown that despite training of medical staff, provision for analgesia for children with burns is lacking and needs further clarification.[14] Intramuscular (IM) or subcutaneous routes should never be used because fluid resuscitation could result in unpredictable patterns of uptake.[5] No topical antimicrobial agents should be applied in the field.[5,15] The patient should then be wrapped in a clean sheet and blanket to minimize heat loss and to control temperature during transport.

Transport to Hospital Emergency Department

Rapid, uncontrolled transport of a burn victim is not the highest priority, except in cases where other life-threatening conditions coexist. In the majority of accidents involving major burns, ground transportation of victims to a hospital is available and appropriate. Helicopter transport is of greatest use when the distance between an accident and a hospital is 30–150 miles or when a patient's condition warrants.[15] Whatever the mode of transport, it should be of appropriate size and have emergency equipment available as well as trained personnel, such as a nurse, physician, paramedic, or respiratory therapist.

An estimate of burn size and depth assists in making a determination of severity, prognosis, and disposition of a patient. Burn size directly affects fluid resuscitation, nutritional support, and surgical interventions. The size of a burn wound is most frequently estimated by using the rule-of-nines method (Fig. 7.1). The American Burn Association identifies certain injuries as usually requiring a referral to a burn center. Patients with these burns should be treated in a specialized burn facility after initial assessment and treatment at an emergency department. Questions about specific patients should be resolved by consultation with a burn center physician (Box 7.1).[4,16]

Keeping the Patient Warm and Dry

Hypothermia is detrimental to traumatized patients and can be avoided or at least minimized by the use of sheets and blankets. Wet dressings should be avoided.

Pain Control

The degree of pain experienced initially by the burn victim is inversely proportional to the severity of the injury.[11] No medication for pain relief should be given intramuscularly or subcutaneously. For mild pain, acetaminophen 650 mg orally every 4–6 hours may be given. For severe pain, morphine, 1–4 mg intravenously every 2–4 hours, is the drug

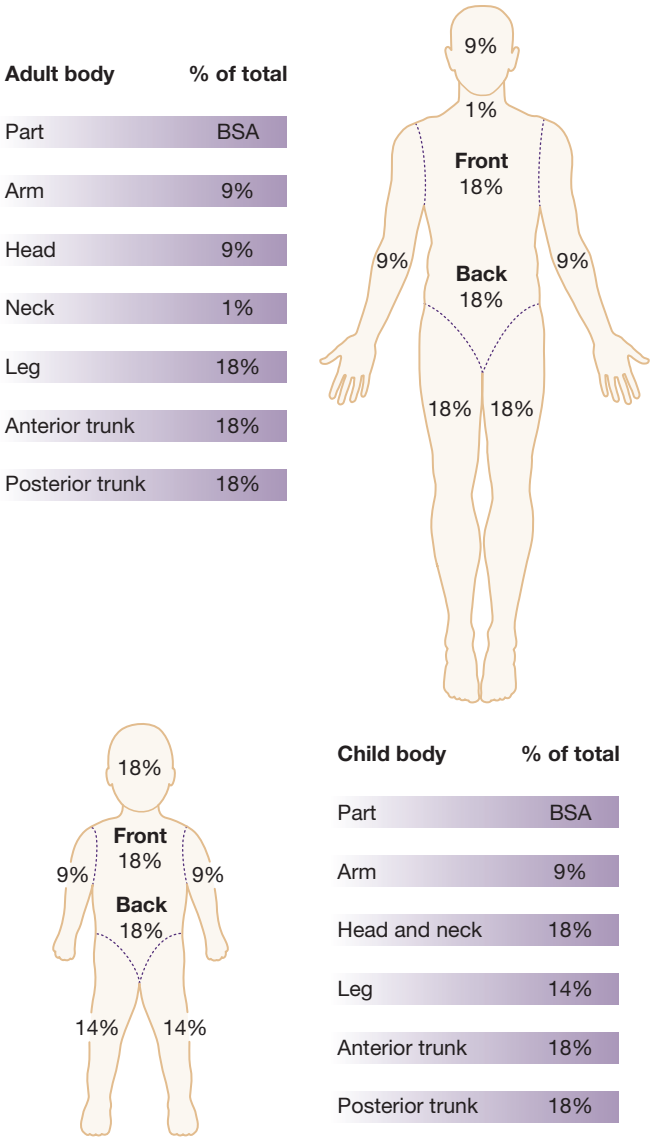

Fig. 7.1 Estimation of burn size using the rule-of-nines. (From American Burn Association. *Advanced Burn Life Support Providers Manual*. Chicago, IL: American Burn Association; 2011)

Box 7.1 Criteria for Transfer of a Burn Patient to a Burn Center

- Second-degree burns >10% total body surface area (TBSA)
- Third-degree burns
- Burns that involve the face, hands, feet, genitalia, perineum, and major joints
- Chemical burns
- Electrical burns including lightning injuries
- Any burn with concomitant trauma in which the burn injuries pose the greatest risk to the patient
- Inhalation injury
- Patients with pre-existing medical disorders that could complicate management, prolong recovery, or affect mortality
- Hospitals without qualified personnel or equipment for the care of critically burned children

From American Burn Association. Advanced Burn Life Supporters Manual. *Chicago, IL: American Burn Association; 2011.*

of choice, although meperidine (Demerol) 10–40 mg by IV push every 2–4 hours may be used.[5] Recommendations for tetanus prophylaxis are based on the patient's immunization history. All patients with burns should receive 0.5 mL of tetanus toxoid. If prior immunization is absent or unclear, or if the last booster was more than 10 years ago, 250 units of tetanus immunoglobulin is also given.[5]

Transferring a Burn Patient

The appearance of burned skin is rather obvious and has the potential to mask or cover any other potential injuries that the burn patient could have. The burn patient is a trauma patient with burns and should be promptly and effectively evaluated to include other potential injuries. It is important to establish effective communication between the transferring unit and the receiving center. The American Burn Association has referral guidelines that identify those patients needing to be transferred to a burn center.[7,16]

Once the need to transfer the patient is identified, the transferring process begins. The doctor-to-doctor referral process starts with the initial care facility. Available phone numbers and doctor information should be available to centers, and the center should promptly call and ask for all the information needed for the transfer.

The referring physician should give a brief and concise history of the event that includes the time of injury and all resuscitation efforts prior to the call. The ABCs of trauma resuscitation should be discussed and the most current vital signs and physical examination findings should be presented. The accepting facility should then fill out an intake form that details all the information. Understanding the patient's current status is essential for a successful and uneventful transfer. It is imperative that physicians participate in the process by adding to the already available information gathered by other personnel.

Transferring a patient without the needed information can potentially lead to bad outcomes and/or unnecessary expense. For example, a burn patient with an underlying anoxic brain injury could be transferred to a burn center when instead the diagnosis of brain death could have been made at the initial care facility.

Physicians can access patient information utilizing different technologies. Although a doctor-to-doctor phone call is preferred by many, today's technology allows patient data, including pictures and laboratory results as well as any other clinical information needed to further assess the patient's needs, to be transferred.[17] While some physicians still prefer the immediacy of the telephone, secure electronic messaging tools are beginning to supplement phone calls and beepers to facilitate communication among physicians.[7,18]

Privacy and Security Issues

Perhaps the most fundamental choice physicians must make when selecting tools to communicate electronically with each other and with patients is how they will manage the privacy and security of the information exchanged.

The Health Insurance Portability and Accountability Act (HIPAA) is technology neutral, in that it does not require any set form of encryption or information safeguarding. It is also scalable, in that it allows small practices to do what they can afford to do without requiring them to purchase expensive communication security systems.[17,19]

For electronic communications, the physician should have an informed consent form signed by each patient specific to the form of communication being used, such as e-mail. The form should verify the patient's e-mail address; should discuss the security risks involved (e.g., that other parties on the patient's end might have access to their e-mail accounts and that standard [unencrypted, nonsecure] e-mail can be intercepted by unintended parties); should discuss allowable content of the communication; and should include a provision to hold the physician harmless if security is breached.

While there is no private right of action under the HIPAA (i.e., a patient cannot sue physicians for breach of HIPAA's privacy or security provisions), the federal agencies that oversee the HIPAA have recently announced plans to step up their audits, and they could conduct an inquiry if a patient files a complaint. Although federal investigations seem more likely to focus on hospitals than physician offices, carelessness could also have legal repercussions. For example, information could be sent to the wrong recipient because of failure to verify the address field before sending the message. Physicians using standard e-mail should use as many practical safeguards as possible to minimize liability exposure. This could include a privacy and security disclaimer footer on each e-mail, requesting the patient's permission before continuing to respond to certain issues by e-mail, limiting the amount of medical detail in the messages, and password-protecting e-mail access on office and home workstations, as well as on portable devices such as PDAs and Blackberries, in case they are lost.

Another way to alleviate security or HIPAA compliance concerns is to leave out protected health information (PHI) in standard e-mail: data that both personally identifies a patient and reveals a specific diagnosis or condition. While standard e-mail works and is offered free of charge by service providers such as Yahoo, Gmail, Comcast, and many others, vendors of secure messaging networks are quick to point out multiple deficiencies (Box 7.2).

Box 7.2 Deficiencies of Electronic Mail Services for the Transmission of Medical Information

- Lack of encryption or authentication
- Can be used by anyone to access a physician if they simply know the physician's e-mail address
- Have no "terms of service" or legal disclaimers to protect physicians
- Can easily expose patient e-mail addresses and identities to unintended third parties
- Can breach patient privacy by using employer e-mail networks
- Offer no charge capture function
- Have no template or medical records features
- Lack of consistency with HIPAA or medical liability insurance company standards

Whether or not electronic communication is encrypted or secure, physicians should guard against being lulled by the casual nature of e-mail which, unlike a conversation or phone call, is not erased from a computer's hard drive when deleted and is potentially discoverable in litigation.

In the future, the use of telemedicine may allow more accurate and timely access to critical information that may adjunct the care given during the golden hour of trauma care. In the absence of a skilled burn specialist, the use of telemedicine services can expedite the process and aid in the treatment plan. Telemedicine has already gained acceptance and support from many public funding projects. It is considered user-friendly, almost infinitely adaptable, and cost effective.[20]

Transportation Guidelines

The primary purpose of any transport teams is not to bring a patient to an intensive care unit but to bring that level of care to the patient as soon as possible. Therefore, the critical time involved in a transport scenario is the time it takes to get the team to the patient. The time involved in transporting a patient back to a burn center becomes secondary. Communication and teamwork are the keynotes to an effective transport system.

When transportation is required from a referring facility to a specialized burn center, a patient can be fairly well stabilized before being moved. Initially, the referring facility should be informed that all patient referrals require physician-to-physician discussion. Pertinent information needed includes patient demographic data, time, date, cause and extent of burn injury, weight and height, baseline vital signs, neurological status, laboratory data, respiratory status, previous medical and surgical history, and allergies.

A referring hospital is informed of specific treatment protocols regarding patient management prior to transfer. To ensure patient stability, the following guidelines are offered:

- Establish two IV sites, preferably in an unburned upper extremity, and secure IV tubes with sutures.
- Insert a Foley catheter and monitor for acceptable urine output (30 mL/h adult; 1 mL/kg/h child.
- Insert a nasogastric tube and ensure that the patient remains NPO.
- Maintain body temperature between 38°C and 39.0°C (taken rectally).
- Stop all narcotics.
- For burns less than 24 hours old, only use LR solution. The staff physician will advise on the infusion rate, which is calculated based on the percentage of total body surface area burned.

Following physician-to-physician contact and collection of all pertinent information, the physicians will make recommendations regarding an appropriate mode of transportation. The options are based on distance to a referring unit, patient complexity, and comprehensiveness of medical care required. Options include:

- Full medical intensive care unit transport with a complete team consisting of a physician, a nurse, and a respiratory therapist from the burn facility

- Medical intensive care transport via fixed wing aircraft or helicopter with a team from the referring facility
- Private plane with medical personnel to attend patient
- Commercial airline
- Private ground ambulance
- Transport van with appropriate personnel.

TRANSPORT TEAM COMPOSITION

Because stabilization and care for a burned patient is so specialized, team selection is of the utmost importance. Traditionally, these patients were placed in an ambulance with an emergency medical technician and transported with little effort made to stabilize the patient prior to transfer. As levels of care and technology have evolved, the need for specialized transport personnel has increased. Today most transport teams are made up of one or more of the following healthcare members: a registered nurse, a respiratory therapist, and/or a staff physician or house resident. Because a large number of burned patients require some type of respiratory support due to inhalation injury or carbon monoxide intoxication, the respiratory therapist and nurse team have proved to be an effective combination. The background and training of nurses and therapists differ in many ways, so such a team provides a larger scope of knowledge and experience when both are utilized. Team members ideally should be cross-trained so that each member can function at the other's level of expertise.

TRAINING AND SELECTION

Because the transport team will work in a high-stress environment, often with life-or-death consequences, these individuals must be carefully selected. The selection process should involve interviews with a nursing administrator, a director of respiratory therapy, and a medical director of a transport program.

Minimum requirements for transport team members should include:

- Transport nurse qualifications:
  - a registered nurse;
  - minimum of 6 months burn care experience;
  - current cardiopulmonary resuscitation (CPR) certification;
  - advanced cardiac life support (ACLS) or pediatric advanced life support (PALS) certification;
  - ability to demonstrate clinical competency;
  - observation of two transports;
  - a valid passport for international response.
- Transport respiratory therapist qualifications:
  - registered respiratory therapist with 6 months burn care experience;
  - licensed by appropriate regulatory agency as a respiratory care practitioner;
  - have current BLS;
  - ACLS or PALS certification;
  - ability to demonstrate clinical competency;
  - observation of two transports;
  - demonstrate a working knowledge of transport equipment;
  - a valid passport for international response.

Because all the care rendered by a transport team outside a hospital is given as an extension of care from a transporting/receiving facility, specific steps must be taken to protect staff and physicians from medical liability and to provide consistent care for all patients. Strict protocols are used to guide all patient care; team members should be in constant communication with an attending physician regarding a patient's condition and the interventions to be considered. Team members must be proficient in a number of procedures that may be needed during transport or while stabilizing a patient prior to transport. To keep up with current technology and changes, team members should be included in discussions of recent transports and current management techniques so that they can discuss patient care issues, receive ongoing in-service education, and participate in a review of the quality of transports.

MODES OF TRANSPORTATION

Once the need for transport of a burned patient is established, the decision must be made concerning what type of transportation vehicle is to be used (Table 7.1). There are two models of transport commonly used: ground (ambulance/transport vehicle), air (helicopter, fixed wing), or a combination of both. Factors to be considered when selecting a mode of transportation are the condition of the patient and the distance involved. The level of the severity of the burn mandates the speed with which the team must arrive in order to stabilize and transport a patient.

Ground Transport

Ground transport should be considered to cover distances of 70 miles or less; however sometimes a patient's condition may require air transport, particularly helicopter transport, even though the distance is within the 70-mile range. The ground transport vehicle should be modified with special equipment needed for intensive care transport, and there must be enough room to comfortably seat team members and hold equipment.

Air Transport

Air transport is used primarily when long distances or the critical nature of an injury separate a team from a patient. Air transport does, however, present its own unique set of problems. Aviation physiology is a specialty unto itself, and the gas laws play an important role in air transport and must be taken into consideration.

Dalton's law states that, in a mixture of gases, the total pressure exerted by the mixture is equal to the sum of the pressures each would exert alone.[21] This is important when changing a patient's altitude because as altitude increases, barometric pressure decreases. The percentage of nitrogen, oxygen, and carbon dioxide remain the same, but the partial pressures exert change.[22]

Altitude is an important factor in the oxygenation of a transported patient, and constant monitoring by a team is required under such circumstances. Boyle's law states that the volume of gas is inversely proportional to the pressure to which it is subject at a constant temperature. This gas law significantly affects patients with air leaks and free air in the abdomen because, as altitude increases, the volume of air in closed cavities also increases.[23] For this reason, all

Table 7.1 Transport Criteria: Mode and Team Composition, Burns ≤6 Days Postburn

Weight (kg)	% Burn	Distance (miles)	Team[a]	Transport Mode
≤3	Any	≤75	C	Van, helicopter
		76–250	C	Turboprop airplane
		≥251	C	Learjet
3.1–20	≤10	≤75	N-RT	Van, helicopter
		76–500	N-RT	Commercial flight or turboprop airplane
		≥501	N-RT	Commercial airplane or Learjet
	>10	≤75	C	Van, helicopter
		76–250	C	Turboprop airplane
		≥251	C	Learjet
≥20	≤20	≤75	N	Commercial flight or turboprop airplane
		76–500	N-RT	
		≥501	N-RT	Commercial airplane or Learjet
	>20	≤75	N	Van, helicopter
		76–500	C	Turboprop plane
		≥501	C	Jet

If any of the following criteria exist, the transport shall be changed to the fastest mode with a complete team:

- depressed mental status;
- drug depression;
- respiratory support;
- unstable cardiovascular system;
- presence of associated diseases;
- decreased urine output/unresponsiveness to appropriate fluid administration;
- absent or marginal venous access;
- hypothermia unresponsive to corrective measures.

[a]C, complete team (doctor, nurse, respiratory therapist); N, nurse; RT, respiratory therapist.

air that can be reached should be evacuated prior to an increase in altitude. Intrathoracic air and gastric air must be removed via functional chest tubes or nasogastric tubes and periodically checked during transport. Other factors that should be considered during air transport are reduced cabin pressure, turbulence, noise and vibration, changes in barometric pressure, and acceleration/deceleration forces. Physiologic changes that affect a patient and team members include middle ear dysfunction, pressure-related problems with sinuses, air expansion in a gastrointestinal tract, and motion sickness. Utilizing transport vehicles that have pressurized cabins can reduce or eliminate most of these problems.[21–23]

Helicopters and Fixed-Wing Aircraft. Helicopters and fixed-wing aircraft have both advantages and disadvantages related to patient care. Helicopters are widely used for short-distance medical air transport. Medical helicopters, because they are usually based on hospital premises, have no need to use airport facilities or ambulance services and therefore reduce team response time. Helicopters are able to land close to a referring hospital. Additionally, helicopters provide ease in loading and unloading patients and equipment.[24] The disadvantages of helicopter transport include its limited range, usually less than 150 miles,[24] and its nonpressurized cabin, which limits the altitude at which patients can be safely carried. The low-altitude capabilities also subject the aircraft to variability in weather (i.e., fog, rain, and reduced visibility); therefore, helicopter flights experience much more interference due to weather. Other disadvantages include noise, vibrations, reduced air speed, small working space, lower weight accommodation, and high maintenance requirements.[24]

When long distances must be traveled (more than 150 miles) or when increased altitude is necessary, fixed-wing aircraft are considered a viable mode of transport for patients. The advantages of using fixed-wing aircraft include long-range capabilities, increased speed, ability to fly in most weather conditions, control of cabin pressure and temperature, larger cabin space, and more liberal weight restrictions. Disadvantages of fixed-wing aircraft include the need for an airport with adequate runway length, difficulty in loading and unloading patients and equipment, and the pressure of air turbulence and noise.

EQUIPMENT

Because medical equipment used in intensive care units has evolved tremendously in the past 10 years, there is no reason that these advances should not be extended to the equipment used in a transport program. The transport team must be able to provide ICU-level care whenever needed. Most hospitals are well stocked and able to provide necessary supplies for initial patient stabilization and resuscitation; however, specialty items relating to the care of burn patients may not be present or adequate to meet the needs of burn victims. It is imperative that adequate equipment be available to handle any situation that may arise during a transport process (Fig. 7.2). Extra battery packs and electrical converters on fixed-wing aircraft are recommended

Fig. 7.2 Typical equipment used in transport of a patient.

due to long transport times and delays caused by unforeseeable circumstances of weather or logistics.

Portable Monitor

A portable electrocardiogram (ECG) monitor capable of monitoring two pressure channels should accompany all patients in transport. This allows for continuous monitoring of heart rate, rhythm, and arterial blood pressure. The second pressure channel may be used for patients with a pulmonary artery catheter or those who need intracranial pressure monitoring. This monitor should be small and lightweight but able to provide a display bright enough to be seen from several feet away. The monitor should have its own rechargeable power supply that continuously charges while connected to an alternating current (AC) power supply. One suitable unit is the Protocol Systems Propaq 106 portable monitor. This monitor has two pressure channels; it provides a continuous display of ECG; heart rate; and systolic, diastolic, and mean blood pressure; it can display temperature and oxygen saturation; and it is also capable of operating a non invasive blood pressure cuff. High and low alarms for each monitored parameter can be set, silenced, or disabled by a trained operator.

Infusion Pump

Continuous delivery of fluids and pharmacological agents must not be interrupted during transport. Infusion pumps can be easily attached to stretchers and are usually capable of operating for several hours on internal batteries. These devices should have alarms to warn of infusion problems and should be as small and lightweight as possible.

Ventilator

Size, weight, and oxygen consumption are the primary concerns in selecting transport ventilators. A weight under 5 pounds (2.2 kg) is desirable, and a ventilator's dimensions should make it easy to mount or to place on a bed. Orientation of controls should be along a single plane, and inadvertent movement of dials should be difficult.[23] The ventilator breathing circuit and exhalation valve should be kept simple, and incorrect assembly should be impossible. One type of transport ventilator that has become popular is the TXP transport ventilator. The TXP transport ventilator (Percussionaire Corporation, Sand Point, ID) is a portable pressure-limited time-cycled ventilator and is approved for in-flight use by the US Air Force. The transport ventilator weighs 1.5 pounds (0.68 kg), can be set to provide respiratory rates of between 6 and 250 breaths per minute and provides tidal volumes of between 5 and 1500 cc. This ventilator is powered entirely by oxygen and requires no electrical power. All timing circuit gases are delivered to the patient so that operation of the ventilator does not consume additional oxygen. The inhale to exhale (I:E) ratios are preset at the factory from 1 : 1 at frequencies of 250 cycles per minute to 1 : 5 at a rate of 6 cycles per minute. As a result, breath stacking and undesired overinflation due to air trapping may be avoided.[23–25]

Stabilization

One of the primary reasons for a specialized transport team is so that a patient can be transported in as stable condition as possible. Current practice has evolved to embrace the concept that events during the first few hours following burn injury may affect the eventual outcome of the patient; this is especially true with regard to fluid management and inhalation injury. Stabilization techniques performed by the transport team have been expanded to include procedures that are usually not performed by nursing or respiratory personnel. Such techniques include interpreting radiographs and laboratory results and then conferring with fellow team members, referring physicians, and the team's own medical staff to arrive at a diagnosis and plan for stabilization. The transport team may perform such procedures as venous cannulation, endotracheal intubation, arterial blood gas interpretation, and management of mechanical ventilators. Team members may request new radiographs to assess catheter or endotracheal tube placement or to assess the pulmonary system's condition. Team members may aid in the diagnosis of air leaks (pneumothorax) and evacuate the pleural space of the lung by needle aspiration as indicated. All of these procedures may be immediately necessary and life-saving. Cross-training of all team members so that they are able to perform the others' jobs is recommended to safeguard patients in the event that any team member becomes incapacitated during transport. All these skills can be learned via experience in a burn intensive care unit, through formal training seminars, and via a thorough orientation program. Mature judgment, excellent clinical skills, and the ability to function under stress are characteristics needed when selecting candidates for a transport program.

Patient Assessment Prior to Transport to a Specialized Burn Care Unit From a Referring Hospital

Initial assessment on arrival of a flight team should include a list of standard procedures for determining a burned patient's current condition. First, a thorough review of the patient's history concerning the accident and past medical

history must be done. This process provides the transport team with an excellent base from which to begin to formulate a plan of action. The patient will certainly have been diagnosed by a referring physician; however a transport team often finds problems overlooked in initial evaluations. Since burn care is a specialized field, modes of treatment may vary greatly outside the burn treatment community. Frequently, a referring hospital is not well-versed in the treatment of burn victims and should not be expected to display the expertise found among clinicians who work with such patients every day. Thus the next step in stabilizing a burn patient is a physical assessment done by the transport team. These procedures should always be performed in the same order and in a structured fashion. Assessment of a burn patient begins with the ABCs of a primary survey, including airway, breathing, circulation, cervical spine immobilization, and a brief baseline neurological examination. All patients should be placed on supplemental oxygen prior to transport in order to minimize the effects of altitude changes on oxygenation. Two IV lines should be started peripherally with a 16-gauge catheter or larger. Ideally, IV lines should be placed in nonburned areas but may be placed through a burn if they are the only sites available for cannulation. Intravenous lines should be sutured in place because venous access may not be available after the onset of generalized edema. The fluid of choice for initial resuscitation is LR solution.

In addition to initial stabilization procedures, blood should be obtained for initial laboratory studies if not already done. Initial diagnostic studies include hematocrit, electrolytes, urinalysis, chest X-ray, arterial blood gas, and carboxyhemoglobin levels. Any correction of laboratory values must be done prior to transfer and verified with repeat studies. ECG monitoring should be instituted on any patient prior to transfer. Placement of electrode patches may be a problem because the adhesive will not stick to burned skin. If alternative sites for placement cannot be found, an option for monitoring is to insert skin staples and attach the monitor leads to them with alligator clips. This provides a stable monitoring system, particularly for the agitated or restless patient who may displace needle electrodes. A Foley catheter with an urometer should be placed to accurately monitor urine output. Acceptable hydration is indicated by a urine output of more than 30 mL/h in an adult (5 mL/kg/h) and at least 1 mL/kg/h in a child.

With the exception of escharotomies, open chest wounds, and actively bleeding wounds, management during transport consists of simply covering wounds with a topical antimicrobial agent or a biological dressing. Wet dressings are contraindicated because of the decreased thermoregulatory capacity of patients sustaining large burns and the possibility of hypothermia. To combat the problem of a gastric ileus, a nasogastric tube should be inserted in all burn patients in order to decompress the stomach. This is especially important for patients being transferred at high altitudes. Hypothermia can be avoided or minimized by the use of heated blankets and/or aluminized Mylar space blankets. The patient's rectal temperature must be kept between 37.5°C and 39.0°C.

A clear, concise, chronological record of the mechanism of injury and assessment of airway, breathing, and circulation should be kept in the field and en route to the hospital. This information is vital for a referring facility to better understand and anticipate the condition of the patient. Additionally, all treatments, including invasive procedures, must be recorded, along with a patient's response to these interventions.

Summary

Burn injuries present a major challenge to a health care team, but an orderly, systematic approach can simplify stabilization and management. A clear understanding of the pathophysiology of burn injuries is essential for providing quality burn care in the prehospital setting, at the receiving health care facility, and at the referring hospital prior to transport. After a patient has been rescued from an injury-causing agent, assessment of the burn victim begins with a primary survey. Life-threatening injuries must be treated first, followed by a secondary survey, which documents and treats other injuries or problems. Intravenous access may be established in concert with logical/regional medical control and appropriate fluid resuscitation begun. Burn wounds should be covered with clean, dry sheets, and the patient should be kept warm with blankets to prevent hypothermia. The patient should be transported to an emergency room in the most appropriate mode available.

At the local hospital, it should be determined if a burn patient needs burn center care according to the American Burn Association Guidelines. In preparing to organize the transfer of a burn victim, consideration must be given to the continued monitoring and management of the patient during transport. In transferring burn patients, the same priorities developed for prehospital management remain valid. During initial assessment and treatment and throughout transport, the transport team must ensure that the patient has adequate airway/breathing, circulation, fluid resuscitation, urine output, and pain control. Ideally, transport of burn victims will occur through an organized, protocol-driven plan that includes specialized transport mechanisms and personnel. Successful transport of burn victims, whether in the prehospital phase or during interhospital transfer, requires careful attention to treatment priorities, protocols, and details.

Complete references available online at
www.expertconsult.inkling.com

Further Reading

American Burn Association. *Advanced Burn Life Support Providers Manual*. Chicago, IL: American Burn Association; 2010.

American Burn Association. Radiation injury. In: *Advanced Burn Life Support Manual* (Appendix 1). Chicago, IL: American Burn Association; 2010.

Brooks RG, Menachemi N. Physician's use of email with patients: factors influencing electronic communication and adherences to best practices. *J Med Internet Res*. 2006;8(1):e2.

Herndon DN, Rutan RL, Rutan TC. Management of the pediatric patient with burns. *J Burn Care Rehabil*. 1993;14(1):3-8.

Mandl KD, Kohane IS, Brandt AM. Electronic patient–physician communication: problems and promise. *Ann Intern Med*. 1998;129(6):495-500.

References

1. Boswick JA, ed. *The Art and Science of Burn Care*. Rockville, MD: Aspen; 1987.
2. Vivo C, Galerias R, del Caz MD. Initial evaluation and management of the critical burn patient. *Med Intensiva*. 2016;40(1):49-59.
3. Dimick AR. Triage of burn patients. In: Wachtel TL, Kahn V, Franks HA, eds. *Current Topics in Burn Care*. Rockville, MD: Aspen Systems; 1983:15-18.
4. Wachtel TL. Initial care of major burns. *Postgrad Med*. 1989;85(1):178-196.
5. Lau EY, Tam YY, Chiu TW. Triage of burn patients. *Hong Kong Med J*. 2016;22(2):152-157.
6. American Burn Association. *Advanced Burn Life Support Providers Manual*. Chicago, IL: American Burn Association; 2011.
7. reference removed at revises
8. American Burn Association. Radiation injuries. In: *Advanced Burn Life Support Providers Manual*. Chicago, IL: American Burn Association; 2011.
9. Eastman AL, Arnold BA, Hunt JL, Purdur GF. Pre-burn center management of the burned airway: do we know enough? *J Burn Care Res*. 2010;31(5):701-705.
10. Bartholomew CW, Jacoby WD. Cutaneous manifestations of lightning injury. *Arch Dermatol*. 1975;26:1466-1468.
11. Committee on Trauma, American College of Surgeons. Burns. In: *Advanced Trauma Life Support Course Book*. Chicago: American College of Surgeons; 1984:155-163.
12. Rauscher LA, Ochs GM. Pre-hospital care of the seriously burned patient. In: Wachtel TL, Kahn V, Franks HA, eds. *Current Topics in Burn Care*. Rockville, MD: Aspen Systems; 1983:1-9.
13. Hettiatatchy Shenan, Dziewulski Peter. ABC of burns: Pathophysiology and types of burns. *BMJ*. June 12, 2004;328-335
14. Marvin JA, Heinback DM. Pain control during the intensive care phase of burn care. *Crit Care Clin*. 1985;1:147-157.
15. Rutkowska A, Skotnicka-Klonowicz G. Pre-hospital pain management in children with traumatic injuries. *Pediatr Emerg Care*. 2015;31(5):317-320.
16. Goldfarb JW. The burn patient. In: *Air Medical Crew National Standards Curriculum*. Phoenix: ASHBEAMS; 1988. http://www.americanburn.org/Chapter14.pdf. Accessed 19 October 2016.
17. Fotsch EV. Online physician communication. *Phys News Digest*. 2008. Accessed www.physiciansnews.com.
18. Mandl KD, Kohane IS, Brandt AM. Electronic patient–physician communication: problems and promise. *Ann Intern Med*. 1998;129(6):495-500.
19. Brooks RG, Menachemi N. Physician's use of email with patients: factors influencing electronic communication and adherences to best practices. *J Med Internet Res*. 2006;8(1):e2.
20. Atiyeh B, Dibo SA, Janom HH. Telemedicine and burns: an overview. *Ann Burns Fire Disast*. June 2015;27(2): Accessed https://www.ncbi.nlm.noh.gov/pmc/articles/PMC4396801/pfd/Ann-Burns-and-Fire-Disasters-27-87.pdf.
21. McNeil EL. *Airborne Care of the Ill and Injured*. New York: Springer-Verlag; 1983.
22. Federal Regulations for Pilots. Government publication; 1987.
23. Branson RD. Intrahospital transport of critically ill, mechanically ventilated patients. *Respir Care*. 1992;37:775-793.
24. Jacobs B. *Emergency Patient Care, Pre-Hospital Ground and Air Procedures*. New York: Macmillan; 1983.
25. Johannigman JA, Branson RD, Cambell R, et al. Laboratory and clinical evaluation of the MAX transport ventilator. *Respir Care*. 1990;35:952-959.

8 Pathophysiology of Burn Shock and Burn Edema

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Introduction and Historical Notes

Extensive cutaneous thermal injury invariably results in the severe derangements of cardiovascular function and end-organ perfusion known as *burn shock*. Shock is an abnormal physiologic state in which tissue perfusion is insufficient for oxygen and nutrient delivery and cellular waste removal. Before the 19th century, investigators demonstrated that, after a burn, fluid is lost from the blood and the blood becomes thicker; in 1897, saline infusions for severe burns were first advocated.[1,2] Frank Underhill derived a more complete understanding of burn pathophysiology[3] when he demonstrated that unresuscitated burn shock was associated with increased hematocrit values, which are secondary to fluid and electrolyte loss after burn injury. Thus increased hematocrit values after severe burn injury are a consequence of a plasma volume deficit. Cope and Moore[4] furthered these finding, demonstrating that the hypovolemia of burn injury resulted from fluid and protein translocation into both burned and unburned tissues.

Animal and clinical studies have established the importance of fluid resuscitation for burn shock. Investigations have focused on correcting the rapid and massive fluid sequestration in the burn wound and the resultant hypovolemia. The literature contains a large experimental and clinical database on the circulatory and microcirculatory alterations associated with burn shock and edema generation in both the burn wound and unburned tissues. Substantial research has focused on identifying and defining the mechanisms and effects of the many inflammatory mediators produced and released after burn injury.[4]

Burn shock occurs from the coalescence of three cardinal causes: (1) hypovolemia resulting from intravascular fluid leaking into the interstitial space causing burn edema, (2) cardiac depression due to humoral factors and loss of preload, and (3) increased systemic vascular resistance. Later in the resuscitation process vasoplegia can replace the increase in system vascular resistance. Burn shock is a complex process of circulatory and microcirculatory dysfunction that is not easily or fully repaired by fluid resuscitation. Severe burn injury results in significant distributive shock and substantial tissue trauma, both of which cause the formation and release of many local and systemic mediators.[5–7] Burn shock results from the interplay of direct tissue injury, hypovolemia, and the release of multiple mediators of inflammation, with effects on both the microcirculation and the function of the heart and lungs. Subsequently burn shock continues as a significant pathophysiologic state even if hypovolemia is corrected. Increases in pulmonary and systemic vascular resistance (PVR, SVR) and myocardial depression occur despite adequate preload and volume support.[7–11] Such cardiovascular dysfunctions can further exacerbate the whole-body inflammatory response into a vicious cycle of accelerating organ dysfunction.[6,7,12]

This chapter examines our current understanding of the pathophysiology of the early events in burn shock, focusing on the many facets of the microcirculatory, organ, and systemic effects resulting directly from burns and circulating mediators. Intracellular pathways are not presented.

Inflammatory shock mediators, both local and systemic, that are implicated in the pathogenesis of burn shock include histamine, serotonin, bradykinin, nitric oxide, oxygen radicals, tumor necrosis factor (TNF), interleukins, and products of the eicosanoid acid cascade including prostaglandins and thromboxanes. Additionally certain hormones and mediators of cardiovascular function are elevated several fold after burn injury: these include epinephrine, norepinephrine, vasopressin, angiotensin II, and neuropeptide-Y. Other mediators and unknown factors yet to be defined are also involved.

Hypovolemia and Rapid Edema Formation

Burn injury causes extravasation of plasma into the burn wound. Extensive burn injuries are hypovolemic in nature and are characterized by hemodynamic changes similar to those that occur after hemorrhage, including decreased plasma volume, cardiac output, and urine output and an increased SVR with resultant reduced peripheral blood flow.[5,7,13–15] However, whereas in hemorrhage there is a fall in hematocrit with blood loss due to autotransfusion of interstitial fluid into the vasculature, in burn shock hematocrit may rise due to plasma extravasation. This is particularly common when fluid therapy is inadequate.

As in the treatment of other forms of hypovolemic shock, the primary initial therapeutic goal is to promptly restore intravascular volume and to preserve tissue perfusion and minimize tissue ischemia. However burn resuscitation is complicated not only by severe burn wound edema, but also by extravasated and sequestered fluid and protein in unburned soft tissue. Large volumes of resuscitation solutions are required to maintain intravascular volume during the first several hours after an extensive burn.

Note: The opinions or assertions contained herein are the private views of the authors, and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Edema develops when the rate at which fluid is filtered out of the capillaries exceeds the flow in the lymph vessels. Edema formation often follows a biphasic pattern. An immediate and rapid increase in the water content of burned tissue is seen in the first hour after burn injury.[15,18] A second and more gradual increase in fluid flux of both the burned skin and unburned soft tissue occurs during the first 12–24 hours after burn injury.[6,16] The amount of edema formation in burned skin depends on the type and extent of injury,[14,16] on whether fluid resuscitation is provided, and on the type and volume of fluid administered.[17] Fluid resuscitation elevates blood flow and capillary pressure thereby contributing to further fluid extravasation. Without sustained IV replacement of intravascular fluid losses edema formation is somewhat self-limited, as tissue blood flow and capillary pressure decrease.

Edema formation in thermally injured skin is characterized by an extremely rapid onset. Tissue water content can double within the first hour after burn.[14,18] Leape found a 70–80% increase in water content in a full-thickness burn wound 30 minutes after burn injury, with 90% of this change occurring in the first 5 minutes.[15,19,20] There was only a modest increase in burn wound water content after the first hour in nonresuscitated animals. In resuscitated animals or animals with small wounds, adequate tissue perfusion continues to "feed" the edema for several hours. Demling et al.[16] used dichromatic absorptiometry to measure edema development during the first week after an experimental partial-thickness burn injury on one hind limb in sheep. Although edema formation was rapid, with more than 50% occurring in the first hour, maximum water content was not present until 12–24 hours after burn injury. The mass of the burned tissue is significantly less than that of the remainder of the body. As such most fluid shifts likely occur from the blood into the unburned tissue due to the humoral actions of inflammatory mediators causing endothelial activation and glycocalyx injury.

Normal Microcirculatory Fluid Exchange

An understanding of the physiologic mechanisms of the rapid formation of burn edema requires an understanding of the mechanisms of microvascular fluid balance. Under physiologic steady-state conditions blood pressure in capillaries causes filtration of fluid into the interstitial space. The bulk of the filtrate is removed from the interstitial space by lymphatic drainage.[21–23] Fluid transport across the microcirculatory wall in normal and pathological states has been described by the original "classic" Starling equation that did not include the glycocalyx:

$$J_v = K_f[(P_c - P_{if}) - \sigma(\pi_p - \pi_{if})]$$

Starling sought to explain the interaction of physical forces that govern fluid transfer between intravascular and extravascular compartments. J_v is the flux (flow rate) of fluid that crosses the microvasculature barrier. K_f is the capillary filtration coefficient, which is the product of the surface area and hydraulic conductivity (water permeability) of the capillary wall; P_c is the capillary hydrostatic pressure; P_{if} is the interstitial fluid hydrostatic pressure; π_p is the colloid osmotic pressure of plasma; π_{if} is the colloid osmotic pressure of interstitial fluid; σ is the osmotic reflection coefficient. Edema occurs when the lymphatic drainage rate (J_L) does not keep pace with the increased J_v (Fig. 8.1). Fig. 8.1 shows the key structures and microvascular forces of the classic Starling equation.

There is now evidence that suggests the plasma colloid osmotic pressure does not exert its full effect at the capillary wall because of a protective barrier that excludes protein: the glycocalyx on the luminal endothelium.[24–26] The effective colloid osmotic absorptive force is generated by the gradient across the glycocalyx. However the role of the glycocalyx in burns is largely unexplored. It remains useful

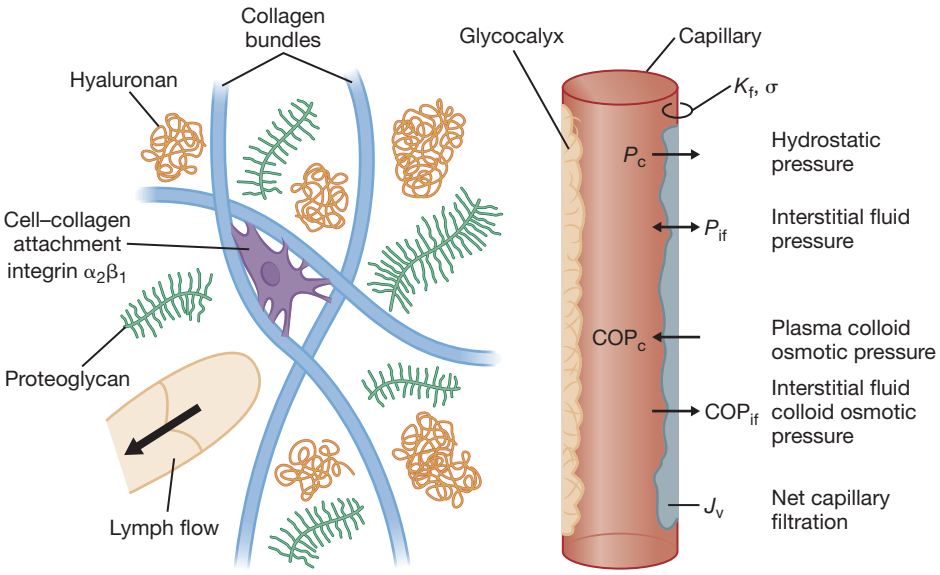

Fig. 8.1 The classic Starling equation and microvascular forces.

to review each term of the classic Starling equation and its role in burn edema before addressing the possible the implications of a modified Starling equation.

Mechanisms of Burn Edema

Transvascular blood-to-tissue transport of fluid and protein increase with elevation in K_f, P_c, or π_{if}, and with decreases in P_{if}, or σ. Burn edema is unique in its rapidity compared to other types of edema because it is only in burn edema that all of these variables change significantly in the direction required to increase fluid filtration. Each Starling variable is discussed individually next.

CAPILLARY FILTRATION COEFFICIENT (K_f)

Burn injury causes direct and indirect mediator-modulated changes in the permeability of the blood–tissue barrier of the capillaries and venules. Arturson and Mellander[27] showed that, in the scalded hindlimb of dogs, K_f immediately increased two to three times, suggesting that the hydraulic conductivity (water permeability) of the capillary wall increased. K_f is a function of both hydraulic conductivity and the capillary surface area. Thus local vasodilation and microvascular recruitment contribute to the increased K_f in addition to increased hydraulic conductivity. Measuring K_f and the rate of edema formation (J_v) allowed Arturson and Mellander to determine the changes in transcapillary forces necessary to account for the increased capillary filtration. Their calculations indicated that a transcapillary pressure gradient of 100–250 mm Hg was required to explain the extremely rapid edema formation that occurred in the first 10 minutes after a scald injury. They concluded that only a small fraction of the early formation of burn edema could be attributed to the changes in K_f and permeability. They further suggested that osmotically active molecules generating sufficiently large osmotic reabsorption pressures are released from burn-damaged cells. This hypothesis was never confirmed, and subsequent studies described herein show that large increases in filtration forces result from an increased P_c, and from a large decrease in P_{if} (Table 8.1).

CAPILLARY PRESSURE (P_c)

In most forms of shock, arteriolar vasoconstriction results in transfer of less arterial pressure to the capillaries; capillary and venous pressures decrease. However in studies using the vascular occlusion technique in the scalded hindlimb of dogs, P_c doubled from approximately 25 mm Hg to approximately 50 mm Hg during the first 30 minutes after burn injury and slowly returned to baseline over 3 hours.[28]

INTERSTITIAL HYDROSTATIC PRESSURE (P_{if})

Burned tissue has been demonstrated to have a significantly decreased interstitial hydrostatic pressure. Using micropipettes and a tissue oncometer, Lund[29] reported that dermal P_{if} was rapidly reduced from its normal value of −1 mm Hg to less than −100 mm Hg in isolated nonperfused samples of skin. This large negative interstitial hydrostatic pressure constitutes a powerful "suction force" or imbibition pressure promoting microvascular fluid filtration and sustained burn wound edema. In vivo measurements show a temporary reduction of −20 to −30 mmHg; the less negative P_{if} in vivo is due to the continued tissue perfusion and fluid extravasation that relieves the imbibition pressure. Kinsky[30] reported a continued negative pressure providing a partial explanation for the sustained edema during the first 4 hours post injury.

The mechanism for the large decrease in P_{if} is due, at least in part, to the release of cellular tension exerted on the collagen and microfibril networks in the connective tissue via the collagen-binding β_1-integrins. This tends to expand the interstitial space and induces the imbibition pressure. The integrins are transmembrane adhesion receptors that mediate cell–cell and cell–matrix adhesion, thereby allowing the glycosaminoglycan ground substance, which is normally underhydrated, to expand and take up fluid.[31] McGee et al. confirmed this hydration potential with T2-weighted MRI[32] and noted that it is reversible by application of negative pressure treatment. This supports the mechanism of interfascial rather than colloidal osmotic fluid transfer as a mechanism for burn edema and supports the collagen structural transitions as therapeutic targets.[33]

OSMOTIC REFLECTION COEFFICIENT (σ)

The osmotic reflection coefficient is an index of the proportion of the full osmotic pressure generated by the concentration gradient of plasma proteins across the microvascular blood-to-tissue barrier. A value of $\sigma = 1.0$ represents a barrier impermeable to protein but permeable to water and $\sigma = 0$ represents a barrier that is completely permeable to

Table 8.1 Effect of Burn Injury on Changes in the Classic Starling Equation Variables

Variable	Normal or Baseline	Post-Burn	Δ	References
P_c	~25 mm Hg	~50 mm Hg	↑ ~25 mm Hg	28
Π_P	25–30 mm Hg	15 to 18 mm Hg	↓ ~10 mm Hg	22, 36, 37
P_{if}	−2 to 0 mm Hg	~100 mm Hg non-resuscitated non-perfused skin and −5 mm Hg perfused skin	↓ ~100 mm Hg ↓ 3–5 mm Hg	29, 30
Π_{if}	10–15 mm Hg	13–18 mm Hg in burn wound ↓ and with resuscitation hypoproteinemia in unburned skin	↑ ~3 mm Hg	22, 35, 37
σ	~0.9	~0.5	↓ ~0.4	22, 28, 34, 35
K_f	~0.003 mL/min/mm Hg/100 g (leg)	↑ 2–5×		27

protein and water. The reflection coefficient is traditionally attributed to the endothelial cellular junctions but may well be primarily determined by the glycocalyx. In skin, the normal σ of albumin is reported to be 0.85–0.99.[22,34] Thermal injury causes an increase in capillary permeability to protein, resulting in a reduced σ, an effective reduction in the absorptive oncotic gradient across the microvascular barrier, and a resulting increase in net fluid filtration. Lymph sampled from burned skin has shown elevated protein concentrations consistent with the large and sustained increases in capillary permeability,[14,34,35] whereas a transient and smaller increase in microvascular permeability occurs over 8–12 hours following injury in other soft tissue not directly burned.[35] Pitt et al.[28] estimated the σ for skin from dog hindpaw using a lymph wash-down technique and reported a normal σ of 0.87 for albumin and a reduction to 0.45 after scald injury.

PLASMA COLLOID OSMOTIC PRESSURE (π_p)

The normal plasma protein concentration of 6–8 g/dL and its associated π_p of 25–30 mm Hg, would produce a significant transcapillary absorptive force counterbalancing the other Starling forces that favor filtration.[13,22] However, the glycocalyx blocks most of the impact of π_p on transendothelial fluid movement,[24–26] as described later. Plasma colloid osmotic pressure decreases in nonresuscitated burn-injured animals as protein-rich fluid extravasates into burn wounds and a significant volume of protein-poor interstitial fluid initially enters the circulation from transvascular reabsorption and lymph of unburned tissue, such as skeletal muscle.[13,36–38] Plasma is further diluted and π_p is further reduced after crystalloid resuscitation. Increased fluid filtration is less due to the fall in π_p and more likely attributed to increased K_f, reductions in P_{if} and σ due to a damaged glycocalyx. Initial therapy with colloid solution has always been advocated by some clinicians[6] but is often delayed 8–24 hours after injury based on the reasoning that normalization of microvascular protein permeability in injured tissue must occur before colloid therapy is cost effective.[7] However, the ability of plasma protein and, in particular, albumin to repair the permeability of the glycocalyx suggests a rationale for the earlier use of albumin therapy for burn resuscitation. Evidence for the use of albumin for resuscitation is also covered in Chapter 9 on burn resuscitation.[39–41] Animal studies have shown that albumin use during burn resuscitation does not reduce the edema in the tissue of burn wounds, but it does reduce total fluid needs and thus reduces edema in unburned tissues.[42] Furthermore, as discussed later, albumin can have a trophic effect on the endovascular glycocalyx, acting to stabilize it.

INTERSTITIAL COLLOID OSMOTIC PRESSURE (π_{if})

The π_{if} in skin is normally 10–15 mm Hg or about one-half that of plasma.[13,22] Experimental studies in animals using lymph as representative of interstitial fluid suggest that the colloid osmotic pressure in lymph from burned skin initially increases 4–8 mm Hg after burn injury.[35] With crystalloid resuscitation, π_p and π_{if} decrease because the protein concentration of microvascular filtrate remains less than that of plasma despite an increased permeability. The osmotic reflection coefficient, σ, decreases with burns but never equals zero; thus protein concentration in capillary filtrate is always less than in plasma even in burn-injured skin.[35] Compared to unburned skin, the π_i remains significantly higher in the burn wound, supporting the view that sustained increases in protein permeability contribute to the persistence of burn edema.[13,22,30] However, compared with the large changes in P_c and particularly P_{if}, increased microvascular protein permeability is not the predominant mechanism for the early, rapid rate of edema formation in injured skin.[43]

ENDOTHELIAL DYSFUNCTION AND THE GLYCOCALYX

Demling and colleagues[44,45] suggested that the edema caused by burns and hypoproteinemia alone could be partially attributed to alterations in the structure of interstitium increasing water transport and hydraulic conductivity across the entire blood–tissue–lymph barrier. Similar changes occur when hypoproteinemia is induced by plasmapheresis. Several clinical and animal studies have established that maintaining higher levels of total plasma protein concentration can ameliorate the overall net fluid retention and edema.[6,46,47] Endothelial activation and endothelial dysfunction play a major role in burn edema and the resultant distributive shock, particularly as it pertains to edema remote from the area of direct thermal trauma. Turk et al. prospectively investigated the endothelial dysfunction associated with burn injury in a cohort of burned patients in which they demonstrated an in vivo alteration of flow-mediated dilation reaching a nadir on post burn day 7. These clinical data support experimental findings on endothelial dysfunction after burn injury.[48] The value of colloid osmotic pressure under the glycocalyx (π_g) before or after burn injury has not been measured.

Plasma is further diluted and π_p is further reduced after crystalloid resuscitation. Increased fluid filtration is less due to the fall in π_p and more likely attributed to increased K_f and reductions in P_{if} and σ due to a damaged glycocalyx.

Many of these changes in endothelial and interstitial function can be attributed to the glycocalyx—a glycoprotein and polysaccharides layer on the luminal side of endothelial cells that maintains the barrier between the endothelium and plasma by reducing the osmotic gradient and thereby reducing filtration. The thickness of the glycocalyx varies from 20 nm in capillaries to 3000 nm in larger vessels. Based on studies of the glycocalyx, the paradigm of the classic Starling equation of microcirculatory forces has been challenged, and a revised equation has been proposed. Levick and Michel, along with others, proposed the revised Starling equation shown here and in Fig. 8.2:[25,49–51]

$$Jv = K_f[(P_c - P_{if}) - \sigma(\pi_p - \pi_g)]$$

In the revised Starling equation the fluid flux across the blood–tissue barrier is driven primarily by differences in hydrostatic pressures, $(P_c - P_{if})$ and by a colloid osmotic gradient between the fluid in the glycocalyx and just below the glycocalyx $(\pi_p - \pi_g)$. Further studies by Kozar et al.[52] have demonstrated that crystalloid resuscitation of hemorrhagic shock in rats causes a loss of glycocalyx that can be

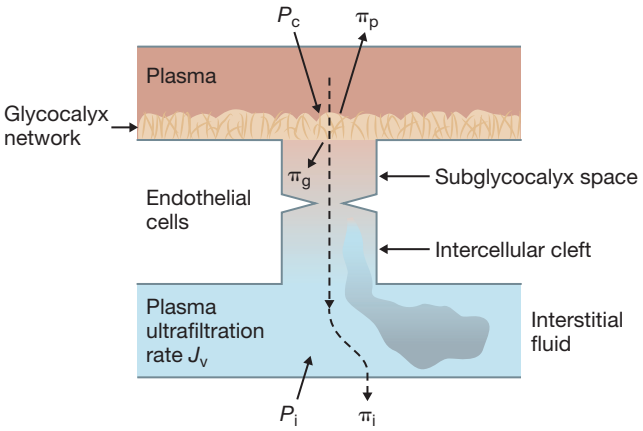

Fig. 8.2 The forces of the New Starling Equation taking into account the role of the glycocalyx.

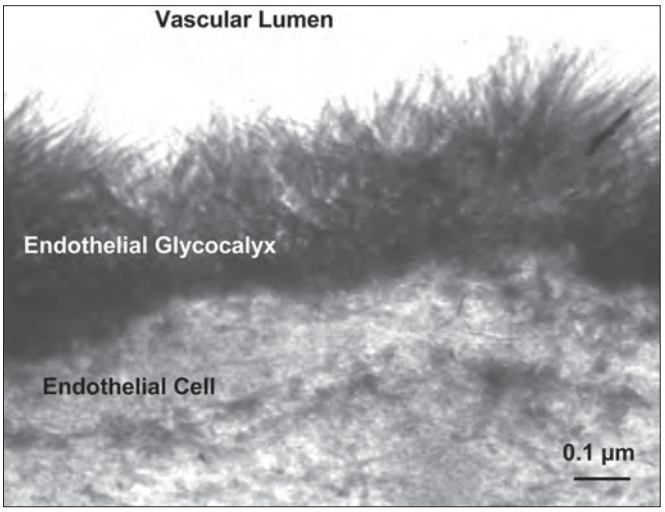

Fig. 8.3 A healthy vascular endothelium showing the fuzz-like coat of transmembrane and membrane bound molecules of the glycocalyx.

largely prevented by plasma resuscitation. Fig. 8.3 shows a photomicrograph of the glycocalyx.

Unburned Tissue

Generalized edema in soft tissues not directly injured is another characteristic of large cutaneous burns. Brouhard et al.[53] reported increased water content in unburned skin even after a 10% total body surface area (TBSA) burn, with the peak edema occurring 12 hours postburn. Arturson reported an increased transvascular fluid flux (lymph flow) from unburned tissue and a transient increase in permeability as measured by an increase in the lymph concentration of plasma protein and macromolecular dextran infused as a tracer.[14,34] Harms et al.[35] extended these findings by measuring changes in lymph flow and protein transport in noninjured soft tissue for 3 days after injury. They found that skin and muscle permeability (flank lymph from sheep) were elevated for up to 12 hours postburn for molecules the size of albumin and immunoglobulin G, but the microvascular permeability of the lung (lymph from caudal mediastinal node) showed no increase. Maximum increased lymph flow and tissue water content were observed to correlate with the severe hypoproteinemia that occurred during the early resuscitation period of a 40% burn injury in sheep.[7,54]

The mechanism by which burn injury induces microvascular hyperpermeability remote from the injury has been the subject of extensive study utilizing plasma from burned animals transfused into unburned recipients by Kremer et al.[55] These transfusions cause endothelial activation, albumin leakage, and leukocyte adhesion and rolling via an undefined transfused circulating factor. This model allows testing of the effects of various inhibitory and therapeutic agents in ameliorating the resultant physiologic derangements. High-dose vitamin C, an antioxidant, administered to the recipient rat was found to significantly reduce capillary leakage but not leukocyte-endothelial interactions.[55,56] Ketanserin, a 5-HT_{2a} antagonist, reduced plasma extravasation and leukocyte-endothelial interactions after burn plasma transfer.[57] These findings were further confirmed with the serotoninergic receptor-blocking agents cinanserin and methysergide.[58,59] When the burn wounds of donor burned rats were bathed in cerium nitrate, a topical antimicrobial and putative anti-inflammatory agent, the resulting plasma no longer induced injury in transfused rats.[60] In further burn plasma transfer studies Hernekamp et al.[61,62] also demonstrated that the cholinergic anti-inflammatory pathway stimulated by cbp-choline or pretreatment with physostigmine can similarly attenuate albumin efflux and leukocyte adhesions.

Altered Cellular Membranes and Cellular Edema

In addition to a loss of microvascular barrier integrity, thermal injury also causes changes in the cellular membrane. In skeletal muscle cellular transmembrane potentials decrease at sites distant from the injury.[9] It would be expected that the directly injured cell would have a damaged cell membrane thus increasing sodium and potassium fluxes and resulting in cellular swelling. However this process also occurs in cells that are not directly heat-injured. Micropuncture techniques in hemorrhaged animals have demonstrated partial depolarization in the skeletal muscle membrane potential of −90 mV to levels of −70 to −80 mV; cell death occurs at −60 mV. These shock-induced decreases in membrane potentials are associated with increases in intracellular water and sodium.[63–65] Similar alterations in skeletal membrane functions and cellular edema have been reported in hemorrhagic shock[63,65] and in cardiac, liver, and endothelial cells.[66–68] Action potentials become dampened or nonexistent, with likely delays in signal propagation in nerves, brain, skeletal muscle, heart, diaphragm, and gastrointestinal organs. Encephalopathy, muscle weakness, impaired cardiac contractility, and gut dysfunction are associated with major burn injury and may be due in part to reduced membrane potentials.

Early investigators of this phenomenon postulated that a decrease in adenosine triphosphate (ATP) levels or ATPase activity was the mechanism for membrane depolarization.

However more recent research suggests that it may result from an increased sodium conductance in membranes or that an increase in sodium–hydrogen antiporter activity is the primary mechanism.[64,67] Resuscitation of hemorrhage rapidly restores depolarized membrane potentials to normal, but resuscitation of burn injury only partially restores the membrane potential and intracellular sodium concentrations to normal levels, demonstrating that hypovolemia alone is not totally responsible for the cellular swelling seen in burn shock.[69] A circulating shock factor(s) is likely to be responsible for the membrane depolarization.[70–72] When plasma from a burn-injured animal is superfused to an isolated muscle preparation, membrane depolarization occurs. Furthermore, the depolarization can be reversed by changing the superfusate to normal plasma or saline.[69] Surprisingly the molecular characterization of such circulating factors has not been elucidated, suggesting that they have a complex and perhaps dynamic structure. Data suggest a large molecular weight, greater than 80 kDa.[73] Membrane depolarization may be caused by different factors in different states of shock. Very little is known about the time course of the changes in membrane potential in clinical burns. Furthermore, we do not know the extent to which the altered membrane potentials affect total volume requirements and organ function in burn injury.

Inflammatory Mediators of Burn Injury

Many local and circulating mediators are produced in the blood or released by cells after thermal injury. These mediators play important but complex roles in the pathogenesis of edema and the cardiovascular abnormalities of burn injury. For example, mediators alter vascular permeability and transvascular fluid flux, either directly or indirectly, by increasing the microvascular hydrostatic pressure and surface area via the arteriolar vasodilation superimposed on an already injured endothelial barrier. The exact mechanism(s) of mediator-induced injury are of considerable clinical interest because this understanding would allow for the development of pharmacologic modulation of burn edema and shock by mediator inhibition. Unfortunately most strategies directed at mediator blockage have only been effective in small localized burn wounds in patients or in animal studies and have had no clinical impact on the care of patients with major burns.

HISTAMINE

Histamine is a key mediator of very early increases in microvascular permeability following thermal injury. Histamine is released from mast cells in thermally injured skin; however the increase in histamine levels and its actions are only transient. Histamine causes large endothelial gaps to transiently form as a result of the contraction of venular endothelial cells.[74,75] Histamine is released from mast cells in thermally injured skin; however the increase in histamine levels and its actions are only transient. Histamine also can cause the rise in capillary pressure (P_c) by arteriolar dilation and venular contraction. Reductions in localized edema have been achieved with histamine blockers and mast cell stabilizers when tested in animal models.[74] Friedl et al.[42] demonstrated that the pathogenesis of burn edema in the skin of rats appears to be related to the interaction of histamine with xanthine oxidase and oxygen radicals. Histamine and its metabolic derivatives increased the catalytic activity of xanthine oxidase in rat plasma and in rat pulmonary artery endothelial cells.[76] In thermally injured rats, levels of plasma histamine and xanthine oxidase rose in parallel, in association with the increase in uric acid. Burn edema was greatly attenuated by treating rats with the mast cell stabilizer cromolyn, complement depletion, or the H_2 receptor antagonist cimetidine but was unaffected by neutrophil depletion.[76–78] Despite encouraging results in animals, beneficial antihistamine treatment of human burn injury has not been demonstrated.

PROSTAGLANDINS

Prostaglandins are potent vasoactive autocoids synthesized from the arachidonic acid released from burned tissue and inflammatory cells, and they contribute to the inflammatory response following burn injury.[79,80] Activated macrophages and neutrophils infiltrate the wound and release prostaglandin as well as thromboxanes, leukotrienes, and interleukin-1 (IL-1). These wound mediators have both local and systemic effects. Prostaglandin E_2 (PGE_2) and leukotrienes LB_4 and LD_4 increase microvascular permeability both directly and indirectly.[81] Prostacyclin (PGI_2) is produced in burn injury and is also a vasodilator, and it may cause direct increases in capillary permeability. PGE_2 appears to be one of the more potent inflammatory prostaglandins, causing postburn vasodilation and increased microvascular surface area in wounds that, when coupled with the increased microvascular permeability, amplifies edema formation.[82,83] Prostacyclin (PGI_2) is a vasodilator and may cause increases in capillary permeability.

THROMBOXANE

Thromboxane A_2 (TXA_2) and its metabolite, thromboxane B_2 (TXB_2) are produced locally in burn wounds by platelets.[74] Vasoconstrictor thromboxanes may be less important in edema formation; however by reducing blood flow they can contribute to a growing zone of ischemia under the burn wound and may be responsible in part for the conversion of a partial-thickness wound to a deeper, full-thickness wound. The serum level of TXA and TXA_2/PGI_2 ratios are significantly increased in burn patients.[84] Heggers showed that TXB_2 is released at the burn wound and is associated with local tissue ischemia, while thromboxane inhibitors prevented the progressive dermal ischemia associated with thermal injury and thromboxane release.[85,86] The TXA_2 synthesis inhibitor anisodamine also showed beneficial microcirculatory effects by restoring the hemodynamic and rheological disturbances toward normal. LaLonde[83] showed that topically applied ibuprofen (which inhibits the synthesis of prostaglandins and thromboxanes) reduces both local edema and prostanoid production in burned tissue without altering systemic production. On the other hand, systemic administration of ibuprofen did not modify early edema, but did attenuate the postburn vasoconstriction that impaired adequate oxygen delivery to tissue in burned

sheep.[87] Although cyclooxygenase inhibitors have been used after burn injury, they have not entered into routine clinical use.

KININS

Bradykinin is a local mediator of inflammation that increases venular permeability. It is likely that bradykinin production is increased after burn injury, but its detection in blood or lymph can be difficult because of the simultaneous increase in kininase activity and the rapid inactivation of free kinins. The generalized inflammatory response after burn injury favors the release of bradykinin.[88] Pretreatment of burn-injured animals with aprotinin, a general protease inhibitor, should have decreased the release of free kinin, but no effect on edema was noted.[89] On the other hand, pretreatment with a specific bradykinin receptor antagonist was reported to reduce edema in burn wounds in rabbits (Table 8.2).[90] Tao et al. demonstrated that blocking neurokinin-1 decreased the vascular permeability tissue around the wound and remotely in the jejunum of burned rats and that treated rats recovered more quickly than controls.[91]

SEROTONIN

Serotonin is released early after burn injury.[92] This agent is a smooth-muscle constrictor of large blood vessels. Antiserotonin agents such as ketanserin have been found to reduce peripheral vascular resistance after burn injury but not to reduce edema.[92] On the other hand, pretreatment with methysergide, a serotonin antagonist, reduces hyperemic or increased blood flow response in the burn wounds of rabbits and reduces burn edema.[90] Ferrara et al.[93] found a dose-dependent reduction in burn edema when methysergide was given to dogs prior to burn injury but claimed that this was not attributable to blunting of the regional vasodilation response. Zhang et al. reported a reduction in skin blood flow after methysergide administration to burned rabbits.[94]

CATECHOLAMINES

Circulating catecholamines epinephrine and norepinephrine are increased several fold after burn injury.[6,95,96] On the arteriolar side of the microvessels these agents cause

Table 8.2 Cardiovascular and Inflammatory Mediators of Burn Shock

Mediators	Central Cardiovascular Effects (at High Concentrations)	Load Tissue Effects	References
Histamine	↓ Blood pressure; hypovolemia	Arteriolar dilation; Venular constriction ↑ Blood flow ↑ Permeability	42, 74, 76, 77, 92, 160
Prostaglandin E_2 (PGE_2)	↓ Systemic arterial and pulmonary arterial blood pressure	Vasodilation ↑ Blood flow ↑ Permeability	74, 79, 85
Prostacyclin ($PG1_2$)	↓ Blood pressure	↑ Permeability	81, 83
Leukotrienes LB_4 LD_4	Pulmonary hypertension		74
Thromboxane A_2 (TXA_2) Thromboxane B_2 (TXB_2)	GI ischemia Pulmonary hypertension	Vasodilation ↑ Blood flow ↑ Permeability	84–87
Bradykinin	↓ Blood pressure Hypovolemia	Vasodilation, ↑ Permeability	74, 160
Serotonin		↑ Permeability	92–94
Catecholamines Epinephrine Norepinephrine	↑ Heart rate ↑ Blood pressure ↑ Metabolism	Vasoconstriction (receptors); Vasodilation (β_2 receptors in muscle); block ↑ permeability due to histamine & bradykinin via β receptors	74, 161
Oxygen radicals: Superoxide Anion (O_2^-) Hydrogen peroxide (H_2O_2) Hydroxyl Ion (OH^-) Peroxynitrite ($ONOO^-$)	Cardiac dysfunction	Tissue damage ↑ Permeability	42, 74, 76, 97, 99, 100
Platelet aggregation factor	↑ Blood pressure	Vasoconstriction	89, 113
Angiotensin II	GI ischemia ↑ Blood pressure	Vasoconstriction	114, 115, 117
Vasopressin	GI ischemia ↑ Blood pressure	Vasoconstriction	117

Enhanced microvascular blood flow typically opens recruits capillaries and increases surface area of exchange vessels.
Permeability refers to protein permeability of the microvascular barrier, which is often linked to hydraulic conductivity.

vasoconstriction via α_1-receptor activation, which tends to reduce capillary pressure, particularly when combined with the hypovolemia and reduced venous pressure of burn shock.[74] Reduced capillary pressure may limit edema and may induce transvascular refill of protein-poor interstitial fluid reabsorbed from unburned skin, skeletal muscle, and visceral organs, especially in under-resuscitated burn shock. Even in nonresuscitated animals, plasma protein concentration falls. Furthermore, catecholamines, via β-agonist activity, may also partially inhibit increased microvascular permeability induced by histamine and bradykinin.[74] These potentially beneficial effects of catecholamines may not be operative in directly injured tissue and may also be offset in unburned tissue by the deleterious vasoconstrictor and ischemic effects. The hemodynamic effects of catecholamines will be discussed later in the chapter.

REACTIVE OXYGEN SPECIES

Reactive oxygen species (ROS), also know as oxygen radicals, play an important inflammatory role in all types of shock, including burn shock. These short-lived elements are highly unstable reactive metabolites of oxygen; each one has an unpaired electron, making all of them strong oxidizing agents.[97] Superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl ion (OH^-) are produced and released by activated neutrophils after any inflammatory reaction or reperfusion of ischemic tissue. The hydroxyl ion is believed to be the most potent and damaging of the three. Evidence that these agents are formed after burn injury is the increased lipid peroxidation found in circulating red blood cells and biopsied tissue.[76,97,98]

Antioxidants, namely agents that either bind directly to the oxygen radicals (scavengers) or cause their further metabolism, have been evaluated in several experimental studies.[99,100] Catalase removes H_2O_2 and superoxide dismutase (SOD), lessens radical O_2^-, and is reported to reduce plasma loss after burn injury in dogs and rats.[76,99]

The plasma of thermally injured rats showed dramatic increases in levels of xanthine oxidase activity, with peak values appearing as early as 15 minutes after thermal injury. Excision of the burned skin immediately after the injury significantly diminished the increase in plasma xanthine oxidase activity.[42,76] The skin permeability changes were attenuated by treating the animals with antioxidants (catalase, SOD, dimethyl sulfoxide, dimethylthiourea) or an iron chelator (DFO), thereby supporting the role of oxygen radicals in the development of vascular injury as defined by increased vascular permeability.[76] Allopurinol, a xanthine oxidase inhibitor, markedly reduced both burn lymph flow and levels of circulating lipid peroxides and further prevented all pulmonary lipid peroxidation and inflammation. This suggests that the release of oxidants from burned tissue was in part responsible for local burn edema, as well as for systemic inflammation and oxidant release.[98] The failure of neutrophil depletion to protect against the vascular permeability changes and the protective effects of the xanthine oxidase inhibitors (allopurinol and lodoxamide tromethamine) suggests that plasma xanthine oxidase is the more likely source of the oxygen radicals involved in the formation of burn edema. These oxygen radicals can increase vascular permeability by damaging microvascular endothelial cells.[42,76] The use of antioxidants has been extensively investigated in animals, and some clinical trials suggest benefit.

Antioxidants (vitamin C and E) are routinely administered to patients at many burn centers. High doses of antioxidant ascorbic acid (vitamin C) have been found to be efficacious in reducing fluid needs in burn-injured experimental animals when administered postburn.[101–104] Beyond the action of vitamin concentrations are the use of high doses (e.g., 66 mg/kg per hour) of vitamin C, which was shown to, effectively reduce volume requirements in one clinical trial but was ineffective, in others, albeit with somewhat different doses.[102,105] High-dose vitamin C has been receiving wider clinical use, but the burn community awaits more definitive trials.

NITRIC OXIDE

Nitric oxide (NO) is a significant inhibitor of vascular smooth muscle tone and thus is a proximate cause of vasoplegia and distributive shock following burn injury. Blockade of guanylate cyclase with methylene blue as a treatment for vasoplegia has been described in several small case series.[106] NO has also been shown to be a significant driver of pulmonary dysfunction in inhalation injury. In an ovine model, blockade of inducible nitric oxide synthase (iNOS) and neuronal nitric oxide synthase (nNOS) fully prevented increases in pulmonary shunt, peak inspiratory pressure, and lung lymph flow and attenuated the decline in the PaO_2–FiO_2 ratio.[107]

Both beneficial and deleterious effects of NO have been described during the acute phase of burn shock. NO generated simultaneously with the superoxide anion can lead to the formation of peroxynitrite ($ONOO^-$). The presence of nitrotyrosine in burned skin found in the first few hours after injury suggests that peroxynitrite may play a deleterious role in burn edema.[108] Blockade of NOS did not reduce burn edema, whereas treatment with the NO precursor arginine reduced burn edema.[109] NO may be important for maintaining perfusion and limiting the zone of stasis in burn skin.[110] An $ONOO^-$ decomposition catalyst administered following smoke inhalation injury and burn was able to significantly reduce pulmonary microvascular hyperpermeability and improved pulmonary function in an ovine model.[111] A further study showed that low-dose arginine vasopressin given from 1 hour for up to 24 hours post smoke inhalation and burn injury in sheep significantly reduced NO plasma levels and edema formation.[112] Both the beneficial and deleterious effects of NO have been described to occur during the acute phase of burn shock and thus the long-term benefits of an acute NO reduction remain controversial. In brief, the value of acute NO reduction in burns remains controversial.

PLATELET AGGREGATION FACTOR

Platelet aggregation (or activating) factor (PAF) can increase capillary permeability and is released after burn injury.[89,113] Ono et al.[113] showed in scald-injured rabbits that TCV-309 (Takeda Pharmaceutical Co Ltd., Japan), a PAF antagonist, infused soon after burn injury, blocked edema formation in the wound and significantly inhibited PAF increase in

the damaged tissue in a dose-dependent manner. In contrast, the SOD content in the group treated with TCV-309 was significantly higher than that of the control group. These findings suggest that the administration of large doses of a PAF antagonist immediately after injury may reduce burn wound edema and the subsequent degree of burn shock by suppressing PAF and superoxide radical formation.

ANGIOTENSIN II AND VASOPRESSIN

Angiotensin II and vasopressin or antidiuretic hormone (ADH) are two hormones that participate in the normal regulation of extracellular fluid volume by controlling sodium balance and osmolality through renal function and thirst.[74] During burn shock, sympathetic tone is high and volume receptors sense hypovolemia, both of which elevate angiotensin II and ADH to supranormal levels in the blood. Both are potent vasoconstrictors of terminal arterioles with less effect on the venules. Angiotensin II may be responsible for the selective gut and mucosal ischemia, which can cause translocation of endotoxins and bacteria and the development of sepsis and even multiorgan failure.[114,115] In severely burn-injured patients angiotensin II levels were elevated two to eight times normal in the first 1–5 days after injury, with peak levels occurring on day 3.[116] Vasopressin had peak levels of 50 times normal upon admission and declined toward normal over the first 5 days after burn injury. Along with catecholamines, vasopressin may be largely responsible for increased SVR and increased left heart afterload, which can occur in resuscitated burn shock. Sun et al.[117] used vasopressin-receptor antagonists to improve hemodynamics and survival time in rats with burn shock, whereas vasopressin infusion exacerbated burn shock.

OTHER MEDIATORS

Hydrogen sulfide (H_2S) is a small-molecule mediator receiving increased attention in inflammatory shock. It is capable of both inducing and inhibiting inflammation. Murine data support H_2S as being an endogenous inflammatory mediator increasing both pro-inflammatory cytokine levels and NF-κB signaling. Studies are similarly being carried out to define concentrations and clinical utility for its anti-inflammatory characteristics.[57] Hu et al. used a 50% TBSA burn-injured dog model and reported that use of a *nicotinic agonist* with resuscitation increased survival, improved hemodynamics, increased plasma volume and urine output, and decreased TN-α, IL-1, and lactic acid.[118] Wiggins et al. elucidated a role of *metalloproteinases* (MMP) in lung edema and endothelial damage when a culture of lung endothelial cells had increased MMP activity and decreased tissue inhibitor of metalloproteinases (TIMP-2) after burn serum exposure. These cells had increased monolayer permeability, damaged adhesion junction proteins, and incited actin stress fiber formation. This damage was inhibited effectively by exogenous TIMP-2.[119] *Endothelin-1* has been shown to play a role in alveolar fluid clearance and pulmonary edema. ET-1 inhibits alveolar fluid clearance by inhibition of amiloride-sensitive epithelial sodium channels and increases capillary pressure.[120]

Hemodynamic Consequences

The cause of reduced cardiac output (CO) during the resuscitative phase of burn injury has been the subject of considerable debate. There is an immediate depression of cardiac output before any detectable reduction in plasma volume. The rapidity of this response may result from impaired neurotransmission of cardiac signaling and increased afterload due to vasoconstriction. Soon after injury a developing hypovolemia and reduced venous return undeniably contribute to the reduced cardiac output. The subsequent persistence of reduced CO after apparently adequate fluid therapy, as evidenced by restoration of arterial blood pressure and urinary output, has been attributed to circulating myocardial depressant factor(s), which possibly originates from the burn wound.[10,11] Demling et al.[16] showed a 15% reduction in CO despite aggressive volume replacement protocol after a 40% scald burn in sheep. However there are also sustained increases in catecholamine secretion and elevated systemic vascular resistance for up to 5 days after burn injury.[95,116] Michie et al.[121] measured CO and SVR in anesthetized dogs resuscitated after burn injury. They found that CO fell shortly after injury and then returned toward normal; however reduced CO did not parallel the blood volume deficit. They concluded that the depression of CO resulted not only from decreased blood volume and venous return, but also from an increased SVR and from the presence of a circulating myocardial depressant substance. After the resuscitation phase of burn shock, patients need a supranormal CO. This is associated with a hypermetabolic state and systemic inflammatory response syndrome (SIRS).

MYOCARDIAL DYSFUNCTION

Increases in the afterload of both the left and the right heart occur due to elevated SVR and PVR. Stroke volume and CO can be maintained despite contractile depression by augmented adrenergic stimulation, albeit at a cost of increased myocardial oxygen demands. The right ventricle has a minimal capacity to compensate for increased afterload. Myocardial function can be compromised after burn injury due to direct depression of contractility shown in isolated heart studies.[122,123] In severe cases, desynchronization of the right and left ventricles is deleteriously superimposed on a depressed myocardium.[124] Howard et al.[125] demonstrated both systolic and diastolic dysfunction in burn-injured children during the first few weeks post injury. Burn injury of greater than 45% TBSA can produce intrinsic contractile defects. Several investigators reported that aggressive early and sustained fluid resuscitation failed to correct left ventricular contractile and compliance defects.[123,124,126] These data suggest that hypovolemia is not the sole mechanism underlying the myocardial defects observed with burn shock. Serum from patients failing to sustain a normal CO after thermal injury have exhibited a markedly negative inotropic effect on in vitro heart preparations, which may be due to the circulating shock factor described earlier.[69,127] In other patients with large burn injuries and normal cardiac indices, little or no depressant activity was detected.

Traber and colleagues studied intact, chronically instrumented sheep after a 40% TBSA flame burn injury and smoke inhalation injury, and after smoke inhalation injury alone. They found that contractile force was reduced after either burn injury or inhalation injury alone.[128,129] Horton et al.[130] demonstrated decreased left ventricular contractility in isolated, coronary-perfused guinea pig hearts harvested 24 hours after burn injury. This dysfunction was more pronounced in hearts from aged animals and was not reversed by resuscitation with isotonic fluid. It was largely reversed by treatment with 4 mL/kg of hypertonic saline dextran (HSD) but only if administered during the initial 4–6 hours of resuscitation.[131,132] These authors also effectively ameliorated the cardiac dysfunction of thermal injury with infusions of antioxidants, arginine, and calcium channel blockers.[132–134] Cioffi and colleagues,[135] using an ex vivo myocardial preparation, observed persistent myocardial depression after burn when the animals received no resuscitation after injury. As opposed to most studies, Cioffi reported that immediate and full resuscitation totally reversed abnormalities of contraction and relaxation after burn injury. Murphy et al.[136] showed elevations of a serum marker for cardiac injury, troponin I, for patients with a TBSA burn of greater than 18%, despite good cardiac indices. Resuscitation and cardiac function studies emphasize the importance of early and adequate fluid therapy and suggest that functional myocardial depression after burn injury may be minimized in patients receiving prompt and adequate volume therapy.

The primary mechanisms by which burn shock alters myocardial cell membrane integrity and impairs mechanical function remain unclear. Oxygen-derived free radicals may play a key causative role in the cell membrane dysfunction that is characteristic of several low-flow states. Horton et al. showed that a combination therapy of free radical scavengers SOD and catalase significantly improved burn-mediated defects in left ventricular contractility and relaxation when administered along with adequate fluid resuscitation. Antioxidant therapy did not alter the volume of fluid resuscitation required after burn injury.[137]

Increased Systemic Vascular Resistance and Organ Ischemia

CO may remain below normal after adequate volume replacement in burn patients and experimental animals. Increased afterload after burn injury is the result of release of catecholamines, vasopressin, angiotensin II, and neuropeptide-Y.[116,117] These agents cause contraction of the arteriolar smooth muscle, which is systemically manifested by increased afterload and SVR. The increased SVR after burn injury is also, in part, the result of increased blood viscosity secondary to the hemoconcentration.

Hilton and others performed experiments in anesthetized dogs in which infusion of various peripheral vasodilators improved CO after burn injury.[121,138] They demonstrated a reduction in the SVR and augmented CO after verapamil, but the myocardial force of contraction remained depressed. Pruitt et al. demonstrated the utility of a vasodilator, hydralazine, to reduce SVR and augment CO (with the caveat that hypovolemia should first be corrected).[139]

There are several organs particularly susceptible to ischemia, organ dysfunction, and organ failure when burn resuscitation is delayed or inadequate. These include the kidney and the gastrointestinal tract. Renal ischemia can result directly from hypovolemia and increased sympathetic tone, but elevations in plasma hemoglobin, and particularly myoglobin, correlate with increased renal failure.[140,141] Renal failure rates have declined dramatically because of standardized regimens of adequate fluid therapy, but when therapy is delayed or associated with hypotension acute renal failure is not uncommon.[140–142]

Mesenteric vasoconstriction can occur despite apparently "adequate" resuscitation.[115,143] Bacterial and endotoxin translocation that can contribute to the development of sepsis is one consequence of visceral ischemia.

Encephalopathy is not uncommon after large cutaneous burns, particularly in children, but the exact cause remains unclear. Studies in anesthetized sheep subjected to a 70% TBSA scald show that cerebral autoregulation is well maintained in the immediate postburn period, but 6 hours after resuscitation increased cerebral vascular resistance reduced cerebral blood flow by 50%.[144]

PULMONARY CIRCULATION AND LUNG EDEMA

In large burns there is a pronounced increase in PVR that corresponds with the increased SVR.[7,54] In contrast to the systemic circulation, however, pulmonary edema is unusual and typically does not occur until after the fluid resuscitation phase is complete. Pulmonary wedge pressure is increased more than left atrial pressure after experimental burn injury due to postcapillary venular constriction.[54,145] By increasing capillary pressure, venular constriction may contribute to pulmonary edema. It is likely that some degree of left heart failure also contributes to the increased capillary pressure. However hypoproteinemia may be the greatest contributing factor to postburn pulmonary edema.[146] Analysis of lung lymph sampled in large animal models after 40% TBSA burn injury showed no evidence of increased microvascular permeability. Furthermore, lung lymph flow may increase considerably to counteract interstitial fluid accumulation. As a result, clinical studies of burn-injured patients suggest that, in the absence of inhalation injury, the lungs do not typically develop edema.[147,148] Pulmonary dysfunction associated with inhalation injury is discussed in a separate chapter.

FLUID OVERLOAD AND ABDOMINAL COMPARTMENT SYNDROME

Prompt and adequate fluid resuscitation has undoubtedly improved the outcome of burn-injured patients, and Chapter 9 describes resuscitation strategies in detail. Despite the advances in burn shock resuscitation, massive edema of both burned and unburned tissues continues to be a repercussion of large-volume fluid resuscitation.

It is now clear that there is a trend toward providing fluid in excess of the published formula, which has been termed "fluid creep."[149] Over-resuscitation and the resulting edema are fraught with complications. The problems of the over-resuscitated burn patient may include optic neuropathy due to intraocular hypertension,[150] pulmonary edema,[151,152]

the need for prolonged mechanical ventilation or tracheostomy,[153] graft failure, or the need for fasciotomy of uninjured extremities[154] due to massive edema.

The most life-threatening complication of edema, with a mortality rate of 75%, is abdominal compartment syndrome (ACS).[155] Intra-abdominal hypertension (IAH) is defined as an intra-abdominal pressure of more than 12 cm H_2O and is most often seen during the acute resuscitation phase up to 48 hours postburn.[156] ACS is sustained IAH of greater than 20 mmHg combined with new organ failure (e.g., elevated peak inspiratory pressures or oliguria despite aggressive fluid resuscitation). The syndrome typically leads to multiple organ dysfunction, characterized by impaired renal and hepatic blood flow, bowel ischemia, pulmonary dysfunction, depressed cardiac output, elevated intracranial pressures, and death.[157,158] ACS can occur after major abdominal trauma or surgery; the condition in the absence of abdominal injury is known as secondary ACS.[159] A review showed that the prevalence of ACS is between 4% and 17% in the severely burned.[155] The use of albumin during resuscitation may reduce the risk of ACS.[41] Massive edema of burned and unburned tissues continues to be a problem in burn-shock resuscitation.

Conclusion

Thermal injury results in massive fluid shifts from the circulating plasma into the interstitial space of both burned tissue and (in burns >20–30% TBSA) unburned tissue, causing hypovolemia and edema. Changes in the variables comprising the Starling equation favor fluid extravasation from blood to tissue. In burned tissue rapid edema formation is predominantly due to the development of strongly negative interstitial fluid pressure and, to a lesser degree, by an increase in microvascular pressure and permeability. In uninjured soft tissues, increased microvascular permeability is mainly the result of glycocalyx loss and endothelial activation. The type, volume, and timing of fluid used to resuscitate affect the magnitude of these fluid shifts.

Secondary to the thermal injury there is release of inflammatory mediators and stress hormones. These circulating mediators deleteriously increase microvascular permeability and alter cellular membrane function by which water and sodium enter cells. Circulating mediators also favor renal conservation of water and salt, impair cardiac contractility, and cause vasoconstriction. The end result of this complex chain of events is decreased cardiac output, end-organ ischemia, and metabolic acidosis. Without early and effective resuscitation these derangements can result in organ dysfunction, cardiovascular collapse, and death.

Resuscitation is a double-edged sword in that it increases edema in both burned and unburned tissue. Edema likely contributes to decreased tissue oxygen diffusion and further ischemic injury to already damaged cells. Research should continue to define better treatments that ameliorate burn shock and burn edema. The success of this research will require the identification of key circulatory factors that alter microvascular permeability, cause vasoconstriction, depolarize cellular membranes, and depress myocardial function. Cellular or systemic methods to prevent the release or block the activity of specific mediators are needed.

Complete references available online at www.expertconsult.inkling.com

Further Reading

Cancio LC, Chavez S, Alvarado-Ortega M, et al. Predicting increased fluid requirements during the resuscitation of thermally injured patients. *J Trauma*. 2004;56(2):404-413.

Cartotto R, Zhou A. Fluid creep: the pendulum hasn't swung back yet! *J Burn Care Res*. 2010;31(4):551-558.

Lawrence A, Faraklas I, Watkins H, et al. Colloid administration normalizes resuscitation ratio and ameliorates "fluid creep". *J Burn Care Res*. 2010;31(1):40-47.

Malbrain MLNG, Keulenaer BL, Oda J, et al. Intra-abdominal hypertension and abdominal compartment syndrome in burns, obesity, pregnancy, and general medicine. *Anaesthesiol Intensive Ther*. 2015;47:228-240.

Navickis RJ, Greenhalgh DG, Wilkes MM. Albumin in burn shock resuscitation: a meta-analysis of controlled clinical studies. *J Burn Care Res*. 2016;37(3):e268-e278.

References

1. Cockshott WP. The book shelf; the history of the treatment of burns. *Surg Gynecol Obstet*. 1956;102(1):116-124.
2. Haynes BW. The history of burn care. In: Boswick JAJ, ed. *The Art and Science of Burn Care*. Rockville, MD: Aspen; 1987:3-9.
3. Underhill FP. Changes in blood concentration with special reference to the treatment of extensive superficial burns. *Ann Surg*. 1927;86(6):840-849.
4. Youn YK, LaLonde C, Demling R. The role of mediators in the response to thermal injury. *World J Surg*. 1992;16(1):30-36.
5. Aulick LH, Wilmore DW, Mason AD, et al. Influence of the burn wound on peripheral circulation in thermally injured patients. *Am J Physiol*. 1977;233(4):H520-H526.
6. Settle J. Fluid therapy in burns. *J R Soc Med*. 1982.
7. Demling RH. Fluid replacement in burned patients. *Surg Clin North Am*. 1987;67(1):15-30.
8. Demling RH, Will JA, Belzer FO. Effect of major thermal injury on the pulmonary microcirculation. *Surgery*. 1978;83(6):746-751.
9. Baxter CR. Fluid volume and electrolyte changes of the early postburn period. *Clin Plast Surg*. 1974;1(4):693-703.
10. Baxter CR, Cook WA, Shires GT. Serum myocardial depressant factor of burn shock. *Surg Forum*. 1966;17:1-2.
11. Hilton JG, Marullo DS. Effects of thermal trauma on cardiac force of contraction. *Burns Incl Therm Inj*. 1986;12(3):167-171.
12. Clark W. Death due to thermal trauma. In: Dolecek R, Brizio-Moteni L, Moletni A, et al., eds. *Nedocrinology of Thermal Trauma*. Philadelphia, PA: Lea & Febiger; 1990:6-27.
13. Lund T, Reed RK. Acute hemodynamic effects of thermal skin injury in the rat. *Circ Shock*. 1986;20(2):105-114.
14. Arturson G. Pathophysiological aspects of the burn syndrome with special reference to liver injury and alterations of capillary permeability. *Acta Chir Scand Suppl*. 1961;Suppl 274:1-135.
15. Leape IL. Kinetics of burn edema formation in primates. *Ann Surg*. 1972;176(2):223-226.
16. Demling RH, Mazess RB, Witt RM, et al. The study of burn wound edema using dichromatic absorptiometry. *J Trauma*. 1978;18(2):124-128.
17. Onarheim H, Lund T, Reed R. Thermal skin injury: II. Effects on edema formation and albumin extravasation of fluid resuscitation with lactated Ringer's, plasma, and hypertonic saline (2,400 mosmol/l) in the rat. *Circ Shock*. 1989;27(1):25-37.
18. Arturson G, Jakobsson OP. Oedema measurements in a standard burn model. *Burns Incl Therm Inj*. 1985;12(1):1-7.
19. Leape LL. Early burn wound changes. *J Pediatr Surg*. 1968;3(2):292-299.
20. Leape LL. Initial changes in burns: tissue changes in burned and unburned skin of rhesus monkeys. *J Trauma*. 1970;10(6):488-492.
21. Landis EM, Pappenheimer JR. Exchange of substances through the capillary walls. In: Hamilton WF, Dow P, eds. *Handbook of Physiology Circulation*. Washington D.C.: American Physiologic Society; 1963:961-1034.
22. Aukland K, Reed RK. Interstitial-lymphatic mechanisms in the control of extracellular fluid volume. *Physiol Rev*. 1993;73(1):1-78.
23. Reed RK, Rubin K. Transcapillary exchange: role and importance of the interstitial fluid pressure and the extracellular matrix. *Cardiovasc Res*. 2010;87(2):211-217. doi:10.1093/cvr/cvq143.
24. Chappell D, Jacob M, Hofmann-Kiefer K, et al. A rational approach to perioperative fluid management. *Anesthesiology*. 2008;109(4):723-740.
25. Jacob M, Chappell D, Rehm M. The "third space": fact or fiction? *Best Pract Res Clin Anaesthesiol*. 2009;23(2):145-157.
26. Woodcock TE, Woodcock TM. Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. *Br J Anaesth*. 2012;108(3):384-394.
27. Arturson G, Mellander S. Acute changes in capillary filtration and diffusion in experimental burn injury. *Acta Physiol Scand*. 1964;62:457-463.
28. Pitt RM, Parker JC, Jurkovich GJ, et al. Analysis of altered capillary pressure and permeability after thermal injury. *J Surg Res*. 1987;42(6):693-702.
29. Lund T, Wiig H, Reed RK. Acute postburn edema: role of strongly negative interstitial fluid pressure. *Am J Physiol*. 1988;255(5 Pt 2):H1069-H1074.
30. Kinsky MP, Milner SM, Button B, et al. Resuscitation of severe thermal injury with hypertonic saline dextran: effects on peripheral and visceral edema in sheep. *J Trauma*. 2000;49(5):844-853.
31. Reed RK, Berg A, Gjerde EA, et al. Control of interstitial fluid pressure: role of beta1-integrins. *Semin Nephrol*. 2001;21(3):222-230.
32. McGee MP, Morykwas MJ, Argenta LC. The local pathology of interstitial edema: surface tension increases hydration potential in heat-damaged skin. *Wound Repair Regen*. 2011;19(3):358-367.
33. McGee MP, Morykwas M, Campbell D, et al. Interstitial-matrix edema in burns: mechanistic insights from subatmospheric pressure treatment in vivo. *Wound Repair Regen*. 2014;22(1):96-102.
34. Arturson G. Microvascular permeability to macromolecules in thermal injury. *Acta Physiol Scand Suppl*. 1979;463:111-122.
35. Harms BA, Bodai BI, Kramer GC, et al. Microvascular fluid and protein flux in pulmonary and systemic circulations after thermal injury. *Microvasc Res*. 1982;23(1):77-86.
36. Zetterström H, Arturson G. Plasma oncotic pressure and plasma protein concentration in patients following thermal injury. *Acta Anaesthesiol Scand*. 1980;24(4):288-294.
37. Pitkänen J, Lund T, Aanderud L, et al. Transcapillary colloid osmotic pressures in injured and non-injured skin of seriously burned patients. *Burns Incl Therm Inj*. 1987;13(3):198-203.
38. Demling RH, Kramer G, Harms B. Role of thermal injury-induced hypoproteinemia on fluid flux and protein permeability in burned and nonburned tissue. *Surgery*. 1984;95(2):136-144.
39. Cochran A, Morris SE, Edelman LS, et al. Burn patient characteristics and outcomes following resuscitation with albumin. *Burns*. 2007;33(1):25-30. doi:10.1016/j.burns.2006.10.005.
40. Lawrence A, Faraklas I, Watkins H, et al. Colloid administration normalizes resuscitation ratio and ameliorates "fluid creep". *J Burn Care Res*. 2010;31(1):40-47.
41. Navickis RJ, Greenhalgh DG, Wilkes MM. Albumin in burn shock resuscitation: a meta-analysis of controlled clinical studies. *J Burn Care Res*. 2016;37(3):e268-e278.
42. Friedl HP, Till GO, Trentz O, et al. Roles of histamine, complement and xanthine oxidase in thermal injury of skin. *Am J Pathol*. 1989;135(1):203-217.
43. Lund T, Onarheim H, Reed RK. Pathogenesis of edema formation in burn injuries. *World J Surg*. 1992;16(1):2-9.
44. Harms BA, Kramer GC, Bodai BI, et al. Effect of hypoproteinemia on pulmonary and soft tissue edema formation. *Crit Care Med*. 1981;9(7):503-508.
45. Meumann M, Demling RH. Colloid vs crystalloid: a current perspective. *Confed Aust Crit Care Nurses J*. 1990;3(3):30-35.
46. Hilton JG. Effects of fluid resuscitation on total fluid loss following thermal injury. *Surg Gynecol Obstet*. 1981;152(4):441-447.
47. Kramer GC, Harms BA, Bodai BI, et al. Mechanisms for redistribution of plasma protein following acute protein depletion. *Am J Physiol*. 1982;243(5):H803-H809.
48. Turk E, Caliskan M, Karagulle E, et al. A prospective clinical study of flow-mediated dilatation in burn injury. *J Burn Care Res*. 2014;35(2):169-175.
49. Adamson RH, Lenz JF, Zhang X, et al. Oncotic pressures opposing filtration across non-fenestrated rat microvessels. *J Physiol*. 2004;557(Pt 3):889-907.
50. Levick JR, Michel CC. Microvascular fluid exchange and the revised Starling principle. *Cardiovasc Res*. 2010;87(2):198-210.
51. Curry F-RE, Adamson RH. Vascular permeability modulation at the cell, microvessel, or whole organ level: towards closing gaps in our knowledge. *Cardiovasc Res*. 2010;87(2):218-229.
52. Kozar RA, Peng Z, Zhang R, et al. Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock. *Anesth Analg*. 2011;112(6):1289-1295.
53. Brouhard BH, Carvajal HF, Linares HA. Burn edema and protein leakage in the rat. I. Relationship to time of injury. *Microvasc Res*. 1978;15(2):221-228.
54. Kramer GC, Gunther RA, Nerlich ML, et al. Effect of dextran-70 on increased microvascular fluid and protein flux after thermal injury. *Circ Shock*. 1982;9(5):529-541.
55. Kremer T, Abé D, Weihrauch M, et al. Burn plasma transfer induces burn edema in healthy rats. *Shock*. 2008;30(4):394-400.
56. Kremer T, Harenberg P, Hernekamp F, et al. High-dose vitamin C treatment reduces capillary leakage after burn plasma transfer in rats. *J Burn Care Res*. 2010;31(3):470-479.

57. Hernekamp JF, Klein H, Schmidt K, et al. 5-HT2a receptor antagonism reduces burn-induced macromolecular efflux in rats. *Eur J Trauma Emerg Surg*. 2015;41(5):565-573.
58. Hernekamp J-F, Hu S, Schmidt K, et al. Cinanserin reduces plasma extravasation after burn plasma transfer in rats. *Burns*. 2013;39(6):1226-1233.
59. Hernekamp JF, Hu S, Schmidt K, et al. Methysergide attenuates systemic burn edema in rats. *Microvasc Res*. 2013;89:115-121.
60. Kremer T, Hernekamp F, Riedel K, et al. Topical application of cerium nitrate prevents burn edema after burn plasma transfer. *Microvasc Res*. 2009;78(3):425-431.
61. Hernekamp JF, Hu SX, Schmidt VJ, et al. Influence of cdp-choline administration on early burn edema in rats. *Ann Plast Surg*. 2015;75(4):388-392.
62. Hernekamp F, Klein H, Schmidt K, et al. Microcirculatory effects of physostigmine on experimental burn edema. *J Burn Care Res*. 2015;36(2):279-286.
63. Shires GT, Cunningham JN, Backer CR, et al. Alterations in cellular membrane function during hemorrhagic shock in primates. *Ann Surg*. 1972;176(3):288-295.
64. Nakayama S, Kramer GC, Carlsen RC, et al. Amiloride blocks membrane potential depolarization in rat skeletal muscle during hemorrhagic shock. *Circ Shock*. 1984;13:106-107.
65. Arango A, Illner H, Shires GT. Role of ischemia in the induction of changes in cell membrane during hemorrhagic shock. *J Surg Res*. 1976;20(5):473-476.
66. Holliday RL, Illner HP, Shires GT. Liver cell membrane alterations during hemorrhagic shock in the rat. *J Surg Res*. 1981;31(6):506-515.
67. Mazzoni MC, Borgström P, Intaglietta M, et al. Lumenal narrowing and endothelial cell swelling in skeletal muscle capillaries during hemorrhagic shock. *Circ Shock*. 1989;29(1):27-39.
68. Garcia NM, Horton JW. L-arginine improves resting cardiac transmembrane potential after burn injury. *Shock*. 1994;1(5):354-358.
69. Button B, Baker RD, Vertrees RA, et al. Quantitative assessment of a circulating depolarizing factor in shock. *Shock*. 2001;15(3):239-244.
70. Evans JA, Darlington DN, Gann DS. A circulating factor(s) mediates cell depolarization in hemorrhagic shock. *Ann Surg*. 1991;213(6):549-557.
71. Trunkey DD, Illner H, Arango A, et al. Changes in cell membrane function following shock and cross-perfusion. *Surg Forum*. 1974;25(0):1-3.
72. Brown JM, Grosso MA, Moore EE. Hypertonic saline and dextran: impact on cardiac function in the isolated rat heart. *J Trauma*. 1990;30(6):646-651.
73. Evans JA, Massoglia G, Sutherland B. Molecular properties of hemorrhagic shock factor. *Biophys J*. 1993;64:A384.
74. Goodman-Gilman A, Rall T, Nies A, et al. *The Pharmacological Basis of Therapeutics*. New York: Pergamon Press; 1990.
75. Räntfors J, Cassuto J. Role of histamine receptors in the regulation of edema and circulation postburn. *Burns*. 2003;29(8):769-777.
76. Till GO, Guilds LS, Mahrougui M, et al. Role of xanthine oxidase in thermal injury of skin. *Am J Pathol*. 1989;135(1):195-202.
77. Boykin JV, Manson NH. Mechanisms of cimetidine protection following thermal injury. *Am J Med*. 1987;83(6A):76-81.
78. Tanaka H, Wada T, Simazaki S, et al. Effects of cimetidine on fluid requirement during resuscitation of third-degree burns. *J Burn Care Rehabil*. 1991;12(5):425-429.
79. Anggård E, Jonsson CE. Efflux of prostaglandins in lymph from scalded tissue. *Acta Physiol Scand*. 1971;81(4):440-447.
80. Harms BA, Bodai BI, Smith M, et al. Prostaglandin release and altered microvascular integrity after burn injury. *J Surg Res*. 1981;31(4):274-280.
81. Arturson G. Anti-inflammatory drugs and burn edema formation. In: Mary R, Dogo G, eds. *Care of the Burn Wound*. Basel: Karger; 1981:21-24.
82. Arturson G, Hamberg M, Jonsson CE. Prostaglandins in human burn blister fluid. *Acta Physiol Scand*. 1973;87(2):270-276.
83. LaLonde C, Knox J, Daryani R, et al. Topical flurbiprofen decreases burn wound-induced hypermetabolism and systemic lipid peroxidation. *Surgery*. 1991;109(5):645-651.
84. Huang YS, Li A, Yang ZC. Roles of thromboxane and its inhibitor anisodamine in burn shock. *Burns*. 1990;16(4):249-253.
85. Heggers JP, Loy GL, Robson MC, et al. Histological demonstration of prostaglandins and thromboxanes in burned tissue. *J Surg Res*. 1980;28(2):110-117.
86. Heggers JP, Robson MC, Zachary LS. Thromboxane inhibitors for the prevention of progressive dermal ischemia due to the thermal injury. *J Burn Care Rehabil*. 1985;6(6):466-468.
87. LaLonde C, Demling RH. Inhibition of thromboxane synthetase accentuates hemodynamic instability and burn edema in the anesthetized sheep model. *Surgery*. 1989;105(5):638-644.
88. Jacobsen S, Waaler BA. The effect of scalding on the content of kininogen and kininase in limb lymph. *Br J Pharmacol Chemother*. 1966;27(1):222-229.
89. Bauer JA, Hafner M, Fritz H. Balanced antiinflammation: the combined application of a PAF inhibitor and a cyclooxygenase inhibitor blocks the inflammatory take-off after burns. *Int J Tissue React*. 1990;12(4):203-211.
90. Nwariaku FE, Sikes PJ, Lightfoot E, et al. Effect of a bradykinin antagonist on the local inflammatory response following thermal injury. *Burns*. 1996;22(4):324-327.
91. Tao K, Wang H-T, Chen B, et al. Effect of nonpeptide NK1 receptor antagonist L-703,606 on the edema formation in rats at early stage after deep partial-thickness skin scalding. *Asian Pac J Trop Med*. 2013;6(5):387-394.
92. Carvajal HF, Brouhard BH, Linares HA. Effect of antihistamine-antiserotonin and ganglionic blocking agents upon increased capillary permeability following burn trauma. *J Trauma*. 1975;15(11):969-975.
93. Ferrara JJ, Westervelt CL, Kukuy EL, et al. Burn edema reduction by methysergide is not due to control of regional vasodilation. *J Surg Res*. 1996;61(1):11-16.
94. Zhang XJ, Irtun O, Zheng Y, et al. Methysergide reduces nonnutritive blood flow in normal and scalded skin. *Am J Physiol Endocrinol Metab*. 2000;278(3):E452-E461.
95. Wilmore DW, Long JM, Mason AD, et al. Catecholamines: mediator of the hypermetabolic response to thermal injury. *Ann Surg*. 1974;180(4):653-668.
96. Hilton JG. Effects of sodium nitroprusside on thermal trauma depressed cardiac output in the anaesthetized dog. *Burns Incl Therm Inj*. 1984;10(5):318-322.
97. McCord JM, Fridovich I. The biology and pathology of oxygen radicals. *Ann Intern Med*. 1978;89(1):122-127.
98. Demling RH, LaLonde C. Early postburn lipid peroxidation: effect of ibuprofen and allopurinol. *Surgery*. 1990;107(1):85-93.
99. Slater T, Benedetto C. Free radical reactions in relation to lipid peroxidation, inflammayion and prostaglandin metabolism. In: Berti F, Veto G, eds. *The Prostaglandin System*. New York: Plenum Press; 1979:109-126.
100. McCord JM. Oxygen-derived free radicals in postischemic tissue injury. *N Engl J Med*. 1985;312(3):159-163.
101. Tanaka H, Matsuda H, Shimazaki S, et al. Reduced resuscitation fluid volume for second-degree burns with delayed initiation of ascorbic acid therapy. *Arch Surg*. 1997;132(2):158-161.
102. Tanaka H, Lund T, Wiig H, et al. High dose vitamin C counteracts the negative interstitial fluid hydrostatic pressure and early edema generation in thermally injured rats. *Burns*. 1999;25(7):569-574.
103. Dubick MA, Williams C, Elgjo GI, et al. High-dose vitamin C infusion reduces fluid requirements in the resuscitation of burn-injured sheep. *Shock*. 2005;24(2):139-144.
104. Kahn SA, Beers RJ, Lentz CW. Resuscitation after severe burn injury using high-dose ascorbic acid: a retrospective review. *J Burn Care Res*. 2011;32(1):110-117.
105. Fischer SR, Bone HG, Powell WC, et al. Pyridoxalated hemoglobin polyoxyethylene conjugate does not restore hypoxic pulmonary vasoconstriction in ovine sepsis. *Crit Care Med*. 1997;25(9):1551-1559.
106. Farina Junior JA, Celotto AC, da Silva MF, et al. Guanylate cyclase inhibition by methylene blue as an option in the treatment of vasoplegia after a severe burn. A medical hypothesis. *Med Sci Monit*. 2012;18(5):HY13-HY17.
107. Lange M, Hamahata A, Enkhbaatar P, et al. Beneficial effects of concomitant neuronal and inducible nitric oxide synthase inhibition in ovine burn and inhalation injury. *Shock*. 2011;35(6):626-631.
108. Rawlingson A, Greenacre SA, Brain SD. Generation of peroxynitrite in localised, moderate temperature burns. *Burns*. 2000;26(3):223-227.
109. Lindblom L, Cassuto J, Yregård L, et al. Importance of nitric oxide in the regulation of burn oedema, proteinuria and urine output. *Burns*. 2000;26(1):13-17.

110. Lindblom L, Cassuto J, Yregård L, et al. Role of nitric oxide in the control of burn perfusion. *Burns*. 2000;26(1):19-23.
111. Lange M, Szabo C, Enkhbaatar P, et al. Beneficial pulmonary effects of a metalloporphyrinic peroxynitrite decomposition catalyst in burn and smoke inhalation injury. *Am J Physiol Lung Cell Mol Physiol*. 2011;300(2):L167-L175.
112. Westphal M, Rehberg S, Maybauer MO, et al. Cardiopulmonary effects of low-dose arginine vasopressin in ovine acute lung injury. *Crit Care Med*. 2011;39(2):357-363.
113. Ono I, Gunji H, Hasegawa T, et al. Effects of a platelet activating factor antagonist on oedema formation following burns. *Burns*. 1993;19:202-207.
114. Fink MP. Gastrointestinal mucosal injury in experimental models of shock, trauma, and sepsis. *Crit Care Med*. 1991;19(5):627-641.
115. Cui X, Sheng Z, Guo Z. [Mechanisms of early gastro-intestinal ischemia after burn: hemodynamic and hemorrheologic features]. *Zhonghua Zheng Xing Shao Shang Wai Ke Za Zhi*. 1998;14(4):262-265.
116. Crum RL, Dominic W, Hansbrough JF, et al. Cardiovascular and neurohumoral responses following burn injury. *Arch Surg*. 1990;125(8):1065-1069.
117. Sun K, Gong A, Wang CH, et al. Effect of peripheral injection of arginine vasopressin and its receptor antagonist on burn shock in the rat. *Neuropeptides*. 1990;17(1):17-22.
118. Hu Q, Du M-H, Hu S, et al. PNU-282987 improves the hemodynamic parameters by alleviating vasopermeability and tissue edema in dogs subjected to a lethal burns shock. *J Burn Care Res*. 2014;35(4):e197-e204.
119. Wiggins-Dohlvik K, Oakley RP, Han MS, et al. Tissue inhibitor of metalloproteinase-2 inhibits burn-induced derangements and hyperpermeability in microvascular endothelial cells. *Am J Surg*. 2016;211(1):197-205.
120. Berger MM, Rozendal CS, Schieber C, et al. The effect of endothelin-1 on alveolar fluid clearance and pulmonary edema formation in the rat. *Anesth Analg*. 2009;108(1):225-231.
121. Michie DD, Goldsmith RS, Mason AD. Effects of hydralazine and high molecular weight dextran upon the circulatory responses to severe thermal burns. *Circ Res*. 1963;13:468-473.
122. Martyn J, Wilson RS, Burke JF. Right ventricular function and pulmonary hemodynamics during dopamine infusion in burned patients. *Chest*. 1986;89(3):357-360.
123. Adams HR, Baxter CR, Izenberg SD. Decreased contractility and compliance of the left ventricle as complications of thermal trauma. *Am Heart J*. 1984;108(6):1477-1487.
124. Merriam TW. Myocardial function following thermal injury. *Circ Res*. 1962;11:669-673.
125. Howard TS, Hermann DG, McQuitty AL, et al. Burn-induced cardiac dysfunction increases length of stay in pediatric burn patients. *J Burn Care Res*. 2013;34(4):413-419.
126. Horton JW, White J, Baxter CR. Aging alters myocardial response during resuscitation in burn shock. *Surg Forum*. 1987;38:249-251.
127. Baxter CR, Shires T. Physiological response to crystalloid resuscitation of severe burns. *Ann N Y Acad Sci*. 1968;150(3):874-894.
128. Sugi K, Theissen JL, Traber LD, et al. Impact of carbon monoxide on cardiopulmonary dysfunction after smoke inhalation injury. *Circ Res*. 1990;66(1):69-75.
129. Soejima K, Schmalstieg FC, Sakurai H, et al. Pathophysiological analysis of combined burn and smoke inhalation injuries in sheep. *Am J Physiol Lung Cell Mol Physiol*. 2001;280(6):L1233-L1241.
130. Horton JW, Baxter CR, White DJ. Differences in cardiac responses to resuscitation from burn shock. *Surg Gynecol Obstet*. 1989;168(3):201-213.
131. Horton JW, White DJ, Baxter CR. Hypertonic saline dextran resuscitation of thermal injury. *Ann Surg*. 1990;211(3):301-311.
132. Horton JW, White DJ, Hunt JL. Delayed hypertonic saline dextran administration after burn injury. *J Trauma*. 1995;38(2):281-286.
133. Horton JW, Garcia NM, White DJ, et al. Postburn cardiac contractile function and biochemical markers of postburn cardiac injury. *J Am Coll Surg*. 1995;181(4):289-298.
134. Horton JW, White J, Maass D, et al. Arginine in burn injury improves cardiac performance and prevents bacterial translocation. *J Appl Physiol*. 1998;84(2):695-702.
135. Cioffi WG, DeMeules JE, Gamelli RL. The effects of burn injury and fluid resuscitation on cardiac function in vitro. *J Trauma*. 1986;26(7):638-642.
136. Murphy JT, Horton JW, Purdue GF, et al. Evaluation of troponin-I as an indicator of cardiac dysfunction after thermal injury. *J Trauma*. 1998;45(4):700-704.
137. Horton JW, White J, Baxter CR. The role of oxygen-derived free radicals in burn-induced myocardial contractile depression. *J Burn Care Rehabil*. 1988;9(6):589-598.
138. Hilton JG. Effects of verapamil on thermal trauma depressed cardiac output in the anaesthetized dog. *Burns Incl Therm Inj*. 1984;10(5):313-317.
139. Pruitt BA, Mason AD, Moncrief JA. Hemodynamic changes in the early postburn patient: the influence of fluid administration and of a vasodilator (hydralazine). *J Trauma*. 1971;11(1):36-46.
140. Holm C, Hörbrand F, von Donnersmarck GH, et al. Acute renal failure in severely burned patients. *Burns*. 1999;25(2):171-178.
141. Chrysopoulo MT, Jeschke MG, Dziewulski P, et al. Acute renal dysfunction in severely burned adults. *J Trauma*. 1999;46(1):141-144.
142. Ibrahim AE, Sarhane KA, Fagan SP, et al. Renal dysfunction in burns: a review. *Ann Burns Fire Disasters*. 2013;26(1):16-25.
143. Tokyay R, Zeigler ST, Traber DL, et al. Postburn gastrointestinal vasoconstriction increases bacterial and endotoxin translocation. *J Appl Physiol*. 1993;74(4):1521-1527.
144. Shin C, Kinsky MP, Thomas JA, et al. Effect of cutaneous burn injury and resuscitation on the cerebral circulation in an ovine model. *Burns*. 1998;24(1):39-45.
145. Demling RH, Wong C, Jin LJ, et al. Early lung dysfunction after major burns: role of edema and vasoactive mediators. *J Trauma*. 1985;25(10):959-966.
146. Demling RH, Niehaus G, Perea A, et al. Effect of burn-induced hypoproteinemia on pulmonary transvascular fluid filtration rate. *Surgery*. 1979;85(3):339-343.
147. Tranbaugh RF, Lewis FR, Christensen JM, et al. Lung water changes after thermal injury. The effects of crystalloid resuscitation and sepsis. *Ann Surg*. 1980;192(4):479-490.
148. Tranbaugh RF, Elings VB, Christensen JM, et al. Effect of inhalation injury on lung water accumulation. *J Trauma*. 1983;23(7):597-604.
149. Pruitt BA. Protection from excessive resuscitation: "pushing the pendulum back". *J Trauma*. 2000;49(3):567-568.
150. Sullivan SR, Ahmadi AJ, Singh CN, et al. Elevated orbital pressure: another untoward effect of massive resuscitation after burn injury. *J Trauma*. 2006;60(1):72-76.
151. Blot S, Hoste E, Colardyn F. Acute respiratory failure that complicates the resuscitation of pediatric patients with scald injuries. *J Burn Care Rehabil*. 2000;21(3):289-290.
152. Zak AL, Harrington DT, Barillo DJ, et al. Acute respiratory failure that complicates the resuscitation of pediatric patients with scald injuries. *J Burn Care Rehabil*. 1999;20(5):391-399.
153. Coln CE, Purdue GF, Hunt JL. Tracheostomy in the young pediatric burn patient. *Arch Surg*. 1998;133(5):537–539–540.
154. Sheridan RL, Tompkins RG, McManus WF, et al. Intracompartmental sepsis in burn patients. *J Trauma*. 1994;36(3):301-305.
155. Strang SG, Van Lieshout EMM, Breederveld RS, et al. A systematic review on intra-abdominal pressure in severely burned patients. *Burns*. 2014;40(1):9-16.
156. Azzopardi EA, McWilliams B, Iyer S, et al. Fluid resuscitation in adults with severe burns at risk of secondary abdominal compartment syndrome–an evidence based systematic review. *Burns*. 2009;35(7):911-920.
157. Bloomfield GL, Dalton JM, Sugerman HJ, et al. Treatment of increasing intracranial pressure secondary to the acute abdominal compartment syndrome in a patient with combined abdominal and head trauma. *J Trauma*. 1995;39(6):1168-1170.
158. Ivatury RR, Diebel L, Porter JM, et al. Intra-abdominal hypertension and the abdominal compartment syndrome. *Surg Clin North Am*. 1997;77(4):783-800.
159. Maxwell RA, Fabian TC, Croce MA, et al. Secondary abdominal compartment syndrome: an underappreciated manifestation of severe hemorrhagic shock. *J Trauma*. 1999;47(6):995-999.
160. Paul W, Douglas GJ, Lawrence L, et al. Cutaneous permeability responses to bradykinin and histamine in the guinea-pig: possible differences in their mechanism of action. *Br J Pharmacol*. 1994;111(1):159-164.
161. Pollard V, Prough DS, DeMelo AE, et al. The influence of carbon dioxide and body position on near-infrared spectroscopic assessment of cerebral hemoglobin oxygen saturation. *Anesth Analg*. 1996;82(2):278-287.

9 Burn Resuscitation

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Introduction

Burns in excess of about 20% of the total body surface area (TBSA) cause shock, manifested by decreased circulating blood volume, decreased cardiac output (CO), and inadequate end-organ perfusion. Fluid resuscitation to address burn shock is one of the key lifesaving interventions in the early care of burn patients. Inadequate or delayed fluid resuscitation causes organ failure and death.[1] On the other hand, provision of excessive amounts of fluid (overresuscitation), by augmenting edema formation and engendering complications such as compartment syndromes, also increases morbidity and mortality.[2] Thus the overarching goal of fluid resuscitation is to achieve a careful balance between the two extremes of over- and underresuscitation; in other words, "to maintain vital organ function at the least immediate or delayed physiologic cost."[3]

The primary cause of burn shock is a reduction in the circulating blood volume due to loss of fluid similar in composition to plasma across the microvasculature. Thus burn shock is hypovolemic shock. Such fluid loss occurs primarily in burned tissues but also, for larger burns, in unburned tissues as well.[4] The term "leaky capillaries" is often used to describe this complex process (for details, see Chapter 8, Pathophysiology of Burn Shock and Burn Edema). Other factors that contribute to burn shock include intense vasoconstriction during the immediate postburn hours, causing increased afterload,[5] and a decrease in intrinsic myocardial contractility.[6,7] These three factors—hypovolemia, vasoconstriction, and decreased myocardial contractility—contribute to decreased CO. The aims of fluid resuscitation are simultaneously (1) to counteract the loss of circulating blood volume with intravenous fluids; (2) to monitor the physiologic response frequently and diligently; (3) to alter treatment strategy based on physiologic response (e.g., by titrating the fluid infusion rate hourly); and (4) to anticipate, guard against, and correct the effects of edema formation. This could be summarized as follows: burn shock mandates *simultaneous fluid resuscitation and edema management strategies*.

Early Approaches to Fluid Resuscitation

A wide variety of resuscitation formulas dominates much of the discussion on the treatment of burn shock (Table 9.1). Knowledge of how these formulas came about is helpful to understanding their advantages and limitations. Intravenous fluid resuscitation for the treatment of burns owes much to early investigations of the pathophysiology and treatment of cholera. In 1831, O'Shaughnessy, an Irish physician, performed studies of the chemical and microscopic features of the blood in cholera patients. Based on these studies, he proposed "the injection into the veins of tepid water holding a solution of the normal salts of the blood." He did canine experiments of this novel therapy but did not apply it to humans. One year later, Thomas Latta, a Scottish physician, read about O'Shaughnessy's work and treated patients with cholera using rectal, oral, and then intravenous saline solutions.[8] In 1906, Dr. Haldor Sneve of St. Paul, Minnesota, described the use of saline solutions, including enemas, for the treatment of burns.[9] His commonsense recommendations were not followed for years because the prevailing point of view at the time was that the main cause of death in patients with extensive burns was not hypovolemia but the absorption of toxic substances from the burned skin ("toxemia").[10] This belief led to the widespread adoption of tanning agents such as tannic acid,[11] the purpose of which was to "fix" the toxins and prevent them from entering the bloodstream.

Subsequent mass-casualty disasters and armed conflict both contributed to resuscitation advances. On November 27, 1921, the Rialto Theatre in New Haven, Connecticut, caught fire, killing 6 and injuring 80. Dr. Frank Underhill examined 21 survivors who were admitted following the fire. Underhill was a veteran of World War I and had previously reported on the effects of chemical warfare agents on the lungs. He drew a parallel between the process whereby the lungs are flooded with fluid following inhalation of toxic gases and that by which edema forms in wounds following thermal injury. He reported that the more severe the burn, the more severe the hemoconcentration (increased hemoglobin), and that fluid replacement must be rapid and is of paramount importance in survival. Additionally he reported that blister fluid was similar in composition to plasma and that the fluid lost could be replaced with an intravenous physiologic salt solution, supplemented rectally, orally, and subdermally.[12] Oral and rectal infusions were de-emphasized until recently, when their utility in austere and combat-casualty-care scenarios was revisited.[13]

In 1931, Alfred Blalock built on Underhill's reports by performing experiments in which anesthetized dogs sustained burns of approximately one-third of the TBSA, localized to one-half of the body (right or left). The animals were not resuscitated. After a period of observation (6–26 hours), the animals were euthanized, bisected, and the carcasses weighed. Thus he quantified the amount of fluid lost across the burn wounds, which averaged 3.34% of the total body weight. This fluid loss was accompanied by a mean increase in the hemoglobin level of 48%. Blalock speculated that this

Note: The opinions or assertions contained herein are the private views of the authors, and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Table 9.1 Common Burn Resuscitation Formulas

Formula	First 24 Hours Post Burn	Next 24 Hours Post Burn
Evans Formula	NS: 1 mL/kg/%TBSA burn	NS: 0.5 mL/kg/%TBSA burn
	Colloid: 1 mL/kg/%TBSA burn	Colloid: 0.5 mL/kg/%TBSA burn
	D5W: 2000 mL	D5W: 2000 mL
Brooke Formula	NS: 1.5 mL/kg/%TBSA burn	NS: 0.5 mL/kg/%TBSA burn
	Colloid: 0.5 mL/kg/%TBSA burn	Colloid: 0.25 mL/kg/%TBSA burn
	D5W: 2000 mL	D5W: 2000 mL
Modified Brooke Formula	LR: 2 mL/kg/%TBSA burn	LR: None
	Colloid: None	Colloid: 0.3–0.5 mL/kg/%TBSA burn
Parkland Formula	LR: 4 mL/kg/%TBSA burn	LR: None
	Colloid: None	Colloid: 5% albumin given at 0.3–1 mL/kg/%TBSA burn/16 per hour
Shriner's Cincinnati (For Children)	LR: 4 mL/kg/%TBSA burn + 1500 mL/m^2, ½ given over first 8 h and the remaining over the next 16 h (older children)	
	LR: 4 mL/kg/%TBSA burn + 1500 mL/m^2 + 50 mEq sodium bicarbonate for the first 8 h, followed by LR alone in second 8 h, followed by 5% albumin in LR in third 8 h (younger children)	
Galveston Formula (For Children)	LR: 5000 mL/m^2 burn + 2000 mL/m^2 total, ½ volume in first 8 h, followed by remainder in 16 h.	

From Hansen SL. From cholera to "fluid creep": a historical review of fluid resuscitation of the burn trauma patient. *Wounds* 2008;20(7): 206–213. For earlier version of the Cincinnati formula, see Merrell SW, Saffle JR, Sullivan JJ, et al. Fluid resuscitation in thermally injured children. *Am J Surg*. 1986;152(6):664–669. For earlier version of the Galveston formula, see Carvajal HF. Fluid resuscitation of pediatric burn victims: a critical appraisal. *Pediatr Nephrol*. 1994;8(3):357–366.

D5W, 5% Dextrose in water; *LR,* lactated Ringer's solution; *NS,* normal saline; *UO,* urinary output; *TBSA,* total body surface area.

process, rather than toxemia, was sufficient to explain the resultant postburn hypotension.[10] Further experiments involving excision of the burn wound as well as cross-transfusion (of burned to unburned dogs) supported his hypothesis.[10]

With World War II on the horizon, and following battles such as the Battle of Britain in 1940 and the attack on Pearl Harbor in 1941, there was great urgency to develop effective methods to care for wartime burn casualties. Meanwhile plasma now became available for intravenous administration. Several formulas were developed for burn-shock resuscitation using plasma. One recommended enough plasma to maintain the peripheral circulation, evidenced by the ease with which blood could be drawn by a needle prick. Others were based on calculations that incorporated the hematocrit and/or the protein levels in the blood.[14] The burn-size-based formulas we use today originated from a conference on January 7, 1942, of the National Research Council (NRC). This committee stated that a burn patient should receive 500 mL of plasma initially, followed by 100 mL of plasma per TBSA burned during the first 24 h post burn. Other fluids (normal saline or dextrose) should not normally exceed the plasma dose.[15] Interestingly, Harkins (who participated in the NRC meeting) described a First Aid Formula at the same time that recommended half this amount, or 50 mL/TBSA of plasma. In addition, patients should receive about 1000 mL of normal saline solution and "large amounts" of dextrose, preferably by mouth.[14,16]

These preparations were tested when, on November 28, 1942, the Cocoanut Grove nightclub in Boston caught fire, killing 492 people and injuring hundreds more in the deadliest nightclub fire in U.S. history. Patients were resuscitated with plasma, which, however, was provided by the blood bank diluted with equal volumes of normal saline.[17] Dr. Cope at the Massachusetts General Hospital provided in the first 24 hours 50 mL of plasma plus 50 mL saline for every 1% TBSA burned, followed by adjustments based on hemoconcentration.[18] Dr. Lund at the Boston City Hospital did not use a formula to guide resuscitation, but rather clinical parameters such as heart rate, blood pressure, and hematocrit.[19]

Later, Cope and Moore reported the first burn formula based on burn surface area for fluid therapy, recommending that 75 mL plasma and 75 mL noncolloid isotonic fluid be administered for every 1% TBSA burned in the first 24 hours, with one-half being given in the first 8 hours and the remaining being given in the next 16 hours. This practice of providing half of the fluid needs within the first 8 hours remains a feature of nearly all modern burn resuscitation formulas. Additionally, 2000 mL fluid was to be given on each day to maintain urine flow, preferably by mouth.[16]

These formulas were based on a normal-sized adult and could be unfavorable at the extremes of weight. Thus formulas based on both weight and TBSA were developed.

Dr. Everett Evans developed one such formula. This formula predicts infusion of 1 mL/kg per TBSA of normal saline and an equal part colloid, plus 2000 mL of 5% dextrose in water (D5W), in the first 24 hours. This is followed by 0.5 mL/kg per TBSA of saline and an equal part colloid and of D5W in the second 24 hours.[20]

BROOKE AND PARKLAND FORMULAS

The original Brooke formula of 1953 represents the beginning of a transition away from colloid use during the first 24 hours. In that formula, fluid needs for the first 24 hours are estimated as 2 mL/kg per TBSA: 0.5 mL/kg per TBSA is given as colloid, and 1.5 mL/kg per TBSA as crystalloid.[21]

Moyer eschewed the use of colloids for burn shock resuscitation, stating that crystalloid solutions alone, such as lactated Ringer's (LR), were sufficient to correct what he termed "sodium deficit shock."[22] G. Tom Shires and colleagues reported that hemorrhagic shock involved a loss not just of blood, but also of functional extracellular fluid (ECF) volume. This led to the use of large volumes of LR in the Emergency Department for the treatment of trauma patients.[23] Further studies showed that this depletion of ECF was accompanied by a decrease in the transmembrane potential difference and by intracellular sodium influx.[24]

In 1968, Baxter and Shires extended these findings to thermal injury. They measured the ECF in animals and humans, demonstrating that restoration of the functional ECF with LR could be performed, required infusion of a greater volume (4 mL/kg per TBSA) than recommended by the extant burn formulas, and led to a more rapid correction of both CO and metabolic acidosis.[6] This occurred despite a plasma volume deficit that persisted at the end of the first 24 hours post burn. During the second 24 hours post burn, plasma became effective as a volume expander and was indicated to correct this deficit. This was the origin of the widely used Parkland formula.[25]

Soon after Baxter's work, Pruitt and colleagues at the U.S. Army Institute of Surgical Research (USAISR) reported that varying the dose of colloid infused during the first 24 hours postburn did not further increase the plasma volume, meaning that colloid was no more effective than crystalloid during this period. During the second 24 h post burn, colloid did become more effective.[5] Estimation of fluid needs as 2 mL/kg per TBSA and elimination of colloid during the first 24 hours, became known as the modified Brooke formula. Also at the USAISR, Goodwin et al. conducted a randomized controlled trial comparing resuscitation with and without albumin from the time of admission. The colloid group received 2.5% albumin in LR from the start of resuscitation, whereas the crystalloid group received LR alone. They found that patients who received early albumin (1) had more rapid restoration of CO, (2) received a lower fluid volume during the first 24 hours, (3) had increased extravascular lung water on days 3–7 postburn, and (4) had increased in-hospital mortality.[26] These data, combined with the earlier study by Pruitt et al., bolstered the argument against albumin use during the first 24 hours.

Both the Parkland and modified Brooke formulas recommend crystalloids during the first 24 h; administration of colloids (i.e., 5% albumin) is reserved until the second 24 hours. This point should be underscored: these are not colloid-free, but delayed-colloid formulas. The modified Brooke formula provides a sliding scale for albumin dosing during the second 24 hours, as follows: 0.3 mL/kg per TBSA for 30–49% TBSA, 0.4 mL/kg per TBSA for 50–69% TBSA, and 0.5 mL/kg per TBSA for 70–100% TBSA.[27]

Today, crystalloid solution, mainly in the form of LR (see later discussion), is predominately used for burn resuscitation in the United States. Most burn centers use some colloid according to physician discretion or other rule.[28] The Parkland and modified Brooke formulas are the two most commonly used formulas to start fluid infusion rates. The 2012 American Burn Association consensus statement on quality improvement in fluid resuscitation concluded that evidence is lacking to recommend a standard of care.[29] On the other hand, the current Advanced Burn Life Support Guidelines recommend starting with the modified Brooke formula at 2 mL/kg per TBSA.[30] For both formulas, half of the volume is programmed for delivery during the first 8 hours post burn and half during the second 16 h post burn. Subsequent adjustment of the fluid infusion rate is made based on clinical status (see later discussion), and no abrupt change is normally made at the postburn hour 8.

To simplify fluid calculation in adults, Chung and colleagues at the USAISR recently described a "Rule of Tens": initial fluid rate (in mL/h) = TBSA × 10. Thus a patient with a 30% burn would be started at 300 mL/h. In addition, patients weighing more than 80 kg receive an additional 100 mL/h for each additional 10 kg. This estimate provides an initial infusion rate that lies between the Parkland and Brooke estimations for 88% of patients.[31] We emphasize that this formula is appropriate only for adults (weight ≥40 kg).

Children

Formulas have been developed specifically for resuscitation of children. Graves et al. at the USAISR performed a retrospective review of children weighing less than 25 kg who were resuscitated with the pediatric modified Brooke formula. This formula estimates 3 mL/kg per TBSA of LR for the first 24 hours, with half given over the first 8 hours;[32] LR is then titrated based on urine output (UO; target UO, 0.5–1.5 mL/kg per hour). Children are also given 5% dextrose in one-half normal saline (D5W½NS) at a maintenance rate, which is not titrated. The actual volume of LR infused was, on average, 3.91 mL/kg per TBSA (3.78 in those whose UO was within the target range). Maintenance fluids added an additional 2.39 mL/kg per TBSA to the total.[33] The 2011 Advanced Burn Life Support manual recommends the use of this 3 mL/kg per TBSA burned formula for children, with the addition of maintenance fluid of D5WLR.[30]

The Shriner's Cincinnati and Galveston pediatric formulas account for the larger body surface area-to-weight ratio of children. For the first 24 hours post burn, the Cincinnati formula provides 4 mL/kg per TBSA (with half given in the first 8 hours), plus maintenance needs (MN), plus evaporative losses (EL). Here, MN = (1500 mL) × (body surface area in m^2), and EL = 35 + (TBSA burned in %) × (body surface area in m^2).[34]

For the first 24 h post burn, the Galveston formula provides 5000 mL × (TBSA burned in m^2) + 2000 mL × (body surface area in m^2), with half given in the first 8 hours post burn.[35,36]

Choice of Fluid

LR is the most frequently used crystalloid solution for burn shock resuscitation. Normal saline (NS) was used in the past, but has been criticized primarily because (1) it may decrease renal blood flow and glomerular filtration rate, thus increasing the risk of acute kidney injury; and (2) in large volumes, it may cause hyperchloremic metabolic acidosis. Clinical trials of NS versus balanced crystalloid solutions such as LR or Plasma-Lyte in nonburn patients are contradictory,[37] and there are no studies in burn patients. Because LR is slightly hypotonic, it may increase brain water content and intracranial pressure (ICP).[38] This may explain, in part, the concerning finding of increased ICP in some burn studies (see later discussion). LR contains a racemic mixture of D- and L-lactate isomers. Ayuste and coauthors reported that resuscitation with standard (i.e., racemic) LR was associated with lung and liver apoptosis, which was prevented by removal of the D-lactate isomer from the LR.[39] Plasma-Lyte has an electrolyte composition and an osmolality that is closer to that of plasma, and it contains gluconate and acetate instead of lactate.[37] However there are no studies comparing Plasma-Lyte to LR in burn patients.

Although crystalloid is the mainstay of burn shock resuscitation, the debate concerning if, when, and how much colloid is needed has continued. There are several systematic approaches to colloid use, including (1) *immediate* (use colloids during all hours of burn resuscitation), (2) *early/rescue* (use colloids when resuscitation is becoming excessive, typically starting at 8–12 hours post injury), and (3) *late* (do not use any colloids for resuscitation during the first 24 hours).[28,40] Increasingly a rational approach to identifying those patients who may benefit from early colloid use is followed at many burn centers.

Demling and colleagues developed an ovine model with chronic lymph fistulas and described the dynamics of edema formation in burned and unburned tissues. Measurement of lymph flow rates (Q_L) and the lymph-to-plasma protein ratio (C_L/C_P) revealed that the ability of the microvasculature to retain plasma proteins began to recover between 8 and 12 hours post burn in unburned but not in burned tissue.[41] This provides evidence that a colloid-containing solution may be more effective than a crystalloid solution beginning about 8–12 hours post burn.

In a prospective randomized trial, O'Mara and colleagues compared fresh frozen plasma (FFP) resuscitation and crystalloid resuscitation.[42] In this trial, the FFP group received a mixture of 75 mL/kg FFP (titrated to maintain a UO of 0.5–1.0 mL/kg per hour) plus 2000 mL LR (83 mL/h), while the crystalloid group received LR according to the Parkland formula (titrated to maintain a UO of 0.5–1.0 mL/kg per hour). The crystalloid group required significantly more fluid than the FFP group (260 vs. 140 mL/kg). FFP resuscitation was associated with a lower peak intra-abdominal pressure (16 vs. 32 mm Hg). Furthermore the crystalloid group developed elevated creatinine, blood urea nitrogen (BUN), and peak airway pressure, whereas the FFP group developed only elevated peak airway pressure.

This and similar studies suggest that, particularly in patients who are at risk for complications like abdominal compartment syndrome (ACS)—e.g., patients with large burns whose early resuscitation hours feature rapid escalation in the infusion rate—early colloid use is reasonable. Consistent with this idea, an approach taken at the University of Utah burn center involves use of "albumin rescue" when the fluid infused-to-UO ratio increases above expected levels.[40,43]

Five percent albumin in NS is the most commonly used colloid for burn resuscitation today. In a previous era in which albumin was not widely available and donor screening was rudimentary, infusion of plasma was associated with a high risk of hepatitis transmission. Today the availability of safe FFP should cause us to raise the question of whether FFP offers advantages over albumin or LR. Pati et al. found that FFP or Kcentra (a factor concentrate) may be superior to albumin in protecting against increases in endothelial permeability induced by vascular endothelial growth factor-A (VEGF-A) or by trauma/hemorrhage.[44] Also in hemorrhagic shock models, Peng and colleagues observed that FFP compared to LR decreases pulmonary shedding of syndecan-1 from the endothelium, reduces endothelial permeability, and decreases neutrophil infiltration.[45] These findings in hemorrhagic shock indicate that more work on the microvascular effects of FFP during burn resuscitation is needed.

Compared with albumin and FFP, there is currently less enthusiasm for the use of hetastarch solutions such as 6% hydroxyethyl starch (HES) for burn shock resuscitation. Vlachou et al. in the United Kingdom resuscitated 26 adults with Hartmann's solution or with a combination of two-thirds Hartmann's solution and one-third HES. They found that the HES group received less fluid (263 mL vs. 307 mL/kg).[46] On the other hand, a Swiss trial in 48 patients compared LR versus 6% HES for the first 72 hours post burn. They found no difference in volume requirements, renal function, acute respiratory distress syndrome (ARDS), length of stay, or mortality.[47] A Cochrane review concluded that HES solutions increase the risk of acute kidney injury and the need for renal replacement therapy.[48] As a consequence of these and other studies, the European Medicines Agency stated in 2013 that HES should not be used in critically ill, septic, or burns patients.[49]

Another approach to reducing the infused volume during burn resuscitation is the use of hypertonic saline. While Shires, Baxter, and colleagues were advocating the rapid correction of the extracellular sodium deficit with large volumes of LR by means of the Parkland formula, Monafo argued that hypertonic lactated saline solution, given intravenously and orally, could just as easily correct the sodium deficit while avoiding the administration of excessive volumes. His fluid contained 300 mEq/L of sodium, 200 mEq/L of lactate, and 100 mEq/L of chloride.[50] Several burn centers have routinely used hypertonic saline during resuscitation. For example, Warden at the Cincinnati Shrine used LR plus 50 mEq of sodium bicarbonate per liter, which results in a mildly hypertonic solution, for the first 8 hours postburn.[51]

During fluid resuscitation using hypertonic solutions, the extracellular fluid volume deficit is partially corrected by means of water flux from the intracellular to the extracellular space, in response to the increased extracellular sodium concentration.[32] The serum sodium should be

monitored during hypertonic resuscitation, since a level of greater than 160 mEq/L has been associated with adverse renal and cerebral effects.[52]

Huang and colleagues described a study in which a first cohort of patients was treated with LR, a subsequent cohort was treated with hypertonic saline (290 mEq/L), and a third cohort was treated with LR. The hypertonic patients had a fourfold increase in the risk of renal failure and twice the mortality.[53] This experience dampened enthusiasm for hypertonic saline. However Oda et al. reported a prospective study of burn patients resuscitated either with hypertonic lactated saline (HLS) or with LR. The concentration of sodium decreased from 300 to 150 mEq/L with each subsequent liter or two administered. Patients who received HLS had a lower prevalence of intra-abdominal hypertension and received less fluid (3.1 vs. 5.2 mL/kg per TBSA).[54] Thus there may be a role for hypertonic saline resuscitation in those patients who are particularly volume sensitive or at risk of overresuscitation.[52]

A different approach to hypertonic therapy in burn shock is to use the much more concentrated fluid, hypertonic saline dextran (HSD), which consists of 7.5% normal saline and 6% dextran-70 and whose sodium concentration is 1280 mEq/L. Elgjo and colleagues in an ovine model demonstrated that 4 mL/kg of HSD given 1 hour postburn rapidly restored CO and reduced early, but not late, fluid requirements.[55] In a follow-up study, this group showed that the fluid-sparing effect of HSD could be sustained to 48 hours by use of a second dose given when net fluid accumulation reached 20 mL/kg.[56] We do not have clinical trials of HSD use in burn shock resuscitation.

Route of Administration

A survey of burn specialists performed by Greenhalgh revealed that the peripheral intravenous route (70%) is preferred for burn resuscitation. However, central venous access is often used (48%).[57] In cases of severe injury with widespread deep burns and edema, use of peripheral veins may not be possible. As a temporary option, intraosseous access may be lifesaving, but flow rates are limited due to the hydraulic resistance of the bone marrow. Later, central venous access can be established in the intensive care setting.

Early initiation of fluid resuscitation (within the first hours of burn injury) is essential for the prevention of organ failure,[1,58] but may be difficult to achieve in austere environments, combat casualty care, and mass-casualty events. Here enteral or oral resuscitation should be considered and may be effective for burns between 10% and 40% TBSA.[59,60] Clinical use of enteral resuscitation of burns was described by several early authors, including Fox in 1944.[61] Its utility might be limited by ileus and reduced gastric function. The effectiveness and safety of enteral resuscitation merit further investigation.[13]

There are no burn-specific oral/enteral fluid resuscitation solutions. World Health Organization (WHO) oral rehydration solution is available as a dry powder that is reconstituted with clean water. It was originally developed for treatment of dehydration secondary to cholera. These, and commercially available solutions, contain sodium, other electrolytes, and sugars. The sugar component is important because it increases the uptake of sodium across the intestinal mucosa. If enteral resuscitation is performed via a nasogastric tube, frequent (e.g., hourly) monitoring of gastric residual fluid volumes is recommended, especially during the initial hours post burn.

Patients at Increased Risk During Resuscitation

Patients with significant comorbidities (e.g., heart failure, cirrhosis, preexisting renal insufficiency, morbid obesity[62]) often do not respond in the usual way to fluid resuscitation and may benefit from closer monitoring, as described later.[63] Patients at the extremes of age—the very young and the very old—are less tolerant of "swings" in volume status; that is, their ability to compensate for hypovolemia or hypervolemia is limited, and they are particularly "volume sensitive." Again, closer attention to detailed monitoring is warranted in these patient populations.

Baxter reported that patients with inhalation injuries and large burns have the greatest fluid requirements in the burn population.[64] Most studies have reported increased fluid requirements of 20%–30% when compared to equal-size burns without inhalation injury.[65] However, this response is unpredictable, such that a modification of the burn resuscitation formulas because of inhalation injury is not commonly recommended.

Patients whose resuscitation is delayed may require more fluids than suggested by the formulas and may have increased complications because of the deleterious effects of prolonged ischemia followed by reperfusion.[58] Again, no modification of practice is commonly recommended in this scenario. Patients with a mechanism of injury suggesting risk of mechanical trauma and who do not respond to resuscitation in the usual fashion, may have a missed injury and ongoing bleeding. Patients with clinically evident myoglobinuria, as may occur following high-voltage electric injury, are typically given fluids at an increased rate in order to decrease pigment deposition in the renal tubules, with a target urine output of 75–100 mL/h in adults.[66]

Monitoring Resuscitation

Optimizing resuscitation—that is, ensuring administration of sufficient volume to achieve organ perfusion at the lowest physiologic cost—requires hourly monitoring (UO, hemodynamics, and clinical signs of adequate perfusion) and titration of fluid based on these endpoints. The most commonly used assessments are vital signs, laboratory assays, and UO. The primary index of the adequacy of resuscitation is most often the UO, with the rationale that it is a surrogate metric for glomerular filtration rate, renal blood flow, and CO. Recommended UO is 30–50 mL/h in adults, 0.5 to 1.0 mL/kg per hour in children of less than 30 kg, and 1.0 to 2.0 mL/kg per hour in infants. Recent trends have many burn caregivers targeting the lower values of these ranges. UO is usually recorded hourly; however studies validating this frequency are lacking. UO may fail as an index of resuscitation adequacy in patients with renal failure and in those

whose UO is elevated by the use of a diuretic, alcohol intoxication, or glycosuria. In these patients, alternate methods of monitoring are recommended.

UO is only one metric of adequate perfusion. Heart rate, blood pressure, central venous pressure, and echocardiography can serve as indices of cardiovascular status, particularly in patients with large burns and complex comorbidities. These variables must be considered in the context of burn shock physiology, however. For example, a well-resuscitated adult with extensive burns should have a heart rate in the 100–130/min range. This is because of the massive release of catecholamines caused by injury and because of the relative hypovolemia that characterizes a prudent resuscitation. A mean arterial pressure (MAP) of 60 mm Hg is a reasonable target for most patients, but some patients will tolerate a MAP as low as 50–55 mm Hg and still achieve adequate UO, cerebral perfusion, and decreasing lactic acidosis.

Laboratory values are an important assessment tool. Complete blood count, electrolytes, glucose, and acid–base status should be monitored frequently, although evidence regarding the optimal frequency of measurement is lacking. Lactate and base deficit (BD) are often used as indices of the adequacy of global perfusion. Elevated BD and serum lactate correlate with larger burn size, inhalation injury, greater fluid requirements, and mortality.[1,67,68] In a prospective study of BD and outcomes in burn patients, Cartotto et al. reported that patients with worse BD had greater fluid requirements as well as higher rates of sepsis, ARDS, and multiple organ dysfunction syndrome.[69] Kamolz et al. showed that lactate levels and the rate of lactate clearance are useful markers of shock and resuscitation status.[70] Additionally, they demonstrated that if the lactate levels were normalized within 24 hours the survival rate was 68%, compared to 32% if lactate normalization did not occur within 24 hours.

The pulmonary artery catheter (PAC) was used for decades during resuscitation to measure pulmonary capillary wedge pressure, systemic and pulmonary vascular resistances, CO, and oxygen consumption, a practice now largely limited to research applications. Transpulmonary thermodilution (TPTD) is a less invasive option that requires one access point via a central venous line as well as one access point via a peripheral artery. Commercial TPTD monitors also provide beat-to-beat estimates of CO (based on arterial waveform contour analysis). In addition, one can measure global end-diastolic volume (GEDV), a marker of cardiac preload, as well as extravascular lung water, a marker of pulmonary edema. Sánchez et al. showed that TPTD, but not MAP or UO, accurately detected hypovolemia during acute resuscitation (within 24 hours of burn).[71] A recent study in burned children by Kraft et al. confirmed these findings.[72]

How best to use TPTD or PAC data during resuscitation is not obvious. Attempts to "normalize" the CO or the GEDV during the first 24 hours postburn are often ill-advised because they may lead to overresuscitation with no net improvement in outcome.[73] Rather, an understanding of the expected dynamics of the successfully resuscitated average patient may allow a determination of whether a given patient is "on course" or "off course" with respect to his progress.[74] Information from Pruitt et al.[5] is helpful in this regard. In that study of successful resuscitations, the plasma volume deficit persisted until after 48 hours post burn, and CO remained below baseline levels until 36 hours post burn.

Echocardiography has largely replaced the PAC for the cardiac evaluation of selected burn patients.[75] Transthoracic echocardiography (TTE) provides information on volume status and cardiac function. TTE can be performed easily without the need for preassessment sedation. Nevertheless, TTE should be performed by well-trained clinicians to minimize user-dependent errors.[76] A further advantage of echocardiography, in comparison to PAC and TPTD, is that it can help diagnose heart failure and determine the response to inotropes. Further prospective randomized controlled trials comparing different echocardiography techniques are warranted.[75]

An increase in the hematocrit (or hemoglobin) during burn shock likely indicates a worsening plasma volume deficit. For this reason, early treatises on burn resuscitation recommended following this value as an index of volume status.[21] Certainly it can provide supportive information, bearing in mind that a decrease in hematocrit below normal levels is frequently seen as resuscitation continues, reflecting red blood cell damage.[5]

Fluid Creep and Edema Management

During resuscitation, the desire to maintain adequate perfusion of vital organs and the failure to titrate fluid input appropriately can lead to overresuscitation.[40] "Fluid creep" was first described by Pruitt as a recent trend toward infusing greater volumes of fluid than those predicted by the burn formulas, leading to organ dysfunction or even life-threatening complications.[2] Overresuscitation may lead to ACS,[77] airway and pulmonary edema,[78] extremity compartment syndrome (ECS),[79] orbital compartment syndrome,[80] and cerebral edema. The risk of cerebral edema is particularly underappreciated. Gueugniaud et al. observed elevated ICP in patients with a TBSA of greater than 60% and no history of head injury, peaking on day 2 postburn.[81] Shin et al. in an ovine 70% TBSA model showed an increase in ICP and a decrease in cerebral blood flow at the end of 6 hours postburn, with increased brain water content at autopsy.[82] Ding and colleagues conducted studies in a rat model and demonstrated increased blood–brain barrier permeability post burn that could be prevented by tumor necrosis factor-α (TNF-α) or matrix metalloproteinase-2 blockade.[83] Gatson et al. demonstrated increased brain cytokine levels in burned rats and their blockade with 17-β-estradiol.[84]

To this list of early complications, we should add the effect of wound edema on the progression of injury depth and on the success of wound healing,[50] the importance of which to survival cannot be overstated.[85]

These complications are highly morbid, and strenuous efforts to forestall them are a critical aspect of burn shock resuscitation in the modern era. For example, ACS in burn patients, when treated by laparotomy, carries a near 100% mortality in many series. ECS (in burned or unburned limbs) may be detected late, leading to muscle necrosis,

nerve injury, and possibly limb loss.[79] Ivy observed that risk of ACS increases when the infused volume exceeds 250 mL/kg during the first 24 hours postburn.[77] For this reason, that volume is often referred to as the "Ivy Index." Early identification of patients who are on course for a resuscitation in which the Ivy Index will be exceeded may permit corrective actions to decrease the infusion rate and preclude or promptly address these complications. Such corrective actions include (1) strategies to reduce the fluid infusion rate and (2) strategies to address edema.

A reduction in fluid infusion rate may be possible by (a) initiation of colloids, (b) tolerance of a subtarget UO, (c) initiation of continuous renal replacement therapy to address acidosis or renal insufficiency, (d) initiation of high-dose ascorbic acid, and/or (e) a diagnostic work up for non–volume-related causes of shock, such as echocardiography to assess cardiac function and the need for inotropes.

Strategies to reduce edema formation or to address its effects include (a) aggressive elevation of burned extremities; (b) monitoring of extremity compartment pressures and/or physical exam, with escharotomies or fasciotomies as needed;[86] (c) monitoring of the bladder pressure to diagnose intra-abdominal hypertension (IAH); (d) use of sedation/paralysis/positioning to reduce IAH; (e) placement of a diagnostic peritoneal lavage (DPL) catheter connected to intravenous tubing to permit evacuation of ascites and reduction in IAH; and (f) measurement of intraocular pressures and lateral canthotomy for orbital compartment syndrome.[80]

Fig. 9.1 shows a plot of actual 24-h volumes infused for burn resuscitation when LR was used and hourly rates were adjusted based on UO. Data are from all studies that were identified between 1980 and 2015. Clearly most studies report volumes that exceed Parkland estimations. While these data suggest a trend toward increased fluid volumes, more striking are the wide variations reported for mean values and the large standard deviations reported for most individual studies. These data stand in sharp contrast to Baxter's original publications that suggest most patients can be resuscitated with 4 mL/kg per %TBSA burned,[25] and

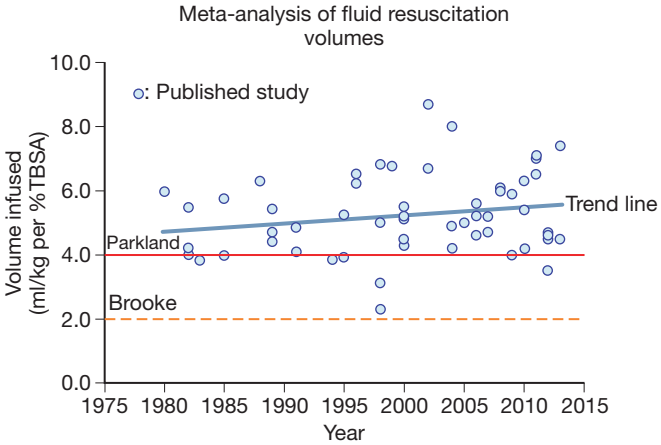

Fig. 9.1 Scatter plot and regression of published studies showing actual fluid infused over 24 hours compared to fluid requirements estimated using the Parkland and Brooke formulae. Studies were from 1980 to 2014 and the mean fluid infused was 5.3 ± 1.2 (SD) mL/kg per %TBSA burned. (Unpublished data, Kramer GC et al.)

Pruitt's, which suggest that most can be resuscitated with slightly less than 3 mL/kg per TBSA.[87]

While there are no randomized controlled trials to suggest the superiority of one burn formula over another, Chung et al. retrospectively analyzed data from combat casualties treated in Iraq. Clinical practice guidelines in place during the war recommended that burn patients be resuscitated using 2–4 mL/kg per TBSA. In practice, the resuscitation of most of these patients was initiated at either 2 or 4 mL/kg per TBSA. This permitted comparison of the modified Brooke and the Parkland formulas. Patients in both groups received more than predicted by the formulas: those started at 2 mL/kg per TBSA received 3.8 mL/kg per TBSA, whereas those started at 4 mL/kg per TBSA received 5.9 mL/kg per TBSA. Patients started at 2 mL/kg per TBSA were less likely to exceed the Ivy Index than were those started at 4 mL/kg per TBSA (29% vs. 57%).[88] This suggests that one answer to fluid creep is to initiate resuscitation using the more conservative modified Brooke formula.

Faraklas et al. and Cancio et al. suggested that clinicians may be more aggressive at increasing fluid infusion rates initially than they are at decreasing fluid infusion rates later.[89,90] Furthermore Faraklas et al. concluded that seriously injured patients, pediatric patients, and patients with combinations of burns and inhalation injuries are more prone to fluid creep. Greater fluid volumes were associated with significantly more escharotomies and complications as well as longer hospital stays.

In 2004, Sullivan et al. suggested that fluid creep might be associated with increased administration of opioids during burn shock resuscitation, a phenomenon termed "opioid creep."[80] They compared fluid requirements in a cohort of burn patients who received low doses of opioids (treated in 1975) to those in a group of patients (treated in 2000) who received four times higher doses of opioids. A significant correlation was noted between opioid dose and fluid requirements within the first 24 hours of acute hospitalization. Nevertheless opioids remain a crucial part of pain management in severely burned patients.[91] The cardiovascular effects of opioids and benzodiazepines need to be considered, and the amount given must be strictly monitored.

Lawrence et al. described a "colloid rescue" in which they provided 5% albumin to patients who were requiring excessive amounts of crystalloids; this approach permitted a subsequent reduction in crystalloid infusion rates.[43] The use of colloids should be considered in patients heading toward fluid needs in excess of Parkland volume estimates (see earlier discussion), particularly after the first 8–12 hours postburn have passed.[41]

Pharmacologic and Extracorporeal Adjuncts

There is a limited role for vasoactive medications during burn shock resuscitation. Traditionally we have been reluctant to use vasoconstrictors such as norepinephrine or vasopressin during burn shock, recognizing that many of these patients respond to injury and hypovolemia with intense catecholamine release and vasoconstriction. However, on a case-by-case basis, such agents may be useful to support

a minimally acceptable mean arterial blood pressure while volume resuscitation proceeds.[92] Likewise, cardiac inotropes such as dobutamine (or agents which reduce afterload, such as hydralazine) should be used with caution in hypovolemic burn patients since afterload reduction in this population may precipitate overt hypotension.[5] However, in volume-replete patients whose CO remains low, inotropes may be appropriate. The choice of vasoactive medication may be facilitated by echocardiography.

High-dose ascorbic acid (vitamin C) has been used as a pharmacologic adjunct during burn resuscitation. Its proposed mechanism of action is that it is a free-radical scavenger capable of reducing post-burn lipid peroxidation and microvascular leakage. At a dose of 66 mg/kg per hour (begun as soon as possible after admission), it was evaluated in a prospective randomized controlled trial by Tanaka and colleagues. They showed that high-dose ascorbic acid significantly reduced 24-hour fluid requirements (from 5.5 to 3.0 mL/kg per TBSA), weight gain, and edema. Additionally, treated patients had fewer ventilator days, less lung water, lower rates of acute lung injury, and lower levels of serum malondialdehyde, a marker of oxidative stress. The ascorbic acid group, although given significantly less fluid than the control group, had comparable hemodynamics and hourly UO.[93] Dubick and coworkers reported that, in an ovine model of burns, high-dose isotonic ascorbic acid reduced total volume infused over the 48-hour study. Furthermore the treatment group had markedly elevated plasma antioxidant potential and reduced lipid peroxidation.[94] A small retrospective study yielded similar findings.[95] Specifically ascorbic acid-treated patients had significantly lower resuscitation volumes and reduced vasopressor use. These studies suggest that high-dose ascorbic acid holds promise in resuscitation, but a multicenter trial is yet to be performed. Ascorbic acid may act as an osmotic diuretic, which may affect the use of UO as an index of resuscitation adequacy. Also, institution of this drug upon admission, rather than at some later time point when a patient appears to be failing resuscitation, makes sense considering its antioxidant mechanism of action.

Extracorporeal adjuncts to burn resuscitation include therapeutic plasma exchange (TPE), continuous renal replacement therapy (CRRT), and extracorporeal blood purification. TPE has been used at a small number of burn centers for the treatment of patients who are not responding to resuscitation appropriately. In TPE, the patient's plasma volume is replaced with FFP. The basis for this intervention is the concept that burn shock is mediated, in part, by circulating cytokines and other factors that can be removed by TPE. Neff et al. reported on experience with 21 patients who underwent TPE when the volume received exceeded 1.2 times the goal of 3 mL/kg per TBSA at any given point during the first 24 hours, along with other evidence of failure such as oliguria or hypotension. TPE was associated with increases in blood pressure and in UO, and decreases in the intravenous fluid rate and lactate. There was no difference in mortality with a control group.[96] Klein et al. applied TPE to 37 patients who typically were receiving twice the volume predicted by the Parkland formula. Findings were similar to those of Neff et al.[97]

There are no data on the utility of CRRT for the treatment of burn shock. Chung et al. reported on burn patients with acute kidney injury (Acute Kidney Injury Network [AKIN] level 3, or level 2 with shock). These patients were initiated on CRRT on mean hospital day 17 ± 24. Compared to historical controls, they had better mortality; fewer of the patients with shock required vasopressors at 24 hours. The authors speculated that the mechanism of action for this improvement could be nonspecific removal of cytokines.[98] Application of these findings to patients with refractory burn shock and who do not meet AKIN criteria for CRRT would be based on this hypothesis.

Extracorporeal blood purification aims to remove inflammatory mediators and/or other molecules from the circulation by means other than CRRT. Linden and colleagues evaluated a novel extracorporeal cytokine-adsorbing column, CytoSorb (CytoSorbents Corporation, Monmouth Junction, NJ), in a porcine model of smoke inhalation injury and 40% TBSA burns. This column removed interleukin-1b (IL-1b), IL-6, IL-10, and myoglobin from the extracorporeal circuit but did not reduce systemic levels. Thus more work would be needed to optimize factors such as therapy duration, blood flow rate, and possibly device size.[99]

Protocol-Driven and Computerized Resuscitation

Nurse-driven burn resuscitation using hourly flow charts is an approach to achieving tighter control of fluid therapy. Nurse-implemented protocols allow nurses to make timely and effective changes to the resuscitation rates without having to wait for physicians' orders, which can delay needed adjustments in therapy. Additionally these protocols diminish the effects that experience and/or comfort level have on titration (a new nurse or intern may be reluctant to make significant changes). Faraklas and colleagues instituted a nurse-driven resuscitation protocol (Fig. 9.2) as a performance-improvement project and showed excellent protocol adherence. However, large-volume fluid resuscitation still occurred in patients with the largest burns or with inhalation injury.[90]

A logical next step to paper protocols is a computerized decision-support system (CDSS). A CDSS is an open-loop system that provides recommendations to the clinical team using data obtained from the patient. Salinas et al. developed an algorithm that calculates, on an hourly basis, the infusion rate most likely to achieve a UO within the target range during the next hour. The inputs used by the algorithm include the linear trend in the past three urine outputs, the burn size, the time post burn, and the current fluid infusion rate. The algorithm was implemented in software and was shown to decrease the total volume delivered while increasing the percentage of time during which UO rates achieved the target range. Ventilator days and ICU length of stay were also decreased.[100] Although encouraging, the study was small and awaits validation in larger trials.

Hourly adjustments in the fluid infusion rate are based on a convenient but arbitrary time interval, whereas the kidneys respond to changes in volume status more rapidly. Thus there may be value in developing a closed-loop system that continuously measures UO and automatically makes corrections to the infusion rate on a more frequent basis. Closed-loop fluid resuscitation systems have been shown to

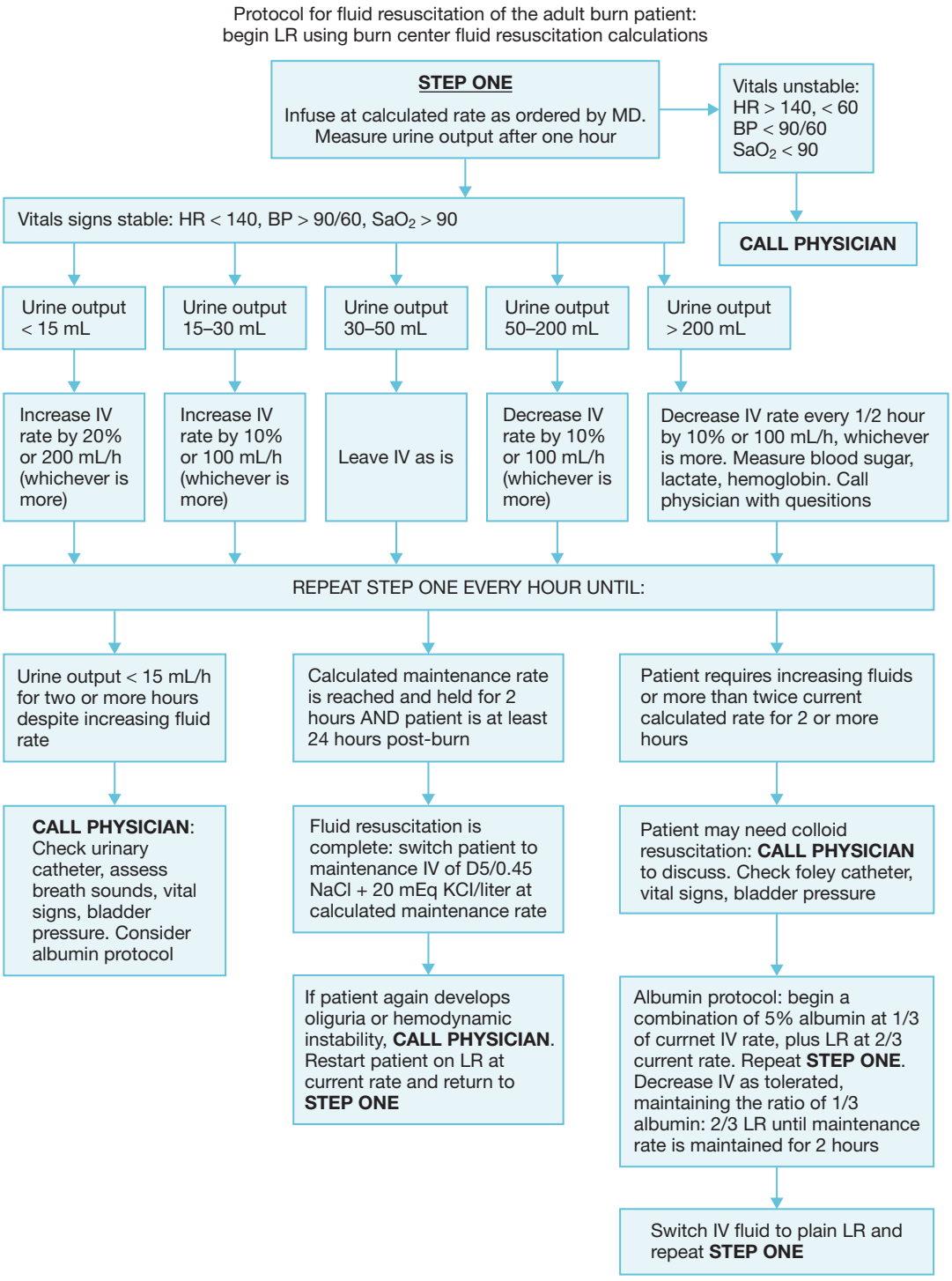

Fig. 9.2 Adult Fluid Resuscitation Protocol used at University of Utah. The pediatric protocol differs from the adult protocol in that urine output is targeted to 1.0–1.9 mL/kg per hour, and patients younger than 2 years receive 25 mL/h of 5% dextrose in lactated Ringer's (LR) throughout resuscitation. (From Faraklas I, Cochran A, Saffle J. Review of a fluid resuscitation protocol: "fluid creep" is not due to nursing error. *J Burn Care Res.* 2012;33(1):74–83.)

be effective (in maintaining resuscitation targets) and efficient (in reducing volume delivered) in large-animal models of both burn injury and hemorrhage.[101] Closed-loop systems could reduce much of the bedside caregiver's time in measuring and transcribing UO and making manual adjustments in infusion rates, allowing more time for other tasks. A closed-loop system may be particularly valuable in non-burn-center settings or mass-casualty scenarios, where burn expertise is lacking, diluted, or degraded. However a closed-loop system should not replace careful patient monitoring and should enhance, rather than reduce, a provider's situational awareness. Such systems must allow the

caregiver to override the computer and regain manual control.[102]

Conclusion

Fluid resuscitation is the important first step in the critical care of burn patients. There is still great controversy surrounding optimal resuscitation of patients: there are a multitude of strategies designed to improve resuscitation, with no single approach having universal acceptance. More important than any formula or technology is a diligent burn team of physicians and nurses assessing the overall adequacy of hemodynamics and end-organ perfusion and making adjustments as needed.

Complete references available online at
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References

1. Wolf SE, Rose JK, Desai MH, et al. Mortality determinants in massive pediatric burns. An analysis of 103 children with ≥80% TBSA burns (≥70% full-thickness). *Ann Surg*. 1997;225(5):554-565.
2. Pruitt BA Jr. Protection from excessive resuscitation: "pushing the pendulum back". *J Trauma*. 2000;49(3):567-568.
3. Pruitt BA Jr. The effectiveness of fluid resuscitation. *J Trauma*. 1979; 19(11 suppl):868-870.
4. Arturson G. Microvascular permeability to macromolecules in thermal injury. *Acta Physiol Scand Suppl*. 1979;463:111-122.
5. Pruitt BA Jr, Mason AD Jr, Moncrief JA. Hemodynamic changes in the early postburn patient: the influence of fluid administration and of a vasodilator (hydralazine). *J Trauma*. 1971;11(1):36-46.
6. Baxter CR, Shires T. Physiological response to crystalloid resuscitation of severe burns. *Ann N Y Acad Sci*. 1968;150(3):874-894.
7. Horton JW. Left ventricular contractile dysfunction as a complication of thermal injury. *Shock*. 2004;22(6):495-507.
8. Baskett TF. William O'Shaughnessy, Thomas Latta and the origins of intravenous saline. *Resuscitation*. 2002;55(3):231-234.
9. Sneve H. The treatment of burns and skin grafting. *J Am Med Assoc*. 1905;45(1):1-8.
10. Blalock A. Experimental shock. VII. The importance of the local loss of fluid in the production of the low blood pressure after burns. *Arch Surg*. 1931;22:610-616.
11. Davidson EC. Tannic acid in the treatment of burns. *Surg Gynecol Obstet*. 1925;41:202-221.
12. Underhill FP. The significance of anhydremia in extensive superficial burns. *JAMA*. 1930;95:852-857.
13. Cancio LC, Kramer GC, Hoskins SL. Gastrointestinal fluid resuscitation of thermally injured patients. *J Burn Care Res*. 2006;27(5):561-569.
14. Harkins HN. The treatment of burns in wartime. *JAMA*. 1942;119(5):385-390.
15. National Research Council, Division of Medical Sciences. Treatment of burns. *War Med (Chic 1941)*. 1942;2:334-339.
16. Cope O, Moore FD. The redistribution of body water and the fluid therapy of the burned patient. *Ann Surg*. 1947;126:1010-1045.
17. Hansen SL. From cholera to "fluid creep": a historical review of fluid resuscitation of the burn trauma patient. *Wounds*. 2008;20(7): 206-213.
18. Cope O, Rhinelander FW. The problem of burn shock complicated by pulmonary damage. *Ann Surg*. 1943;117(6):915-928.
19. Stewart CL. The fire at Cocoanut Grove. *J Burn Care Res*. 2015;36: 232-235.
20. Evans EI, Purnell OJ, Robinett PW, Batchelor A, Martin M. Fluid and electrolyte requirements in severe burns. *Ann Surg*. 1952;135:804-817.
21. Reiss E, Stirman JA, Artz CP, Davis JH, Amspacher WH. Fluid and electrolyte balance in burns. *JAMA*. 1953;152:1309-1313.
22. Moyer CA, Margraf HW, Monafo WW. Burn shock and extravascular sodium deficiency – treatment with Ringer's solution with lactate. *Arch Surg*. 1965;90:799-811.
23. Shires GT, Carrico CJ, Coin D. The role of extracellular fluid in shock. *Int Anesthesiol Clin*. 1964;2(2):435-454.
24. Shires GT, Cunningham JN, Backer CR, et al. Alterations in cellular membrane function during hemorrhagic shock in primates. *Ann Surg*. 1972;176(3):288-295.
25. Baxter CR. Fluid volume and electrolyte changes of the early postburn period. *Clin Plast Surg*. 1974;1:693-709.
26. Goodwin CW, Dorethy J, Lam V, Pruitt BA Jr. Randomized trial of efficacy of crystalloid and colloid resuscitation on hemodynamic response and lung water following thermal injury. *Ann Surg*. 1983;197(5):520-531.
27. Alvarado R, Chung KK, Cancio LC, Wolf SE. Burn resuscitation. *Burns*. 2009;35(1):4-14.
28. Cartotto R. Fluid resuscitation of the thermally injured patient. *Clin Plast Surg*. 2009;36(4):569-581.
29. Gibran NS, Wiechman S, Meyer W, et al. American Burn Association consensus statements. *J Burn Care Res*. 2013;34:361-385.
30. Anonymous. *Advanced Burn Life Support Provider Manual 2011*. Chicago, IL: American Burn Association; 2011.
31. Chung KK, Salinas J, Renz EM, et al. Simple derivation of the initial fluid rate for the resuscitation of severely burned adult combat casualties: in silico validation of the rule of 10. *J Trauma*. 2010;69(suppl 1):S49-S54.
32. Pruitt BA Jr. Fluid resuscitation of burn patients: does clinical "success" necessitate "excess"? *South Med J*. 1976;69(11):1399.
33. Graves TA, Cioffi WG, McManus WF, Mason AD Jr, Pruitt BA Jr. Fluid resuscitation of infants and children with massive thermal injury. *J Trauma*. 1988;28(12):1656-1659.
34. Merrell SW, Saffle JR, Sullivan JJ, et al. Fluid resuscitation in thermally injured children. *Am J Surg*. 1986;152(6):664-669.
35. Carvajal HF. Fluid therapy for the acutely burned child. *Compr Ther*. 1977;3(3):17-24.
36. Carvajal HF. Fluid resuscitation of pediatric burn victims: a critical appraisal. *Pediatr Nephrol*. 1994;8(3):357-366.
37. Weiss SL. Examining crystalloid resuscitation. Society of Critical Care Medicine: Clinical Controversies Highlighted at the 45th Critical Care Congress. August 4, 2016. http://www.sccm.org/Communications/Critical-Connections/Archives/Pages/Examining-Crystalloid-Resuscitation.aspx.
38. Tommasino C, Moore S, Todd MM. Cerebral effects of isovolemic hemodilution with crystalloid or colloid solutions. *Crit Care Med*. 1988;16(9):862-868.
39. Ayuste EC, Chen H, Koustova E, et al. Hepatic and pulmonary apoptosis after hemorrhagic shock in swine can be reduced through modifications of conventional Ringer's solution. *J Trauma*. 2006;60(1):52-63.
40. Saffle JR. The phenomenon of "fluid creep" in acute burn resuscitation. *J Burn Care Res*. 2007;28(3):382-395.
41. DemLing RH, Smith M, Bodai B, et al. Comparison of postburn capillary permeability in soft tissue and lung. *J Burn Care Rehabil*. 1981;2:86-92.
42. O'Mara MS, Slater H, Goldfarb IW, Caushaj PF. A prospective, randomized evaluation of intra-abdominal pressures with crystalloid and colloid resuscitation in burn patients. *J Trauma*. 2005;58(5):1011-1018.
43. Lawrence A, Faraklas I, Watkins H, et al. Colloid administration normalizes resuscitation ratio and ameliorates "fluid creep". *J Burn Care Res*. 2010;31(1):40-47.
44. Pati S, Potter DR, Baimukanova G, et al. Modulating the endotheliopathy of trauma: factor concentrate versus fresh frozen plasma. *J Trauma Acute Care Surg*. 2016;80(4):576-584, discussion 584-585.
45. Peng Z, Pati S, Potter D, et al. Fresh frozen plasma lessens pulmonary endothelial inflammation and hyperpermeability after hemorrhagic shock and is associated with loss of syndecan 1. *Shock*. 2013;40(3):195-202.
46. Vlachou E, Gosling P, Moiemen NS. Hydroxyethylstarch supplementation in burn resuscitation – a prospective randomised controlled trial. *Burns*. 2010;36(7):984-991.
47. Bechir M, Puhan MA, Fasshauer M, et al. Early fluid resuscitation with hydroxyethyl starch 130/0.4 (6%) in severe burn injury: a randomized, controlled, double-blind clinical trial. *Crit Care*. 2013;17(6):R299.
48. Dart AB, Mutter TC, Ruth CA, Taback SP. Hydroxyethyl starch (HES) versus other fluid therapies: effects on kidney function. *Cochrane Database Syst Rev*. 2010;1(1).
49. Mayor S. EMA confirms that hydroxyethyl starch solutions should not be used in critically ill, sepsis, or burns patients. *BMJ*. 2013;347:f6197.
50. Monafo WW. The treatment of burn shock by the intravenous and oral administration of hypertonic lactated saline solution. *J Trauma*. 1970;10(7):575-586.
51. Warden GD. Burn shock resuscitation. *World J Surg*. 1992;16(1): 16-23.
52. Pruitt BA Jr. Does hypertonic burn resuscitation make a difference? *Crit Care Med*. 2000;28(1):277-278.
53. Huang PP, Stucky FS, Dimick AR, et al. Hypertonic sodium resuscitation is associated with renal failure and death. *Ann Surg*. 1995;221(5):543-557.
54. Oda J, Ueyama M, Yamashita K, et al. Hypertonic lactated saline resuscitation reduces the risk of abdominal compartment syndrome in severely burned patients. *J Trauma*. 2006;60(1):64-71.
55. Elgjo GI, Poli de Figueiredo LF, Schenarts PJ, et al. Hypertonic saline dextran produces early (8-12 hrs) fluid sparing in burn resuscitation: a 24-hr prospective, double-blind study in sheep. *Crit Care Med*. 2000;28(1):163-171.
56. Elgjo GI, Traber DL, Hawkins HK, Kramer GC. Burn resuscitation with two doses of 4 mL/kg hypertonic saline dextran provides sustained fluid sparing: a 48-hour prospective study in conscious sheep. *J Trauma*. 2000;49(2):251-263.

57. Greenhalgh DG. Burn resuscitation: the results of the ISBI/ABA survey. *Burns*. 2010;36(2):176-182.
58. Barrow RE, Jeschke MG, Herndon DN. Early fluid resuscitation improves outcomes in severely burned children. *Resuscitation*. 2000;45(2):91-96.
59. Kramer GC, Michell MW, Oliveira H, et al. Oral and enteral resuscitation of burn shock the historical record and implications for mass casualty care. *Eplasty*. 2010;10.
60. Michell MW, Oliveira HM, Kinsky MP, et al. Enteral resuscitation of burn shock using World Health Organization oral rehydration solution: a potential solution for mass casualty care. *J Burn Care Res*. 2006;27(6):819-825.
61. Fox CL. Oral sodium lactate in treatment of burns and shock. *JAMA*. 1944;124:207-212.
62. Rae L, Pham TN, Carrougher G, et al. Differences in resuscitation in morbidly obese burn patients may contribute to high mortality. *J Burn Care Res*. 2013;34(5):507.
63. Pham TN, Cancio LC, Gibran NS. American Burn Association practice guidelines: burn shock resuscitation. *J Burn Care Res*. 2008;29(1):257-266.
64. Baxter CR. Guidelines for fluid resuscitation. *J Trauma*. 1981;21(suppl): 687-689.
65. Navar PD, Saffle JR, Warden GD. Effect of inhalation injury on fluid resuscitation requirements after thermal injury. *Am J Surg*. 1985;150:716-720.
66. Cancio LC, Jimenez-Reyna JF, Barillo DJ, et al. One hundred ninety-five cases of high-voltage electric injury. *J Burn Care Rehabil*. 2005;26(4):331-340.
67. Kaups KL, Davis JW, Dominic WJ. Base deficit as an indicator or resuscitation needs in patients with burn injuries. *J Burn Care Rehabil*. 1998;19(4):346-348.
68. Cancio LC, Galvez E Jr, Turner CE, et al. Base deficit and alveolar-arterial gradient during resuscitation contribute independently but modestly to the prediction of mortality after burn injury. *J Burn Care Res*. 2006;27(3):289-296.
69. Cartotto R, Choi J, Gomez M, Cooper A. A prospective study on the implications of a base deficit during fluid resuscitation. *J Burn Care Rehabil*. 2003;24(2):75-84.
70. Kamolz LP, Andel H, Schramm W, et al. Lactate: early predictor of morbidity and mortality in patients with severe burns. *Burns*. 2005;31(8):986-990.
71. Sánchez M, García-de-Lorenzo A, Herrero E, et al. A protocol for resuscitation of severe burn patients guided by transpulmonary thermodilution and lactate levels: a 3-year prospective cohort study. *Crit Care*. 2013;17(4):1.
72. Kraft R, Herndon DN, Branski LK, et al. Optimized fluid management improves outcomes of pediatric burn patients. *J Surg Res*. 2013;181(1):121-128.
73. Aboelatta Y, Abdelsalam A. Volume overload of fluid resuscitation in acutely burned patients using transpulmonary thermodilution technique. *J Burn Care Res*. 2013;34(3):349-354.
74. Serio-Melvin ML, Salinas J, Chung KK, et al. Burn shock and resuscitation: proceedings of a symposium conducted at the meeting of the American Burn Association, Chicago, IL, 21 April 2015. *J Burn Care Res*. 2017;38(1):e423-e431.
75. Maybauer MO, Asmussen S, Platts DG, et al. Transesophageal echocardiography in the management of burn patients. *Burns*. 2014;40(4):630-635.
76. Howard TS, Hermann DG, McQuitty AL, et al. Burn induced cardiac dysfunction increases length of stay in pediatric burn patients. *J Burn Care Res*. 2013;34(4):413.
77. Ivy ME, Atweh NA, Palmer J, et al. Intra-abdominal hypertension and abdominal compartment syndrome in burn patients. *J Trauma*. 2000;49(3):387-391.
78. Zak AL, Harrington DT, Barillo DJ, et al. Acute respiratory failure that complicates the resuscitation of pediatric patients with scald injuries. *J Burn Care Rehabil*. 1999;20(5):391-399.
79. Sheridan RL, Tompkins RG, McManus WF, Pruitt BA Jr. Intracompartmental sepsis in burn patients. *J Trauma*. 1994;36(3):301-305.
80. Sullivan SR, Friedrich JB, Engrav LH, et al. Opioid creep" is real and may be the cause of "fluid creep. *Burns*. 2004;30(6):583-590.
81. Gueugniaud PY, Jauf RM, Bertin-Maghit M, et al. Cerebral oedema after extensive thermal injury: prognostic significance of early intracranial and cerebral perfusion pressures. *Ann Burns Fire Disasters*. 1997;10(2):http://www.medbc.com/annals/review/vol_10/num_2/text/vol10n2p72.htm.
82. Shin C, Kinsky MP, Thomas JA, Traber DL, Kramer GC. Effect of cutaneous burn injury and resuscitation on the cerebral circulation in an ovine model. *Burns*. 1998;24(1):39-45.
83. Reyes R, Guo M, Swann K, et al. Role of tumor necrosis factor-alpha and matrix metalloproteinase-9 in blood-brain barrier disruption after peripheral thermal injury in rats. *J Neurosurg*. 2009;110(6):1218-1226.
84. Gatson JW, Maass DL, Simpkins JW, et al. Estrogen treatment following severe burn injury reduces brain inflammation and apoptotic signaling. *J Neuroinflammation*. 2009;6:30.
85. Nitzschke SL, Aden JK, Serio-Melvin ML, et al. Wound healing trajectories in burn patients and their impact on mortality. *J Burn Care Res*. 2014;35(6):474-479.
86. Orgill DP, Piccolo N. Escharotomy and decompressive therapies in burns. *J Burn Care Res*. 2009;30(5):759-768.
87. Pruitt BA. Advances in fluid therapy and the early care of the burn patient. *World J Surg*. 1978;2:139-150.
88. Chung KK, Wolf SE, Cancio LC, et al. Resuscitation of severely burned military casualties: fluid begets more fluid. *J Trauma*. 2009;67(2): 231-237.
89. Cancio LC, Chavez S, Alvarado-Ortega M, et al. Predicting increased fluid requirements during the resuscitation of thermally injured patients. *J Trauma*. 2004;56(2):404-413.
90. Faraklas I, Cochran A, Saffle J. Review of a fluid resuscitation protocol: "fluid creep" is not due to nursing error. *J Burn Care Res*. 2012;33(1):74-83.
91. MacLennan N, Heimbach DM, Cullen BF. Anesthesia for major thermal injury. *J Am Soc Anesthesiol*. 1998;89(3):749-770.
92. Ennis JL, Chung KK, Renz EM, et al. Joint Theater Trauma System implementation of burn resuscitation guidelines improves outcomes in severely burned military casualties. *J Trauma*. 2008;64(2 suppl): S146-S151.
93. Tanaka H, Matsuda T, Miyagantani Y, et al. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. *Arch Surg*. 2000;135(3):326-331.
94. Dubick MA, Williams C, Elgjo GI, Kramer GC. High-dose vitamin C infusion reduces fluid requirements in the resuscitation of burn-injured sheep. *Shock*. 2005;24(2):139-144.
95. Kahn SA, Beers RJ, Lentz CW. Resuscitation after severe burn injury using high-dose ascorbic acid: a retrospective review. *J Burn Care Res*. 2011;32(1):110-117.
96. Neff LP, Allman JM, Holmes JH. The use of therapeutic plasma exchange (TPE) in the setting of refractory burn shock. *Burns*. 2010;36(3):372-378.
97. Klein MB, Edwards JA, Kramer CB, et al. The beneficial effects of plasma exchange after severe burn injury. *J Burn Care Res*. 2009;30(2):243-248.
98. Chung KK, Lundy JB, Matson JR, et al. Continuous venovenous hemofiltration in severely burned patients with acute kidney injury: a cohort study. *Crit Care*. 2009;13(3):R62.
99. Linden K, Scaravilli V, Kreyer SF, et al. Evaluation of the CytosorbTM hemoadsorptive column in a pig model of severe smoke and burn injury. *Shock*. 2015;44(5):487-495.
100. Salinas J, Chung KK, Mann EA, et al. Computerized decision support system improves fluid resuscitation following severe burns: an original study. *Crit Care Med*. 2011;39(9):2031-2038.
101. Kramer GC, Kinsky MP, Prough DS, et al. Closed-loop control of fluid therapy for treatment of hypovolemia. *J Trauma Acute Care Surg*. 2008;64(4):S333-S341.
102. Salinas J, Drew G, Gallagher J, et al. Closed-loop and decision-assist resuscitation of burn patients. *J Trauma*. 2008;64(4 suppl): S321-S332.

10 Evaluation of the Burn Wound: Management Decisions

ELISHA G. BROWNSON and NICOLE S. GIBRAN

Introduction

Advances in the resuscitation of burn patients have greatly improved survival so that death from burn shock has become uncommon. In the 21st century, prompt functional recovery for the burn patient hinges on proper early management of the burn wound. The greatest advance in burn care to date has been the institution of early surgical burn wound excision with an immediate or delayed wound closure strategy individualized to each patient.[1-4] For years, burns were treated by daily washing, removal of loose dead tissue, and application of some sort of topical nostrum until wounds healed or granulated. Superficial dermal burns healed within 2 weeks, and deep dermal burns healed over many weeks if infection could be prevented. Full-thickness burns lost their eschar in 2–6 weeks by bacterial enzyme production and daily bedside debridement; split-thickness skin grafts were applied usually 3–8 weeks after injury. A 50% graft survival rate was acceptable, and repeated grafting eventually closed the wound. The prolonged and intense inflammatory response led to hypertrophic scars, contractures, and considerable physical and psychological disability.

Burns that heal within 3 weeks generally do so without significant hypertrophic scarring or functional impairment, although long-term pigmentation is unpredictable. Burns needing longer than 3 weeks to heal often result in unsightly hypertrophic scars and functional impairment. State-of-the-art burn care now involves early excision and grafting. The challenge is to define "early." Knowing which burn wounds benefit from early excision and grafting requires understanding of skin biology and pathophysiological changes caused by thermal injury. In spite of ongoing efforts to objectively assess wound depth, the standard technique for determining burn depth in the 21st century remains clinical assessment of the wound by a burn specialist.

Pathophysiology of the Burn Wound

SKIN BIOLOGY

Skin protects against fluid and electrolyte loss, infection, and radiation and provides thermal regulation. Skin contact provides clues to the surrounding environment through touch, perception of temperature, and pain. In addition, skin appearance is a major determinant of identity and body image and affects interpersonal interactions. The largest organ in the human body, skin is comprised of two layers: the epidermis and the dermis. Epidermal thickness varies among different body parts: from 0.05 mm on the eyelids to over 1 mm on the soles.[5] Most skin thickness comes from the dermis, which varies with age, gender, and body location.

Epidermis derives from ectoderm; the principal cell is the keratinocyte, but epidermis also contains melanocytes, Langerhans cells, Merkel cells, and inflammatory cells. Keratinocytes begin their division and differentiation at the stratum basale and migrate progressively outward over 2–4 weeks[6] through the stratum spinosum, the stratum granulosum, the stratum lucidum, and the stratum corneum, at which point they are flattened anuclear cornified structures. In a wound with a sloughed epidermal basal layer, keratinocytes proliferate and migrate from the wound edges and epidermal appendages (hair follicles, sweat glands, and sebaceous glands) to achieve epithelialization. Melanocytes produce melanin pigment essential for protection against ultraviolet radiation, and Langerhans cells and other inflammatory cells perform phagocytosis and antigen presentation. After injury, melanocytes regenerate more slowly and less predictably, leading to potential permanent pigment changes.[7,8]

Epidermal projections (rete ridges) interdigitate with dermal projections (papillae) at the basement membrane zone, which connects the epidermis and dermis via keratinocyte-derived collagen VII anchoring fibrils, critical structures that stabilize the epidermal–dermal junction.[9,10] Since anchoring fibrils take several months to mature during wound healing, minor shearing forces cause shearing, blistering, and epidermal loss.

The dermis is comprised of the superficial papillary and deeper reticular dermis, separated by a capillary plexus that delivers necessary nutrients to dermal cellular structures. The abundant extracellular matrix, comprised primarily of collagen and elastin fibers, provides the dermal structure; organized collagen fiber orientation provides tensile strength[11] and elastin fibers impart cutaneous elastic recoil properties. Glycosaminoglycans and proteoglycans, such as hyaluronic acid and chondroitin sulfate, attract water to maintain matrix hydration, provide absorption, and regulate cellular cross-talk by binding and releasing inflammatory mediators.[12,13] Protein turnover, accounting for the high plasticity of skin, increases with mechanical stress and responses to injury.[14] After wounding, microvascular endothelial cells mediate local and systemic inflammatory responses and eventually proliferate and migrate to form

new vessels during angiogenesis.[15] Sensory nerves, which traverse into the epidermis, also play a significant role after injury, as they mediate pain and itching, modulate inflammation, and influence the remodeling phase of wound healing.[16,17] The dermis, like other mesoderm-derived structures, heals not by regeneration but by fibrosis and scarring.

Pathophysiological Changes of Thermal Injury

Applied heat at the cellular level causes denaturation of proteins and loss of plasma membrane integrity. Temperature and duration of contact have a synergistic effect; cell necrosis occurs after 1s of exposure at 156°F (69°C), or after 1h at 113°F (45°C).[18] Following a burn, necrosis occurs at the center of the injury and becomes progressively less severe at the periphery. Jackson's description in 1953 of the three zones of injury remains our conceptual understanding of the burn wound (Fig. 10.1).[19] The zone of coagulation at the center of the wound has no remaining viable cells. A mix of viable and nonviable cells, capillary vasoconstriction, and ischemia characterizes the surrounding zone of stasis; this "at-risk" zone may convert to necrosis in the presence of hypoperfusion, desiccation, edema, or infection. Approximately half of the cells in the zone of stasis undergo apoptosis or necrosis as a result of oxidative stress, ongoing inflammation, and decreased blood flow due to microthrombosis.[20] Systemic factors such as advanced age, diabetes, and other chronic illnesses increase risk for "conversion." Efforts to enhance wound healing have focused on prevention of necrosis in the zone of stasis since medical care has little impact on the outcome of the zone of coagulation. Protection of this sensitive area is achieved with adequate fluid resuscitation, avoidance of vasoconstriction and edema, and prevention of infection.[21,22] Optimal wound care consists of nondesiccating dressings, topical antimicrobials, and regular monitoring of the wound.[23–25] At the periphery of the burn wound, the zone of hyperemia contains viable cells with vasodilation mediated by local inflammatory mediators. Tissue in this zone usually recovers unless complicated by infection or hypoperfusion.

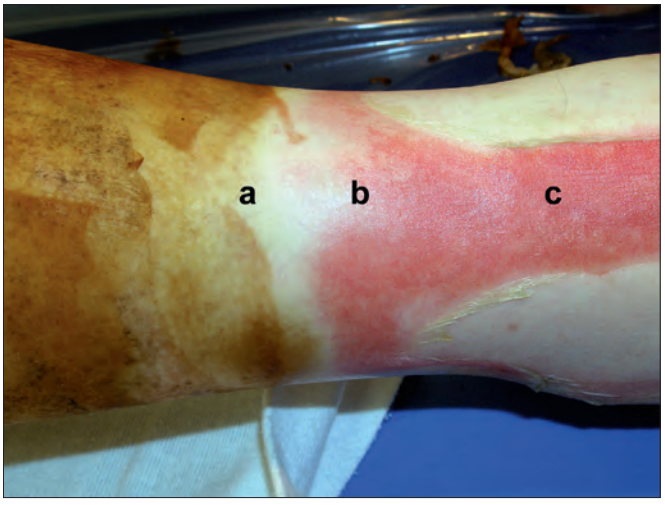

Fig. 10.1 Jackson's three zones of injury on an ankle burn: **(A)** the zone of coagulation; **(B)** the zone of stasis, and **(C)** the zone of hyperemia.

Interest in cooling of the wound to minimize the extent of injury can be traced to antiquity[26] but, firm evidence of its efficacy is lacking. Cooling immediately after injury should not supersede other priorities in the evaluation of the injured patient. The optimal temperature and duration of cooling is unknown[27–29] but excessive or prolonged cooling may be harmful in that it promotes vasoconstriction and systemic hypothermia.[30,31] Current guidelines of the American Burn Association recommend limiting cooling to 30 min in the management of minor burns.[32] Modalities to improve dermal perfusion and block injury from released inflammatory mediators have also garnered much interest. Whereas beneficial effects of many pharmacologic agents such as heparin, steroidal and nonsteroidal anti-inflammatory agents, thromboxane inhibitors, and epidermal growth factor have been reported,[20,33] all remain investigational since none has demonstrated clinical validity.

Assessment of Burn Depth

CLINICAL OBSERVATION

Burn injury may involve one or both layers of the skin and may extend into the subcutaneous fat, muscle, and even bony structures.[34] Burns involving only the outer layers of the epidermis (first-degree burns) are erythematous and very painful, but do not form blisters. Most sunburns fit this category of superficial, epidermal injury. Within 3–4 days, the dead epidermis sloughs and is replaced by regenerating keratinocytes. These burns are not included in burn size calculations for estimates of injury severity and resuscitation fluid estimations.

Superficial dermal burns (superficial second-degree burns) extend into the papillary dermis and characteristically form blisters. Blistering may not occur immediately after injury, and burns initially perceived to be superficial might subsequently be diagnosed as dermal burns. The wound bed underlying a blister on a superficial partial thickness burn is pink, wet, and hypersensitive to touch. Debriding the blister may be painful due to the currents of air passing over the wound. These wounds blanch with pressure because of vasodilation and increased blood flow in the dermis compared to normal skin. With appropriate wound care, superficial dermal burns usually heal within 2 weeks without risk of scarring and therefore do not require operation.

Deep dermal burns (deep second-degree burns) extend into the reticular dermis and generally take 3 or more weeks to heal. They blister, but the underlying wound surface appears mottled pink and white immediately following the injury (Fig. 10.2A). When pressure is applied to the burn, capillaries refill slowly or not at all. The wound is often less sensitive to pinprick than the surrounding normal skin. By postburn day 2, the wound may be white and dry (Fig. 10.2B). As a rule, most partial-thickness

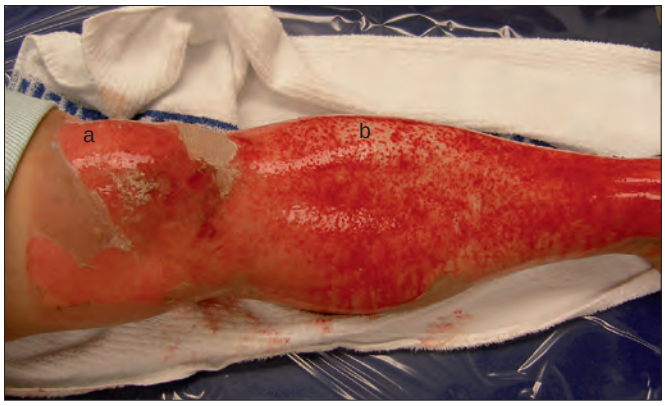

Fig. 10.2 Lower extremity deep dermal burn: **(A)** on day of presentation wound has a wet, pink and moist appearance; **(B)** on day 3 post-injury wound has a mottled appearance with both moist pink and dry white areas.

burns that have not healed by 3 weeks should be excised and grafted.

The most difficult management decision involves intermediate partial-thickness burns. The determining factor as to whether these burns heal in 3 weeks may be less than a millimeter. These burns are aptly called "indeterminate" burns because their healing potential becomes evident with serial assessments over several days after injury. Histologic studies suggest that burn injury is a dynamic process that peaks around 3 days after injury.[35–37] Initial evaluation by an experienced surgeon as to whether an indeterminate dermal burn will heal in 3 weeks is only 50%–70% accurate.[38–40]

Partial thickness scald burns usually should be managed nonoperatively for 10–14 days, unless they are obviously full thickness. However, these burns should be excised and grafted once it is clear that they will not heal by 3 weeks.[41] Serial clinical exams for partial thickness burns for 2 weeks after injury have been associated with excision of significantly smaller areas or avoidance of surgery entirely.

Full-thickness burns (third-degree burns) involve the entire cutaneous layer and may extend into the superficial subcutaneous tissue. Their appearance may be charred, leathery, dry, firm, and depressed when compared to adjoining normal skin. Noncharred full-thickness burns can be deceptive. Like deep dermal burns, they may be mottled in appearance. They rarely blanch on pressure and may have a dry, white appearance. In some cases, the burn may appear translucent with clotted vessels visible. These wounds are insensate to light touch and pinprick. Some full-thickness burns, particularly immersion scalds or "bake" injuries (caused by convective heat), may have a red appearance and can be confused with a superficial dermal burn by an inexperienced observer; these burns do not blanch with pressure. Most full-thickness burns should undergo early excision and grafting to minimize infection and hypertrophic scarring and to expedite patient recovery. Deeper burns that involve adipose tissue (fourth-degree burns), muscle (fifth-degree burns), and bone (sixth-degree burns) also require surgical management.[42]

ADJUNCTS TO CLINICAL EVALUATION

The search for technologies to obtain a more precise method to diagnose burn depth surged when the benefits of early operation were recognized. Multiple modalities have been trialed, including thermography, photometry, nuclear imaging, pulse-echo ultrasound, and, more invasive than the aforementioned, serial tissue biopsy.[43–45] These techniques take advantage of the ability to detect dead cells or denatured collagen (biopsy, ultrasound, vital dyes)[19,46–49]; wound color (light reflectance)[50]; physical changes, such as edema (magnetic resonance imaging)[51]; and altered blood flow (fluorescein, laser Doppler imaging, and thermography).[52–54] Unfortunately, none of these techniques has proved superior to serial clinical assessment by an experienced burn provider. Several groups have recently reported clinical benefit with the use of noncontact laser Doppler imaging in indeterminate thickness burns.[37,43,55] This technique provides a color perfusion map of the burn that can be assessed without direct contact with the skin surface, making this test well tolerated; furthermore, serial exams can track dynamic changes in wound bed perfusion. Although identified as an accurate measurement tool, noncontact laser Doppler imaging remains an adjunct, rather than a substitute, for clinical assessment.[56]

Mechanisms of Thermal Injury

FLASH AND FLAME BURNS

Flash and flame burn injuries represent approximately 40% of the admissions to American regional burn centers.[57] Explosions of natural gas, propane, gasoline, and other flammable liquids cause intense heat for a very brief time, causing flash burns. Flash burns often result from an inappropriate use of a flammable liquid as a fire accelerant on camp, trash, and brush fires. For the most part, flash burns reach progressive layers of the dermis in proportion to the amount and kind of fuel involved. Gasoline, especially, has highly flammable vapors that are 3–4 times denser than air. At room temperature, gasoline vapors diffuse above ground and accumulate in enclosed spaces. Clothing, unless it ignites, is protective in flash burns. Thus, a flash burn injury distribution typically involves exposed skin, with the deepest areas facing the source of ignition. If a flash burn causes clothing or hair to catch on fire, the injury will be more typical of a flame burn. Whereas such flash burns generally heal without extensive skin grafting, they may cover large areas and may be associated with thermal injury to the upper airway.

Flame burns invariably involve deep dermal or full-thickness injury because of prolonged exposure to intense heat. Although the incidence of injuries from house fires has decreased with the advent of smoke detectors, careless smoking, improper use of flammable liquids, automobile accidents, and clothing ignited from stoves or space heaters still exact their toll. Patients whose bedding or clothes have been on fire usually sustain some full-thickness burns. Victims of house fires with prolonged exposure to flames or heat due to immobility, intoxication, or confusion caused by hypoxemia or carbon monoxide toxicity are also prone to

have deeper burns. In one study of several burn centers, 28% of flame burns occurred in patients with high blood ethanol level, and 51% of victims in fires behaved inappropriately when trying to escape.[58] Loss of consciousness exposes victims to convective heat inside a burning room. This type of "bake" injury may deceptively appear shallow with intact epithelium to the inexperienced observer but is really a full-thickness burn.

SCALDS

Hot water scalds are the next most common cause of burns in the United States, representing approximately one third of cases.[57] Despite educational programs, the epidemiology and incidence of scalds worldwide has changed very little. The depth of scald injury depends on the water temperature, skin thickness, and duration of contact. Water at 140°F (60°C) creates a deep dermal burn in 3 s but causes the same injury in 1 s at 156°F (69°C).(18) Freshly brewed coffee from an automatic percolator is generally about 180°F (82°C). Once in the pot, coffee temperature approximates 160°F (70°C). Boiling water often causes a deep dermal burn, unless the duration of contact is very short. Soups and sauces, which are thicker due to proteins and oil, remain in contact longer with the skin and invariably cause deep dermal burns. Exposed areas tend to incur shallower burns because clothing (such as diapers and socks) retains heat and keeps the liquid in contact with the skin longer. Consequently, scalds are often a mosaic of superficial and indeterminate dermal burns. A common example is a toddler who reaches above head level and spills hot water; his face bears a superficial burn, the trunk burn is of indeterminate thickness, and skin under his diaper has a deep dermal burn.

Immersion scalds are often deep because of prolonged skin exposure, although the water temperature may not be as high as with spill scalds.[59,60] They occur in individuals who do not perceive the discomfort of prolonged immersion (i.e., diabetic patients or spinal cord injury patients with peripheral neuropathy), or who are not able to escape from the hot water (i.e., young children, elderly, or people with physical and cognitive disabilities). This latter group of vulnerable individuals is susceptible to nonaccidental scald burns,[61,62] which account for about 2% of all children admitted to our burn center. Circumferential extremity injuries, symmetrical burns to a child's buttocks and perineum represent a few injury characteristics that should raise suspicion of nonaccidental trauma (Fig. 10.3). Allegations of abuse should include expert burn wound assessment by an experienced burn surgeon who is familiar with burn distribution and etiologies.

Grease and hot oils cause deep dermal or full-thickness injuries. During cooking, grease and hot oils are usually heated to a level below their smoke point to avoid unpleasant odors from their decomposition. The smoke point is 350°F (177°C) for butter, 400° F (204°C) for lard, and 450°F (232°C) for corn oil. Cooking oils reach their flash point at 600°F (316°C). Domestic grease burns occur in a

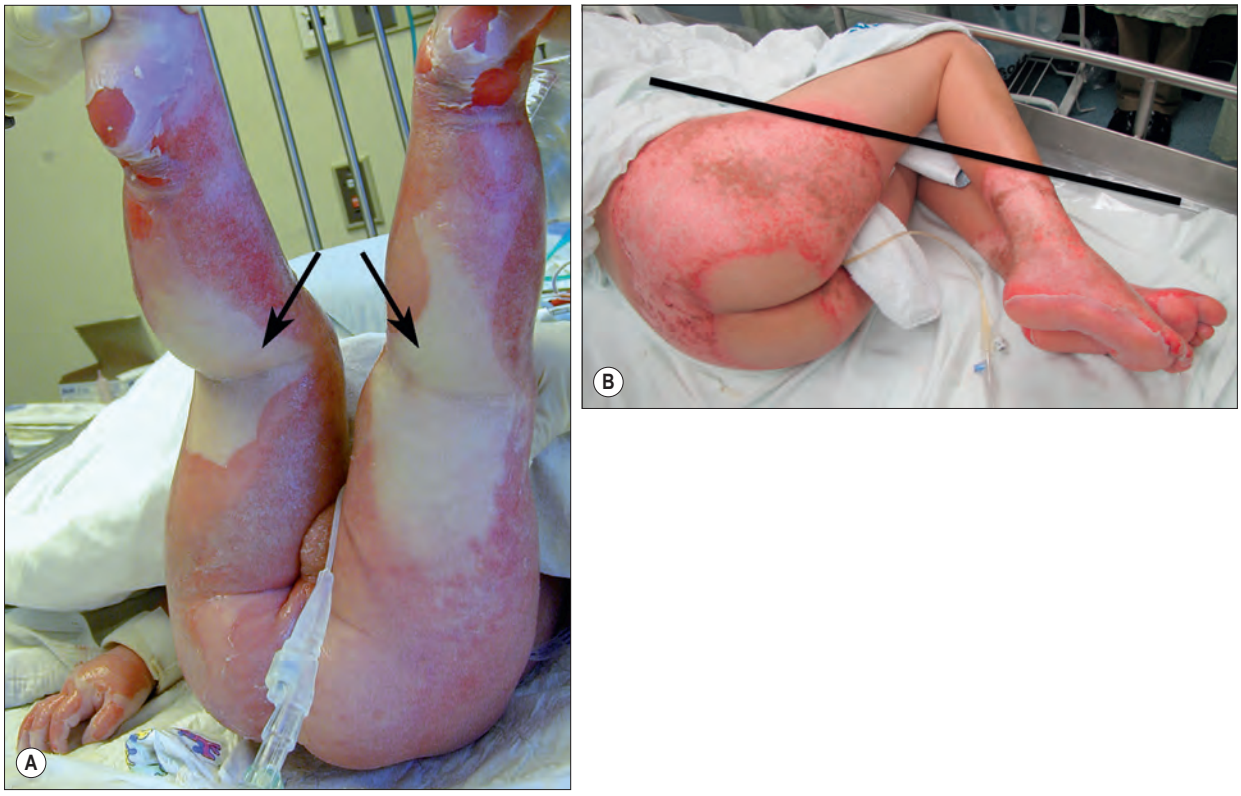

Fig. 10.3 Immersion scald burns: **(A)** on a child; arrows denote sparing of bilateral popliteal fossae: the child by reflex bent his knees to avoid contact with the hot water; **(B)** pattern of nonaccidental trauma: line denotes water level, note soles of feet and buttocks are spared as they were pressed against the bottom of the tub.

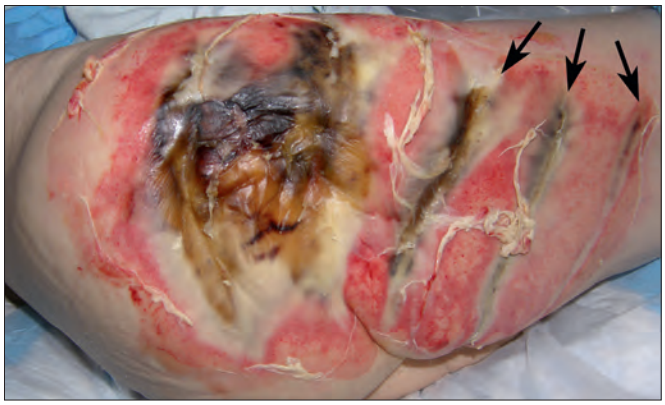

Fig. 10.4 Deep contact burn in an elderly patient who was unconscious next to a space heater. Arrows denote the imprints of the space heater grill on his lateral thigh.

predictable pattern, attributed to patients trying to carry the burning pan of grease outdoors instead of putting the lid on the pan and extinguishing the fire. The majority of patients sustain an isolated upper extremity burn, but injuries may involve the face, lower extremities, or trunk. Approximately 30%–40% of grease burns require excision and grafting.[63,64]

Tar and asphalt represent a special kind of scald. The "mother pot" at the back of the roofing truck maintains tar at a temperature of 400–500°F (204–260°C). Burns caused by tar directly from the "mother pot" are invariably full-thickness. By the time tar is spread on the roof, its temperature has diminished to the point where most of the burns are deep dermal in nature. Initial evaluation and injury depth assessment requires tar removal with application of a petroleum-based ointment that is reapplied every 2–4 hours until the tar has dissolved. Medi-Sol adhesive remover spray (Orange-Sol, Gilbert, AZ, USA) successfully removes tar without injury to the burn wound.

CONTACT BURNS

Contact burns resulting from hot metals, plastic, glass, or hot coals are generally small but are challenging in that the injury is often very deep (Fig. 10.4). The temperature of the material and the duration of contact determine burn depth. Molten materials in industrial accidents instantaneously cause a burn extending below the dermis. An unconscious victim with prolonged contact to a hot surface will often sustain a burn extending into fat and sometimes muscle. Industrial accidents involving presses or other hot, heavy objects may cause both contact burns and crush injuries. In these circumstances, the clinician must anticipate the possibility of extensive myonecrosis and myoglobinuria despite the relative small size of the wound. Contact burns with a hot muffler or engine block are usually full-thickness and often require serial surgeries to achieve wound closure.[65]

In toddlers, contact burns often involve palms and fingers when the child puts his hands on a wood-stove, fireplace insert, clothing iron, or oven door.[66] With aggressive wound care and hand stretching, most intermediate-depth palm burns heal in about 3–4 weeks. Beyond this time, careful consideration of management of the unhealed deep palm

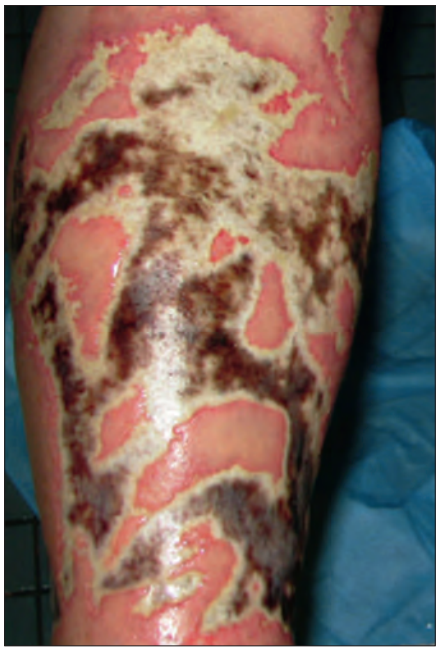

Fig. 10.5 Chemical burn on lower extremity from cement. The discoloration of the skin is characteristic of a full-thickness chemical burn.

burn must be considered. Deep palm burns may epithelialize from the wound edges, allowing granulation tissue development to lead to palmar contracture and permanent disability. However, burn excision and grafting with either thick split-thickness or full-thickness grafts[67,68] results in loss of sensory nerve endings unique to glabrous skin (Pacinian and Meissner's corpuscles). Therefore, an observation period of 3–4 weeks with meticulous wound care and aggressive exercise provides a prudent compromise.

CHEMICAL BURNS

Chemical burns caused by strong acids or alkalis often result from industrial accidents, drain cleaners, assaults, and the improper use of harsh solvents. Chemical burns cause progressive tissue damage until the chemicals are inactivated by reaction with the tissue or by dilution by copious water. Although circumstances vary, acid burns are usually more self-limiting than alkali burns. Acid tends to "tan" the skin, creating an impermeable barrier that limits further penetration of the acid. Conversely, alkali combines with cutaneous lipids to create soap and thereby continues "dissolving" tissue until it the reagent is neutralized. A full-thickness chemical burn may appear deceptively superficial, clinically appearing as a mild brownish discoloration of the skin (Fig. 10.5). The skin may appear intact for the first few days postburn and later will slough spontaneously.

Initial management consists of diluting the agent with copious water for at least 15–20 min, preferably at the site of the accident; to this end, many industrial workplaces are now equipped with showers and eye wash stations. An important exception to immediate irrigation is exposure to a chemical powder, such as dry concrete, cement, and sodium hydroxide; in this instance, it is critical to brush the

agent off before irrigation since moisture activates the chemical. A paper pH test applied to the burn surface can verify that the agent has been neutralized. Attempts to neutralize alkalis with acids (and vice-versa) are contraindicated because the ensuing exothermic reaction leads to a thermal injury superimposed on the chemical burn.

Hydrofluoric acid represents a unique and very destructive chemical, one that is widely used in the circuit board etching process, cleaning solvents, and paint removers. Fluoride ions penetrate the skin, binding with cellular calcium and magnesium and causing progressive deep tissue destruction as sequential cells undergo necrosis.[69,70] Fluoride is also a metabolic poison that inhibits key enzymes of cellular metabolism. A 10% TBSA hydrofluoric acid burn may be life-threatening due to systemic hypocalcemia[71] and may indicate urgent surgical wound excision. A patient may not become symptomatic for several hours after exposure, when severe pain develops in the involved fingers; unfortunately, delayed or inadequate treatment may lead to amputation. Older recommendations of calcium-containing topical gels and direct injection of calcium gluconate into the involved tissue[72,73] have largely been replaced by intra-arterial infusion of calcium gluconate[74–77] which results in immediate cessation of pain and minimal tissue destruction and may be discontinued when acute symptoms resolve.

ELECTRICAL BURNS

Electrical burns are thermal burns from very high-intensity heat generated as the patient's body becomes an accidental resistor. Many electrical burns are work-related (i.e., construction workers, field workers, linemen, utility and electrical workers). Evaluation of the injured patient in these settings must account for associated trauma because these injuries may have occurred in association with associated myoclonic contractions or a fall.

Low-voltage injuries (<440 volts) rarely cause significant damage beyond deep thermal burns at contact points. An exception is the child who chews on an active electrical connection[78]; the child's saliva completes the circuit between the positive and neutral leads, causing a severe burn inside the mouth and lip. Eschar separation at the oral commissure 7–10 days after injury may be associated with brisk labial artery bleeding that requires hemostasis by digital pressure to the corner of the mouth.[79] Burns involving the oral commissure are at high risk for late contracture and warrant an aggressive splinting and exercise regimen.[80,81]

High-voltage injuries (>1000 volts) are more apt to cause deep tissue destruction. In this setting, extensive deep tissue destruction may take place underneath a relatively small, innocuous-appearing wound (Fig. 10.6). High resistance at skin contact points is partially protective because a dry calloused hand may provide twice the resistance of normal skin and five times the resistance of wet skin. High resistance within the body causes more harm due to conversion of electrical energy to heat in proportion to current and electrical resistance. Hence even when superficial muscle appears uninjured, deep muscle necrosis may occur adjacent to bone, which has high resistance.[82,83] Smaller body parts including fingers, hands, forearms, and feet also generate more intense heat with less dissipation and subsequently sustain more injury than the trunk, which may dissipate enough current to prevent extensive damage to internal viscera (unless the contact wound is on the abdomen or chest).[84–86] Arc electrical burns that result because current takes the most direct path occur at joints in close apposition at the time of injury, such as the popliteal fossa with a bent knee, the antecubital fossa with a flexed elbow, and the axilla with the shoulder adducted.

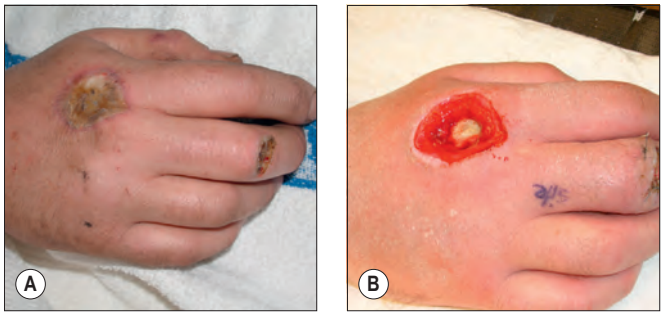

Fig. 10.6 High-voltage contact point on a hand: **(A)** prior to, and **(B)** after débridement. Once wound is debrided, much deeper injury to tendon and bone is revealed.

There are two indications for early operation in a patient with electrical burns: acidosis or myoglobinuria that will not clear with standard resuscitation techniques or the development of compartment syndrome. In these circumstances, urgent fasciotomy, major debridement, and amputation may be needed. If immediate decompression or debridement is not required, definitive operations can be performed 3–5 days after injury, before bacterial contamination occurs and after the tissue necrosis is delineated.[87,88] Extraordinary measures, such as vascular grafting for clotted arteries or free tissue transfer may sometimes be indicated,[89,90] but the zone of injury should be defined before assuming that vascular anastomoses will remain patent. Extensive operative salvage in lieu of a well-fitting prosthesis may increase morbidity and prolong the patient's recovery.

Complete references available online at
www.expertconsult.inkling.com

Further Reading

Burke JF, Bondoc CC, Quinby WC. Primary burn excision and immediate grafting: a method shortening illness. *J Trauma*. 1974;14(5):389-395.

Gray DT, Pine RW, Harnar TJ, et al. Early surgical excision versus conventional therapy in patients with 20 to 40 percent burns. A comparative study. *Am J Surg*. 1982;144(1):76-80.

Jackson DM. The diagnosis of the depth of burning. *Br J Surg*. 1953;40(164):588-596.

Riordan CL, McDonough M, Davidson JM, et al. Noncontact laser Doppler imaging in burn depth analysis of the extremities. *J Burn Care Rehabil*. 2003;24(4):177-186.

Shupp JW, Nasabzadeh TJ, Rosenthal DS, et al. A review of the local pathophysiologic bases of burn wound progression. *J Burn Care Res*. 2010;31(6):1-25.

Yannas IV, Burke JF. Design of an artificial skin. I. Basic design principles. *J Biomed Mater Res*. 1980;14(1):65-81.

References

1. Burke JF, Bondoc CC, Quinby WC. Primary burn excision and immediate grafting: a method shortening illness. *J Trauma*. 1974;14(5):389-395.
2. Engrav LH, Heimbach DM, Reus JL, Harnar TJ, Marvin JA. Early excision and grafting vs. nonoperative treatment of burns of indeterminant depth: a randomized prospective study. *J Trauma*. 1983;23(11):1001-1004.
3. Thompson P, Herndon DN, Abston S, Rutan T. Effect of early excision on patients with major thermal injury. *J Trauma*. 1987;27(2):205-207.
4. Gray DT, Pine RW, Harnar TJ, et al. Early surgical excision versus conventional therapy in patients with 20 to 40 percent burns. A comparative study. *Am J Surg*. 1982;144(1):76-80.
5. Southwood WF. The thickness of the skin. *Plast Reconstr Surg (1946)*. 1955;15(5):423-429.
6. Rudolph R, Ballantyne DL Jr. McCarthy J, eds. *Skin Grafts*. Philadelphia: WB Saunders; 1990:221-274.
7. Tyack ZF, Pegg S, Ziviani J. Postburn dyspigmentation: its assessment, management, and relationship to scarring: a review of the literature. *J Burn Care Rehabil*. 1997;18(5):435-440.
8. de Chalain TM, Tang C, Thomson HG. Burn area color changes after superficial burns in childhood: can they be predicted? *J Burn Care Rehabil*. 1998;19(1 Pt 1):39-49.
9. Compton CC, Press W, Gill JM, et al. The generation of anchoring fibrils by epidermal keratinocytes: a quantitative long-term study. *Epithelial Cell Biol*. 1995;4(3):93-103.
10. Regauer S, Seiler GR, Barrandon Y, Easley KW, Compton CC. Epithelial origin of cutaneous anchoring fibrils. *J Cell Biol*. 1990;111(5 Pt 1):2109-2115.
11. Yannas IV, Burke JF. Design of an artificial skin. I. Basic design principles. *J Biomed Mater Res*. 1980;14(1):65-81.
12. Yannas IV, Burke JF, Gordon PL, Huang C, Rubenstein RH. Design of an artificial skin. II. Control of chemical composition. *J Biomed Mater Res*. 1980;14(2):107-132.
13. Tredget EE, Levi B, Donelan MB. Biology and principles of scar management and burn reconstruction. *Surg Clin North Am*. 2014;94(4):793-815.
14. Wong VW, Gurtner GC, Longaker MT. Wound healing: a paradigm for regeneration. *Mayo Clin Proc*. 2013;88(9):1022-1031.
15. Gibran NS, Heimbach DM. Current status of burn wound pathophysiology. *Clin Plast Surg*. 2000;27(1):11-22.
16. Crowe R, Parkhouse N, McGrouther D, Burnstock G. Neuropeptide-containing nerves in painful hypertrophic human scar tissue. *Br J Dermatol*. 1994;130(4):444-452.
17. Dunnick CA, Gibran NS, Heimbach DM. Substance P has a role in neurogenic mediation of human burn wound healing. *J Burn Care Rehabil*. 1996;17(5):390-396.
18. Moritz AR, Henriques FC. Studies of thermal injury: II. The relative importance of time and surface temperature in the causation of cutaneous burns. *Am J Pathol*. 1947;23(5):695-720.
19. Jackson DM. The diagnosis of the depth of burning. *Br J Surg*. 1953;40(164):588-596.
20. Shupp JW, Nasabzadeh TJ, Rosenthal DS, et al. A review of the local pathophysiologic bases of burn wound progression. *J Burn Care Res*. 2010;31(6):849-873.
21. Rico RM, Ripamonti R, Burns AL, Gamelli RL, DiPietro LA. The effect of sepsis on wound healing. *J Surg Res*. 2002;102(2):193-197.
22. Knabl JS, Bauer W, Andel H, et al. Progression of burn wound depth by systemical application of a vasoconstrictor: an experimental study with a new rabbit model. *Burns*. 1999;25(8):715-721.
23. Winter GD. Formation of the scab and the rate of epithelisation of superficial wounds in the skin of the young domestic pig. 1962. *J Wound Care*. 1995;4(8):366-367, discussion 368-371.
24. Hinman CD, Maibach H. Effect of air exposure and occlusion on experimental human skin wounds. *Nature*. 1963;200:377-378.
25. Palmieri TL, Greenhalgh DG. Topical treatment of pediatric patients with burns: a practical guide. *Am J Clin Dermatol*. 2002;3(8):529-534.
26. Davies JW. Prompt cooling of burned areas: a review of benefits and the effector mechanisms. *Burns*. 1982;9(1):1-6.
27. Boykin JV Jr, Eriksson E, Sholley MM, Pittman RN. Cold-water treatment of scald injury and inhibition of histamine-mediated burn edema. *J Surg Res*. 1981;31(2):111-123.
28. Demling RH, Mazess RB, Wolberg W. The effect of immediate and delayed cold immersion on burn edema formation and resorption. *J Trauma*. 1979;19(1):56-60.
29. King TC, Price PB. Surface cooling following extensive burns. *JAMA*. 1963;183:677-678.
30. Purdue GF, Layton TR, Copeland CE. Cold injury complicating burn therapy. *J Trauma*. 1985;25(2):167-168.
31. Sawada Y, Urushidate S, Yotsuyanagi T. Ishita K. Is prolonged and excessive cooling of a scalded wound effective? *Burns*. 1997;23(1):55-58.
32. American Burn Association. Practice guidelines for burn care. *J Burn Care Rehabil*. 2001;(suppl):10s-13s.
33. Robson MC, Kucan JO, Paik KI, Eriksson E. Prevention of dermal ischemia after thermal injury. *Arch Surg* (Chicago, IL: 1960). 1978;113(5):621-625.
34. Forage AV. The history of the classification of burns (diagnosis of depth). *Br J Plast Surg*. 1963;16:239-242.
35. Boykin JV, Eriksson E, Pittman RN. In vivo microcirculation of a scald burn and the progression of postburn dermal ischemia. *Plast Reconstr Surg*. 1980;66(2):191-198.
36. Nanney LB, Wenczak BA, Lynch JB. Progressive burn injury documented with vimentin immunostaining. *J Burn Care Rehabil*. 1996;17(3):191-198.
37. Riordan CL, McDonough M, Davidson JM, et al. Noncontact laser Doppler imaging in burn depth analysis of the extremities. *J Burn Care Rehabil*. 2003;24(4):177-186.
38. Hlava P, Moserova J, Konigova R. Validity of clinical assessment of the depth of a thermal injury. *Acta Chir Plast*. 1983;25(4):202-208.
39. Niazi ZB, Essex TJ, Papini R, et al. New laser Doppler scanner, a valuable adjunct in burn depth assessment. *Burns*. 1993;19(6):485-489.
40. Yeong EK, Mann R, Goldberg M, Engrav L, Heimbach D. Improved accuracy of burn wound assessment using laser Doppler. *J Trauma*. 1996;40(6):956-961, discussion 961-962.
41. Desai MH, Rutan RL, Herndon DN. Conservative treatment of scald burns is superior to early excision. *J Burn Care Rehabil*. 1991;12(5):482-484.
42. Dupuytren G. *Clinical Lectures on Surgery: Delivered at Hotel Dieu, in 1832* [Doane SA, Trans.]. Boston: Carter, Hendee, & Company; 1833:326.
43. Jaskille AD, Ramella-Roman JC, Shupp JW, Jordan MH, Jeng JC. Critical review of burn depth assessment techniques: part II. Review of laser doppler technology. *J Burn Care Res*. 2010;31(1):151-157.
44. Jaskille AD, Shupp JW, Jordan MH, Jeng JC. Critical review of burn depth assessment techniques: part I. Historical review. *J Burn Care Res*. 2009;30(6):937-947.
45. Hoeksema H, Van de Sijpe K, Tondu T, et al. Accuracy of early burn depth assessment by laser Doppler imaging on different days post burn. *Burns*. 2009;35(1):36-45.
46. Ho-Asjoe M, Chronnell CM, Frame JD, Leigh IM, Carver N. Immunohistochemical analysis of burn depth. *J Burn Care Rehabil*. 1999;20(3):207-211.
47. Moserova J, Hlava P, Malinsky J. Scope for ultrasound diagnosis of the depth of thermal damage. Preliminary report. *Acta Chir Plast*. 1982;24(4):235-242.
48. Cantrell JH Jr. Can ultrasound assist an experienced surgeon in estimating burn depth? *J Trauma*. 1984;24(9 suppl):S64-S70.
49. Kaufman T, Hurwitz DJ, Heggers JP. The india ink injection technique to assess the depth of experimental burn wounds. *Burns*. 1984;10(6):405-408.
50. Heimbach DM, Afromowitz MA, Engrav LH, Marvin JA, Perry B. Burn depth estimation: man or machine. *J Trauma*. 1984;24(5):373-378.
51. Koruda MJ, Zimbler A, Settle RG, et al. Assessing burn wound depth using in vitro nuclear magnetic resonance (NMR). *J Surg Res*. 1986;40(5):475-481.
52. Black KS, Hewitt CW, Miller DM, et al. Burn depth evaluation with fluorometry: is it really definitive? *J Burn Care Rehabil*. 1986;7(4):313-317.
53. Pape SA, Skouras CA, Byrne PO. An audit of the use of laser Doppler imaging (LDI) in the assessment of burns of intermediate depth. *Burns*. 2001;27(3):233-239.
54. Hackett ME. The use of thermography in the assessment of depth of burn and blood supply of flaps, with preliminary reports on its use in Dupuytren's contracture and treatment of varicose ulcers. *Br J Plast Surg*. 1974;27(4):311-317.
55. Jeng JC, Bridgeman A, Shivnan L, et al. Laser Doppler imaging determines need for excision and grafting in advance of clinical judgment: a prospective blinded trial. *Burns*. 2003;29(7):665-670.
56. Shin JY, Yi HS. Diagnostic accuracy of laser Doppler imaging in burn depth assessment: systematic review and meta-analysis. *Burns*. 2016;42(7):1369-1376.

57. American Burn Association. 2016 National Burn Repository: Report of Data from 2006–2015. Chicago: 2016.
58. Byrom RR, Word EL, Tewksbury CG, Edlich RF. Epidemiology of flame burn injuries. *Burns*. 1984;11(1):1-10.
59. Ding YL, Pu SS, Pan ZL, et al. Extensive scalds following accidental immersion in hot water pools. *Burns*. 1987;13(4):305-308.
60. Walker AR. Fatal tapwater scald burns in the USA, 1979–86. *Burns*. 1990;16(1):49-52.
61. Kumar P. Child abuse by thermal injury – a retrospective survey. *Burns*. 1984;10(5):344-348.
62. Bird PE, Harrington DT, Barillo DJ, et al. Elder abuse: a call to action. *J Burn Care Rehabil*. 1998;19(6):522-527.
63. Klein MB, Gibran NS, Emerson D, et al. Patterns of grease burn injury: development of a classification system. *Burns*. 2005;31(6):765-767.
64. Murphy JT, Purdue GF, Hunt JL. Pediatric grease burn injury. *Arch Surg* (Chicago, IL: 1960). 1995;130(5):478-482.
65. Gibran NS, Engrav LH, Heimbach DM, Swiontkowski MF, Foy HM. Engine block burns: Dupuytren's fourth-, fifth-, and sixth-degree burns. *J Trauma*. 1994;37(2):176-181.
66. Yanofsky NN, Morain WD. Upper extremity burns from woodstoves. *Pediatrics*. 1984;73(5):722-726.
67. Pensler JM, Steward R, Lewis SR, Herndon DN. Reconstruction of the burned palm: full-thickness versus split-thickness skin grafts–long-term follow-up. *Plast Reconstr Surg*. 1988;81(1):46-49.
68. Merrell SW, Saffle JR, Schnebly A, Kravitz M, Warden GD. Full-thickness skin grafting for contact burns of the palm in children. *J Burn Care Rehabil*. 1986;7(6):501-507.
69. Bertolini JC. Hydrofluoric acid: a review of toxicity. *J Emerg Med*. 1992;10(2):163-168.
70. Anderson WJ, Anderson JR. Hydrofluoric acid burns of the hand: mechanism of injury and treatment. *J Hand Surg Am*. 1988;13(1):52-57.
71. Mayer TG, Gross PL. Fatal systemic fluorosis due to hydrofluoric acid burns. *Ann Emerg Med*. 1985;14(2):149-153.
72. Bracken WM, Cuppage F, McLaury RL, Kirwin C, Klaassen CD. Comparative effectiveness of topical treatments for hydrofluoric acid burns. *J Occup Med*. 1985;27(10):733-739.
73. Chick LR, Borah G. Calcium carbonate gel therapy for hydrofluoric acid burns of the hand. *Plast Reconstr Surg*. 1990;86(5):935-940.
74. Siegel DC, Heard JM. Intra-arterial calcium infusion for hydrofluoric acid burns. *Aviat Space Environ Med*. 1992;63(3):206-211.
75. Vance MV, Curry SC, Kunkel DB, Ryan PJ, Ruggeri SB. Digital hydrofluoric acid burns: treatment with intraarterial calcium infusion. *Ann Emerg Med*. 1986;15(8):890-896.
76. Velvart J. Arterial perfusion for hydrofluoric acid burns. *Hum Toxicol*. 1983;2(2):233-238.
77. Pegg SP, Siu S, Gillett G. Intra-arterial infusions in the treatment of hydrofluoric acid burns. *Burns*. 1985;11(6):440-443.
78. Rai J, Jeschke MG, Barrow RE, Herndon DN. Electrical injuries: a 30-year review. *J Trauma*. 1999;46(5):933-936.
79. Orgel MG, Brown HC, Woolhouse FM. Electrical burns of the mouth in children: a method for assessing results. *J Trauma*. 1975;15(4):285-289.
80. Holt GR, Parel S, Richardson DS, Kittle PE. The prosthetic management of oral commissure burns. *Laryngoscope*. 1982;92(4):407-411.
81. al-Qattan MM, Gillett D, Thomson HG. Electrical burns to the oral commissure: does splinting obviate the need for commissuroplasty? *Burns*. 1996;22(7):555-556.
82. Chilbert M, Maiman D, Sances A Jr, et al. Measure of tissue resistivity in experimental electrical burns. *J Trauma*. 1985;25(3):209-215.
83. Lee RC, Kolodney MS. Electrical injury mechanisms: dynamics of the thermal response. *Plast Reconstr Surg*. 1987;80(5):663-671.
84. Yang JY, Tsai YC, Noordhoff MS. Electrical burn with visceral injury. *Burns*. 1985;11(3):207-212.
85. Branday JM, DuQuesnay DR, Yeesing MT, Duncan ND. Visceral complications of electrical burn injury. A report of two cases and review of the literature. *West Indian Med J*. 1989;38(2):110-113.
86. Honda T, Yamamoto Y, Mizuno M, et al. Successful treatment of a case of electrical burn with visceral injury and full-thickness loss of the abdominal wall. *Burns*. 2000;26(6):587-592.
87. Mann R, Gibran N, Engrav L, Heimbach D. Is immediate decompression of high voltage electrical injuries to the upper extremity always necessary? *J Trauma*. 1996;40(4):584-587, discussion 587-589.
88. Yowler CJ, Mozingo DW, Ryan JB, Pruitt BA Jr. Factors contributing to delayed extremity amputation in burn patients. *J Trauma*. 1998;45(3):522-526.
89. Bartle EJ, Wang XW, Miller GJ. Early vascular grafting to prevent upper extremity necrosis after electrical burns: anastomotic false aneurysm, a severe complication. *Burns*. 1987;13(4):313-317.
90. Wang XW, Bartle EJ, Roberts BB, et al. Free skin flap transfer in repairing deep electrical burns. *J Burn Care Rehabil*. 1987;8(2):111-114.

11 Treatment of Infection in Burn Patients

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Introduction

Skin is the first immune defense mechanism and functions as a barrier against microorganisms. Infections are a significant problem once open wounds compromise this barrier. According to the U.S. National Burn Repository, the four leading causes of burn morbidity are (1) pneumonia, (2) cellulitis, (3) urinary tract infections, and (4) burn wound infections. Infections are a primary factor contributing to mortality, accounting for 51% of deaths in burn patients, as discussed in both Chapters 30 and 32, on multisystem organ failure and critical care, respectively.[1–3]

A cutaneous burn is initially sterile as commensal skin flora are killed with the skin in the thermal event. Unfortunately the burn wound provides optimal bacterial growth conditions due to a reduced blood supply and a nutrient-rich environment, leading to rapid wound colonization. The 2007 American Burn Association Consensus Conference defined wound colonization as follows: (1) low concentrations of bacteria on the wound surface, (2) absence of invasive infection, and (3) less than 10^5 organisms per gram tissue.[3] In a superficial burn, skin flora can survive in hair follicles and sebaceous glands in the same manner as keratinocytes to repopulate a physiological microbiome.[4-6] However, burns are customarily colonized by pathogens from the environment, the patient's gut, or the nasooropharyngeal tract.

A race thus exists between the patient and the pathogen to dominate the wound surface. In the log phase growth, bacteria double 2–3 times per hour; consequently a single bacterium can become 10 million in 1 day, far faster than any human cell can multiply.[7] Therefore colonization can quickly become an infection capable of converting partial-thickness into full-thickness burns by causing vessel thrombosis and necrosis in viable tissues in the wound penumbra. Gram-positive bacteria tend to colonize an affected area first, with subsequent colonization by gram-negative bacteria. Delayed treatment risks colonization by extended-spectrum pathogens, bloodstream invasion, and the development of sepsis, all of which increase the likelihood of death.[2]

The model of burn care advocated throughout this text is to rig this race for wound dominance in favor of the patient. Early wound excision eliminates the devitalized tissue that is the main reservoir for pathogen nourishment and habitat. Prompt autografting reestablishes skin barrier function and denies pathogens access to the host. Topical antimicrobials suppress bacterial growth and colony counts while allowing host fibroblasts and keratinocytes to proliferate and cover the wound. Assiduous washing technique allows 2-log reduction in colony counts, breaks down and removes biofilms, and purges the devitalized tissue that pathogens thrive upon.[8] Systemic antimicrobials kill and suppress the invading pathogens accessing perfused areas of tissue. Quantitative wound culturing enables effective diagnosis and directed application of the most efficacious antimicrobial with the lowest toxicity. Coordinated critical care, therapy, and nutrition ensure that the wounds have a sufficient supply of nutrients and immune-cell–laden blood to clear pathogens, expand skin grafts, and reepithelialize wounds.

Prevention of Infection

Prevention is the optimal way to minimize infection.[9] Pathogens can be carried into or transmitted around the unit by staff, by visitors, or on equipment. Patients should have single rooms separated from other rooms by a door. Positive pressure in the rooms further aids in minimizing bacterial contamination. Patient rooms should undergo a daily cleaning in addition to deep cleaning upon patient discharge. This terminal cleaning should include washing the walls and ceiling and should be done 72 hours prior to admitting another patient to avoid the transfer of more virulent strains.[10] Another important prevention measure is the use of contact precautions with all patients, including gowns and gloves. These items should be donned before entering and doffed prior to exiting the room, regardless of the bacteriological status of the particular patient. Routine hand hygiene before and after patient interaction is also mandatory to prevent infection. Dressing materials, supplies, devices, and equipment must not be shared between patients. Bathing, showering, tubbing, mobile diagnostic equipment, and operating facilities should be decontaminated between each patient use. Furthermore, fomites, such as ties, rings, watches, and cell phones, should be prohibited since these are possible pathogen vectors.[11,12] Water and air filters ought to screen particles down to 0.2 and 0.3 μm, respectively, be changed monthly, and be cultured routinely as part of infection control monitoring. By maintaining these strict measures, transmission of infectious organisms between patients can be limited.[13]

Diagnosis of Burn Wound Infection

Diagnosis of burn infection in burn wounds can be complicated. The typical cytokine and immune cascades that

create the typical presentations of infection known to all doctors are often initiated in the burn patient via the elaboration of damage-associated molecular patterns (DAMPS) and pathogen-associated molecular patterns (PAMPS) from burn wounds. This complicates diagnoses of infection and sepsis in the burn patient where clinical signs, such as elevated temperature or tachycardia, are normal components of burn pathophysiology, as discussed in Chapter 29 on hypermetabolism.

Wound culturing is a critical tool to guide the treatment of burn wounds and to determine what bacteria are colonizing the burn wound. In patients with major burns, the wound usually becomes colonized 5–7 days after injury.[6] Since most initial infections in burn patients derive from endogenous bacteria flora, it is good clinical practice to perform initial wound cultures upon patient admission. This screening should include swabs of both sides of the groin and axilla, as well as of the nose and throat.[14] In addition, at each burn excision, and whenever suspicion of invasive infection warrants, quantitative tissue cultures may be helpful.

Wound appearance and odor changes can help to diagnose wound colonization versus wound infection (Fig. 11.1). Kwei et al. described three main methods that exist for culturing a wound: qualitative (presence or absence of growth), semi-quantitative (grading of the bacterial presence as scanty, few, moderate, or numerous), and quantitative (an absolute quantity is determined).[15,16] Swabs are useful but limited since they cannot distinguish between infection and colonization and are only accurate for the region sampled. These problems are mitigated by performing multiple tissue biopsies, which can reveal significant quantitative differences in different areas.[17] Although quantitative cultures are more expensive, bacterial counts have been shown to correlate with histological evidence of wound infection in approximately 80% of cases after biopsies are taken or after sterilization of the surface with antimicrobials.[6,18] Histological examinations can be used to confirm invasive bacterial infection when counts exceed 10^5 organisms per gram of tissue. If histological evidence of invasion is present, systemic antibiotics should be administered and the wound excised.[6,19,20]

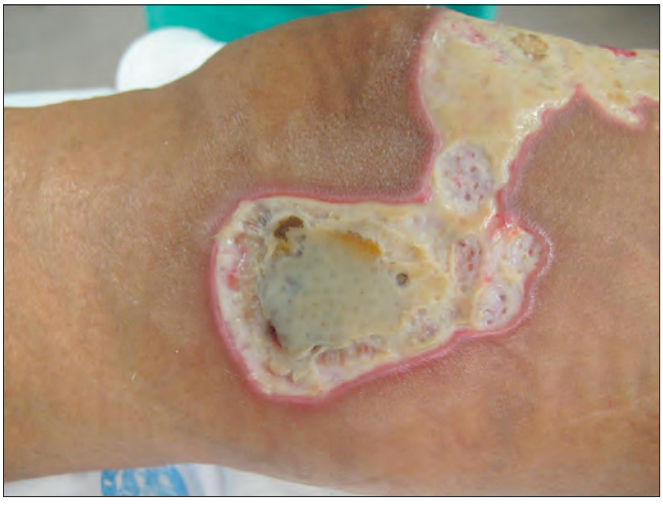

Fig. 11.1 Burn wound colonization. Flame burn to the left medial arm depicted post-burn day 7. The eschar has degraded but is still present. However, the surrounding tissue is not cellulitic.

Studies by Robson demonstrated that if burn wound colony counts from biopsies or after cleaning of the surface of the wound are greater than 10^5/g tissue, the graft survival rate is only 19%, whereas colony counts of less than 10^5/g tissue are associated with a 94% chance of graft survival.[21] Sensitivities to available antibiotics, both systemic and topical, should instruct therapy. In the setting of resistant organisms, antibiotic synergy testing is advised. Thus the ultimate diagnosis of burn wound infection and the guidance of antimicrobials are directed by culture data.

Physical examination of the patient also provides valuable insight into the infectious nature of the burn wound. *Burn wound erythema* is a physiologic phenomenon produced sterilely by the liberation of inflammatory mediators from tissues surrounding the burn area and must not be confused with cellulitis. Normally this erythema presents within 2–3 days of the burn injury and resolves by 1 week post burn (Fig. 11.2). The best differential diagnosis comes from clinical palpation: erythema lacks significant induration or tenderness compared to an infectious process like cellulitis.[8]

Cellulitis is a noninvasive infection of the tissues surrounding the burn wound.[3] Cellulitis can be caused by a variety of pathogens.[6] This infection is characterized by edema, hyperesthesia, erythema, induration, and tenderness detectable upon examination (Fig. 11.3). The color of the wound contour and the odor from the wound may also raise suspicion of cellulitis. Furthermore it can have a lymphangitic component. Particular attention should be given to elderly patients and diabetic patients due to the ease and speed with which infections progress in these populations. Cellulitic burn wounds benefit from systemic antimicrobials to cover likely causative agents in addition to standard burn treatments, such as topical antimicrobials or surgical excision and grafting. Progression of cellulitis despite antibiotics must always trigger suspicions of resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), and these organisms should be covered empirically.[6]

Graft ghosting (impetigo) is a wound infection that can cause late graft loss (Fig. 11.4). This phenomenon can occur after spontaneous closure of a partial-thickness wound, following loss of previously adherent graft sites, and in skin donor sites. Characterized by multiple small abscesses, graft ghosting can lead to the complete destruction of the healed wound.[6] The culprit typically responsible for this condition is *S. aureus*, particularly MRSA. The diagnosis is essentially clinical and can be confirmed by culturing. Treatment requires regular dressing changes, débridement of abscesses, local disinfection, and application of topical antimicrobials, such as mupirocin.

Toxic shock syndrome (TSS) is a complication of severe soft tissue infections (SSTI), which occurs predominately in small burns. This syndrome results from colonization with TSS toxin-1–producing *S. aureus*. This disease is primarily seen in young children with burns covering less than 10% of the total body surface area (TBSA) and that would otherwise be expected to heal without problems. The incidence is approximately 2.6% with a mean age of 2 years. TSS is clinically characterized by a prodromal period lasting 1–2 days with pyrexia, diarrhea, vomiting, and malaise. While

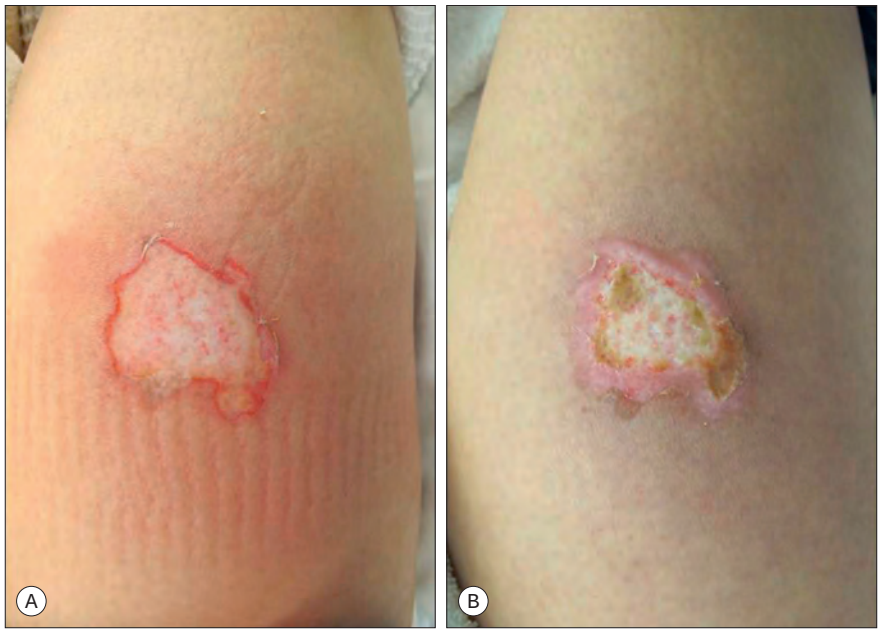

Fig. 11.2 Burn wound erythema. A hot oil scald burn on the lateral thigh is depicted with (A) surrounding erythema noted on post-burn day 2. (B) Resolution of redness and healing on post-burn day 12.

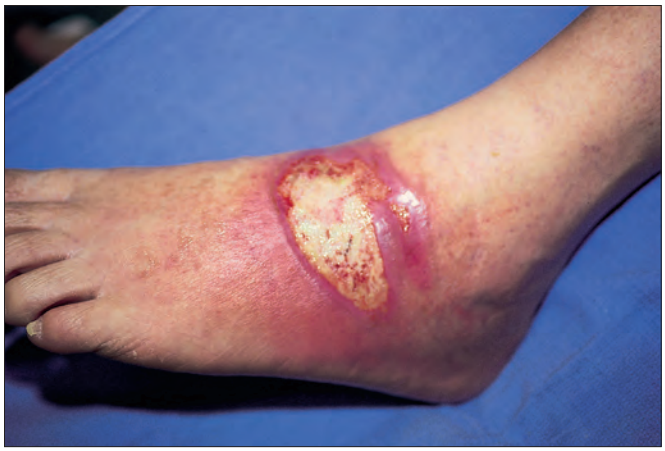

Fig. 11.3 Burn wound cellulitis. Cultures demonstrated *Staphylococcus aureus*. Clinical findings include increased pain, local inflammatory signs, and fever. Treatment includes systemic and topical antibiotics, excision, and autografting.

a rash is often present, at this stage, the burn appears clean (Fig. 11.5). Shock subsequently develops in untreated cases, but determining the cause of shock to be TSS can be complicated in this early phase of the patient's presentation when a litany of potential and more common etiologies of shock exist. Once shock has developed, mortality can be as high as 50%. Awareness and aggressive action are the principal safeguards against the development and progression of TSS. A possible diagnosis of TSS should be considered in small burns where the patient is unexpectedly in shock. Because MRSA has emerged as the most commonly identified cause of SSTI, initiation of empiric anti-MRSA antimicrobials is warranted in all cases of suspected TSS.[19,22]

Invasive wound infections manifest clinically with wound color changes, exudate, and odor. Within a short time, partial-thickness burns progress to full-thickness necrosis and begin expanding into unburned tissues. The 2007 American Burn Association Consensus Conference defined invasive infections as follows: "the presence of pathogens in a burn wound at concentrations sufficient in conjunction with depth, surface area involved, and age of patient, to cause suppurative separation of eschar or graft loss, invasion of adjacent unburned tissue or cause the systemic response of sepsis syndrome."[3] Goal-standard diagnosis is made with histologic examination; however, clinical exam and quantitative cultures usually suffice (Fig. 11.6). It should be noted that sepsis does not always develop during invasive infections (Fig. 11.7). Treatment must be immediate and include aggressive surgical intervention augmented by the administration of systemic and topical antimicrobials. If no culture results are initially available, a broad-spectrum empirical therapy against fungi, drug-resistant gram-positive and -negative organisms should be initiated until culture data become available. Surgical extirpation must be aggressive and encompass excision of all necrotic and infected tissue, including fascia and muscle when warranted. Definitive wound coverage is not always indicated in this extirpative operation as dressing changes and hydrotherapy may be needed to further decrease heavy bacterial loads. In cases where tissue has already been excised or there is a life-threatening infection, limb amputation may be indicated. Topical antimicrobials and assiduous washing technique are indicated after extirpation to suppress microbial growth. However, the optimal methodology is to prevent infection, with swift action being taken should an infection arise.[23]

Sepsis and *septic shock* are complicated diagnoses in burn patients because large burns create a systemic inflammatory response syndrome (SIRS) and hypermetabolism of their own, as discussed in Chapter 8 on the etiology of shock. This hypermetabolism is a natural part of the body's

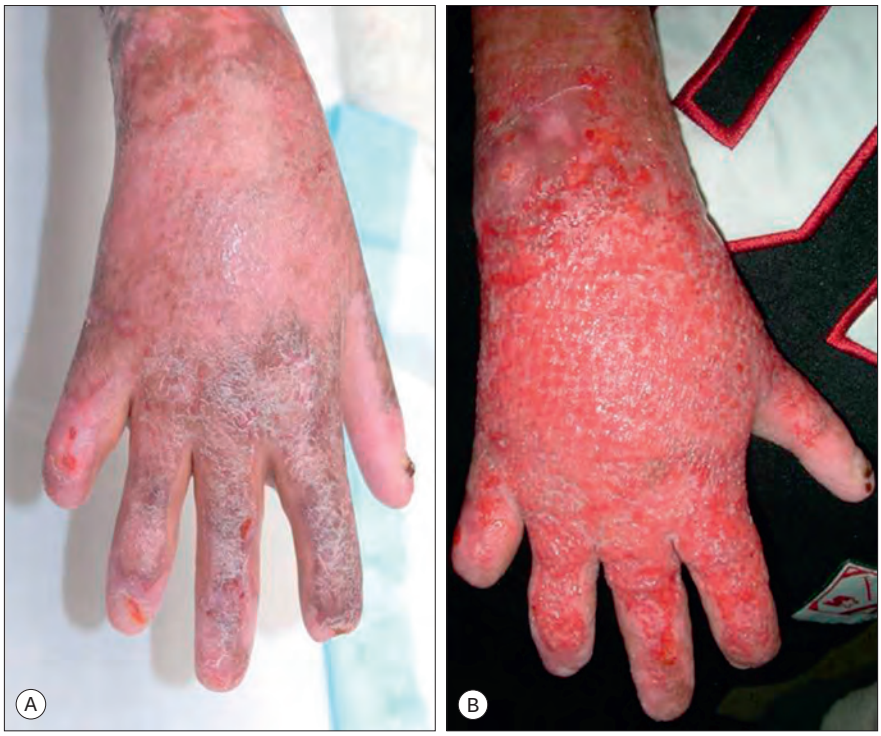

Fig. 11.4 Burn wound impetigo. Right hand in a 13-year-old boy with 85% TBSA burn, third-degree to the hands shown (A) 4 months post-burn at hospital discharge. (B) Three weeks later the patient presented with reopening of the previously taken skin grafts to the hand and clinical impetigo. Cultures were positive for MRSA, and the patient was treated with vancomycin, mupirocin, and tub therapy.

compensatory mechanism to burn injury and can last for up to a year following the insult, making it difficult to fit shock in burn patients into the definitions of sepsis and septic shock established by the Society of Critical Care Medicine.[24–26] Patients with high concentrations of bacteria in the burn wounds in conjunction with delayed admission to a burn center or delayed removal of burned tissues are at the greatest risk of developing sepsis.[8] Rapid and complete closure of deep burns is the best defense against this condition. An additional factor influencing the development of sepsis and increasing mortality during hospitalization in patients with equal burn sizes is decreased lean body mass. The identification of parameters associated with sepsis in burn patients is extremely important and ongoing. The American Burn Association Consensus Conference in 2007 provided criteria (Box 11.1).[3] These criteria are useful markers and indicators for sepsis but are by no means gospel. A skilled physician must take these factors into account along with changes in the patient's clinical condition over time to make a presumptive diagnosis of sepsis. Aggressive treatment should be initiated and de-escalated based upon definitive diagnosis and patient response.

Treatment of Burn Wound Infections

Treatment of burn wound infections is multimodal. Surgical débridement and assiduous washing technique decrease the bacterial and nutritive burden. Aggressive grafting denies the pathogens wound surface area to colonize and infect. Topical antimicrobial compounds reduce pathogen burden in the wound and periwound areas while allowing skin grafts to proliferate and cover the wound. Systemic antimicrobials are administered to treat invasive pathogens and prevent or reduce the systemic spread of infection.

TOPICAL ANTIMICROBIAL COMPOUNDS

Topical antimicrobial compounds have significantly reduced burn mortality.[7,27] However, no single agent is entirely effective. Each possesses its own spectrum, advantages, and disadvantages. Some retard wound healing while others have systemic metabolic effects on the patient. Recent studies have demonstrated that some agents used in the past are now ineffective in inhibiting bacterial growth.[28,29] Wounds may be dressed with any topical agent when quantitative culture counts persist at less than 10^2/g tissue. However, higher colony counts warrant culture-directed topical antimicrobial selection. Topical antimicrobial agents fall into five major classes, each possessing different antimicrobial spectra, duration of action, penetration, and toxicities (Box 11.2).

Soaps are the first form of topical antimicrobial and are employed during washing. They are effective in disrupting biofilms and washing pathogens from the patient. *Biofilms* are coherent clusters of bacterial cells embedded in a biopolymer matrix that, compared with planktonic cells, resist host defenses and show increased tolerance to topically (antiseptics) and systemically (antibiotics) administered antimicrobials, thus creating the perfect environment for bacterial growth.[30] Biofilm bacteria are extremely difficult to remove, requiring surgical or sharp instruments and/or mechanical wound débridement and washing with soap and water. According to recent recommendations, burn

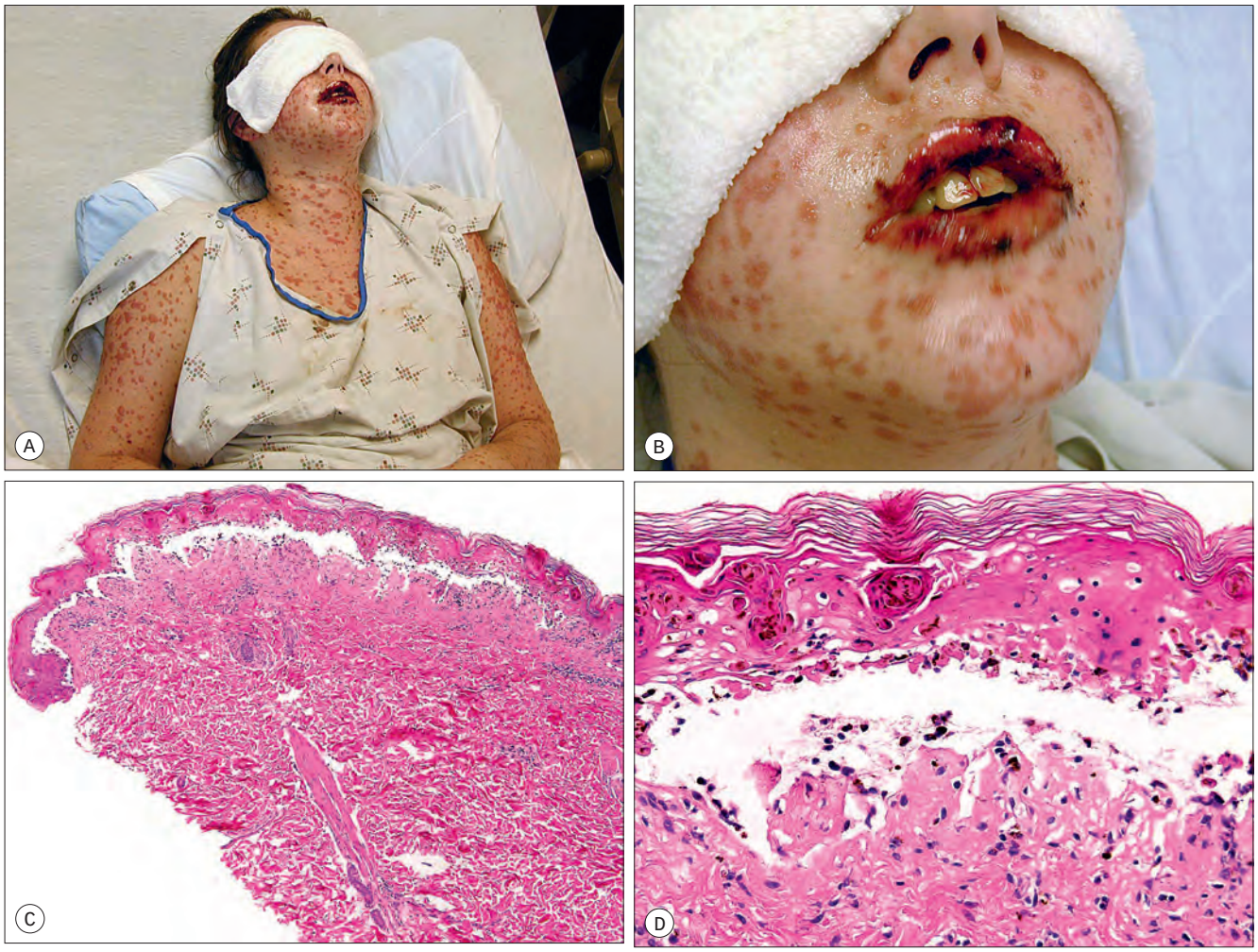

Fig. 11.5 Toxic shock syndrome (TSS) rash. Cutaneous rash commonly seen in patients with TSS. This rash does not universally appear in cases of TSS. Patients with small burns developing shock should be evaluated and treated for TSS with excision, grafting, and vancomycin. (A) A 13-year-old girl presenting TSS rash following a 10% TBSA burn. (B) The typical macular erythroderma lesions. (C) A hematoxylin and eosin 4× magnification micrograph of a TSS rash lesion showing an epidermal blister. (D) Further hematoxylin and eosin 40× magnification micrograph with low inflammation. (Courtesy of Omar P. Sangüeza, MD; Professor and Director of Dermatopathology, Wake Forest University School of Medicine, North Carolina.)

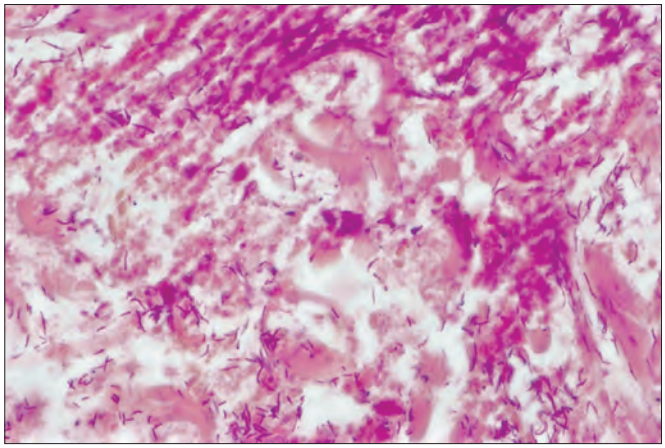

Fig. 11.6 Gram-negative bacilli invading deep viable tissue. Histopathologic confirmation is the gold standard test to diagnose burn wound infection by bacteria in viable tissue. Shown is a typical hematoxylin and eosin stained section at 1000× magnification.

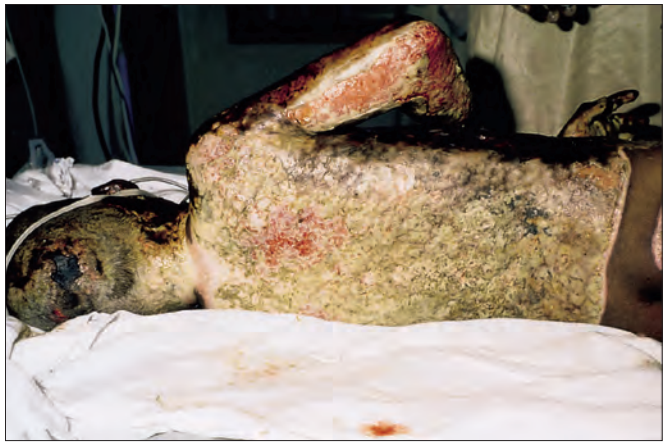

Fig. 11.7 Invasive burn wound infection. Seventy-five percent TBSA full-thickness burns with wound sepsis due to *Enterococcus faecalis* and *Enterobacter cloacae*. Prompt excision, homografting, hemodynamic support, and systemic antibiotics controlled the infection. This patient was subsequently autografted and survived.

Box 11.1 The 2007 American Burn Association Consensus Conference Definition of Sepsis.[3]

"Sepsis is a change in the burn patient that triggers the concern for infection. It is a presumptive diagnosis where antibiotics are usually started and a search for a cause of infection should be initiated. While there is need for clinical interpretation, the diagnosis needs to be tied to the discovery of an infection (defined below). The definition is age-dependent with adjustments necessary for children.

The trigger includes at least three of the following of sepsis:

I. Temperature >39mpera<36.5er
II. Progressive tachycardia
  A. Adults >110 bpm
  B. Children >2 SD above age-specific norms (85% age-adjusted max heart rate)
III. Progressive tachypnea
  A. Adults >25 bpm not ventilated
    i. Minute ventilation >12 L/min ventilated
  B. Children >2 SD above age-specific norms (85% age-adjusted max respiratory rate)
IV. Thrombocytopenia (will not apply until 3 days after initial resuscitation)
  A. Adults <100,000/mcl
  B. Children <2 SD below age-specific norms
V. Hyperglycemia (in the absence of pre-existing diabetes mellitus)
  A. Untreated plasma glucose >200 mg/dL or equivalent mM/L
  B. Insulin resistance – examples include
    i. >7 units of insulin/h intravenous drip (adults)
    ii. Resistance to insulin (>25% increase in insulin requirements over 24 hours)
VI. Inability to continue enteral feedings >24 hours
  A. Abdominal distension
  B. Enteral feeding intolerance (residual >150 mL/h in children or 2ce (residual er 24 hours
  C. Uncontrollable diarrhea (>2,500 mL/d for adults or >400 mL/d in children)

In addition, it is required that a documented infection (defined below) is identified
  A. Culture positive infection, or
  B. Pathologic tissue source identified, or
  C. Clinical response to antimicrobials.

wounds not associated with clinical signs or symptoms of infection yet suspected of having biofilm should be treated with débridement, antimicrobial dressings, antiseptic soaks, and thorough cleansing with antiseptic products to prevent bacterial growth.[31] Findings from Kennedy and colleagues support the significant role played by biofilms in burn wound sepsis and the importance of early excision and closure of the wound.[32] Herndon et al. demonstrated that washing burn wounds with soap and water using assiduous washing techniques can cause a 2-log reduction in bacterial counts over 48 hours, improving autograft take by infected wounds.[8]

Many oxidative halides are used as topical antimicrobials. Classically sodium hypochlorite (Dakin's solution) has been employed due to its broad bactericidal range and effective dissolution of biofilms.[33–36] Commercially available Clorox bleach is 5.25% NaOCl; the original Carrel-Dakin's Solution used in World War I was diluted with water to 0.5% and is described as full-strength Dakin's Solution. Studies have demonstrated full-strength to be tissue toxic, as are the pharmacy-available half- and quarter-strength Dakin's solutions, though they are effective antimicrobials. Investigations by Heggers and coworkers established the efficacy of NaOCl at a concentration of 0.025%, or one-twentieth Dakin's.[23,37,38] Buffered one-twentieth Dakin's was formulated to mimic normal human physiologic parameters, with the added benefits that it is a broad-spectrum antiseptic, yet nontoxic to fibroblasts nor inhibiting of wound healing. It is bactericidal against *P. aeruginosa*, *S. aureus*, methicillin-resistant staphylococci, enterococci, and other gram-negative and gram-positive organisms, and it may be used separately or in combination with other agents.[23] Subsequently Carrel and Dakins developed oxychlorosene (Clorpactin) to allow longer tissue half-life, neutral pH, and lower tissue toxicity. It is used intravesicularly and intrarenally to control hemorrhage in genitourinary cancer cases and has been recently resurging as a topical antimicrobial.[39] It has been demonstrated to be nontoxic to skin grafts when tested as a wound irrigant.[40] Currently products are coming to market using hypochlorous acid as an active oxidizing agent in pH-neutral, isotonic formulations.[41,42] While of interest as topical antimicrobials for burn wounds, they lack the century-long experience of sodium hypochlorite solutions and so require further research.

Povidone-iodine (Betadine) is another halide used as a topical antimicrobial; it is available as a liquid or an ointment in varying concentrations. It has a broad-spectrum of activity, covering gram-positive and gram-negative bacteria, yeast, and fungi. Quantitative bacteriological assessments imply that iodine is most efficacious when administered every 6 hours. Topical application of this agent can be painful. The iodine component of this topical agent may be absorbed more extensively in burn wounds, resulting in iodine toxicity, renal failure, acidosis, and dermatitis (in intact skin). Furthermore povidone-iodine is cytotoxic to fibroblasts and keratinocytes. However, it remains a highly effective disinfectant when used on intact skin.[43,44]

Acetic acid, also called ethanoic acid or vinegar, is a colorless topical agent used as a disinfectant for skin and soft tissue infections. It is effective against gram-negative bacteria, especially *P. aeruginosa.* Its clinical antibacterial efficacy requires a minimum concentration of 0.5%.[45] Philips et al. reported the use of acetic acid as a topical agent for the treatment of superficial wounds infected by *Pseudomonas*[46]; later Sloss et al. investigated topical use of acetic acid at concentrations between 0.5% and 5%.[47] Sloss showed all strains of Pseudomonas exhibited a minimum inhibitory concentration (MIC) of 2% in vitro, yet other studies determined a concentration of 3% acetic acid to have bacteriostatic activity, including against multiple antibiotic-resistant strains of *Pseudomonas.*[45,48] The results of in vitro studies indicate that acetic acid is toxic to fibroblasts and substantially decreases cell viability, effects that increase with the concentration. Although these results are not considered decisive for the treatment of burn wounds, a surgeon should always consider the eventual cytotoxic interaction, especially on fresh skin grafts, while using acetic acid.[49]

Silver ions are a common topical heavy metal antimicrobial. Silver is delivered as solutions, creams, or bound to dressing materials. The silver ions bind to proteins and

Box 11.2 Topical Antimicrobial Agents.

CLASS	AGENTS	ANTIMICROBIAL SPECTRUM	GRAFT TOXICITY	SYSTEMIC TOXICITY
Soaps	Johnson's Baby Shampoo	Broad-spectrum + Biofilm	Low	None
Oxidative Halides	Full-Strength Dakin's Solution (0.5% NaOCl)	Broad-spectrum + Biofilm	High	Hyponatremia
	1/20th Buffered Dakin's Solution (0.025% NaOCl)	Broad-spectrum + Biofilm	Low	None
	Oxychlorosene (Clorpactin)	Broad-spectrum + Biofilm	Low	None
	Hypochlorous acid	Broad-spectrum + Biofilm	Unk.	Unk.
	Povidone-iodine (Betadine)	Broad-spectrum	High	High
Acids	Acetic Acid 0.5%	Bacteriostatic	Low	None
	Acetic Acid 2%	Bacteriostatic	Moderate	Moderate
	Acetic Acid 3%	Bacteriostatic	High	High
Heavy Metals	Silver Nitrate 0.5%	Broad-spectrum	None	Electrolyte imbalance
	Silver Sulfadiazine (Silvadene)	Broad-spectrum	None	Low
	Silver Releasing Dressings	Broad-spectrum	None	Low
	Xeroform - Bismuth tribromophenate	Limited Bacteriostatic	Low	None
	BIPPS - Bismuth subnitrate and iodoform	Bacteriostatic	High	High if >1% TBSA
Antibiotics	Mafenide acetate (Sulfamylon)	Broad-spectrum	Low	Metabolic acidosis
	Gentamicin sulfate (Gentamicin)	Broad-spectrum	Low	Low
	Bacitracin/polymyxin (Polysporin)	Broad-spectrum	Non-toxic	Low
	Nitrofurazone (Furacin)	Broad-spectrum, no *Pseudomonas*	Low	Low
	Mupirocin (Bactroban)	Broad-spectrum, no *Pseudomonas*	Moderate	Moderate
	Nystatin 100,000 U/g (Mycostatin)	Weak Antifungal	Low	Low
	Nystatin 6,000,000 U/g	Strong Antifungal	Low	Low

enzymes, damaging those systems, and to DNA, resulting in an antimicrobial effect via a heavy metal oxidative pathway.[50] In debrided wounds, a 0.5% silver nitrate ($AgNO_3$) solution is a potent disinfectant. It does not injure regenerating epithelium in the wound and is bacteriostatic against *S. aureus*, *E. coli*, and *P. aeruginosa*. $AgNO_3$ has limited wound penetration because the silver binds rapidly to the surface proteins.[27] Its hypotonic nature can cause osmolar dilution, resulting in hyponatremia and hypochloremia, so serum electrolytes must be monitored. $AgNO_3$ turns black when exposed to light or on contact with tissues or chlorine-containing compounds, but this is nontoxic. It can be combined with miconazole powder to yield an aqueous solution of 0.5% silver nitrate and 2% miconazole for greater efficacy in preventing bacterial and fungal overgrowth in burn wounds.[51] *Klebsiella* spp., *Providencia* spp., and other Enterobacteriaceae are less susceptible to 0.5% $AgNO_3$ than other bacteria. Rarely the combination of 0.5% $AgNO_3$ solution with *Enterobacter cloacae* or other nitrate-positive organisms can cause methemoglobinemia by converting nitrate to nitrite in the body.[52]

Silver sulfadiazine (Silvadene, Thermazine, Flamazine, SSD), a 1% water-soluble cream, is a combination of sulfadiazine and silver with antimicrobial efficacy lasting up to 24 hours. While most effective against *P. aeruginosa* and the enterics, silver sulfadiazine has great utility against some yeasts, such as *C. albicans.* However, recent reports of *P. aeruginosa* resistance and inadequacy against some strains of *Klebsiella* have emerged. More frequent dressing changes are required if a creamy exudate develops. Although this topical agent is facile in use and reduces pain, it retards wound healing.[53] Unlike mafenide acetate, tissue-penetration of silver sulfadiazine is limited to the surface epidermal layer, and it is not associated with acid–base disturbances or pulmonary fluid overload. It can be used separately or in combination with other antibacterials. An adverse drug reaction may be a reversible granulocyte reduction due to silver toxicity, although this is controversial and transient.[7,27] Over multiple applications a pseudoeschar of silver sulfadiazine cream builds up on the wound, making assessment of the wound depth difficult because it then bears a strong resemblance to burn eschar. This limits the utility of this topical agent in our center.

Over the past decades there has been a proliferation of silver-containing dressings formulated to remain in place over a prolonged period. On superficial burns, these dressings are utilized as functional skin substitutes to permit re-epithelialization in a bacterially suppressed, moist environment. Many centers employ silver-containing dressings rather than applying solutions of topical antimicrobials like silver nitrate because they are easier to manage, have more consistent antimicrobial levels, and are generally less messy.

The antimicrobial actions of the dressings derive from the silver ions, so their spectrum is thus defined. Each product's dressing substrate and particular silver formulation provide different dressing characteristics; however, the release and efficacy of silver against bacteria in wounds have not been largely studied or reported. Furthermore there are to date no large-scale studies defining the supremacy of any particular product, so preference of the practitioner and cost typically define use. It is important to remember that no dressing, no matter how well marketed, replaces the tenets of burn surgery: aggressive débridement of devitalized tissue, coverage of wounds with skin, assiduous wound cleansing to remove pathogens and contaminants, and physical examination.

Bismuth is another heavy metal commonly employed as a topical antimicrobial. It is bacteriostatic against enterics, but not cytotoxic to dermal fibroblasts and does not inhibit wound healing.[54] It is usually used on the commercially available dressing Xeroform, a gauze impregnated with bismuth tribromophenate and petroleum jelly. Bismuth is also delivered in conjunction with iodine in the compounded paste, BIPP (1 part bismuth subnitrate, 1 part liquid paraffin, and 2 parts iodoform). We have used BIPP effectively on thousands of patients treated in our hospital for more than 50 years. Coated liberally on cotton gauze, this paste is used to dress small, débrided areas of exposed bone and tendons.[55,56] BIPP should not be applied to areas greater than 1% TBSA, and the course of treatment should be as brief as possible to limit the risk of bismuth toxicity.[57,58] In our experience, this compound prevents the development of infection and promotes the prodigious formation of granulation tissue, thereby permitting split-thickness skin grafting over surfaces conventionally described to be ungraftable.

Antibiotic-based topical antimicrobials define the fourth major class, and their mechanism of action is determined by the specific biochemistry characteristic of each particular agent. Mafenide acetate (Sulfamylon), available both as an 8.5% water-soluble cream and a 5% aqueous solution, is among the most commonly employed topical agents. While broad-spectrum, mafenide is particularly effective against all strains of *Pseudomonas* and *Clostridium.*[59] The cream is applied twice a day and has the advantage that it does not require a dressing to adhere to wounds. Studies have reported that the use of 5% mafenide acetate solution in patients with major burns results in a 33% reduction in death.[6] When used as a solution, an eight-ply dressing should be resaturated with fresh solution every 8 hours to remain above MIC. Mafenide has excellent tissue penetration, including eschar. This penetration makes it the topical agent of choice for deep ear burns because it effectively prevents invasive chondritis. It can cause pain on application and, like other sulfa drugs, can lead to allergic reactions. Since mafenide can inhibit carbonic anhydrase, metabolic acidosis can develop. Furthermore protracted use may lead to the growth of *C. albicans.* While it can be used with other antimicrobials, mafenide acetate retards wound healing and reduces the breaking strength of healed wounds.[27]

Gentamicin sulfate (Gentamicin) is an aminoglycoside available as a 0.1% water-soluble cream or solution. It has broad-spectrum bactericidal activity against aerobes and is often deployed against *P. aeruginosa*. However, resistance can develop and sensitivities should be monitored.[60]

Bacitracin/polymyxin (Polysporin) ointment is commonly used to prevent mechanical shear and suppress bacterial growth on newly grafted tissue. Both drugs are cell wall lytic agents, and polymyxin is a topical analogue of colistin, discussed in the systemic antimicrobial section. Drug concentrations available in the ointment do not treat infection. However, many surgeons rely on this topical agent for skin graft coverage as it is nontoxic and maintains the moist wound environment needed for epithelial growth. Effectiveness in contaminated or infected burns post excision can be enhanced by use in combination with other agents, such as silver nitrate or mafenide. Prolonged use is associated with hypersensitivity development.

Nitrofurazone (Furacin), available as an ointment, solution, or cream, has been proved effective in the treatment of methicillin-resistant staphylococci. Furthermore, nitrofurantoin was demonstrated to be 75% effective against gram-negative bacterial isolates other than *P. aeruginosa*, whereas bacitracin/polymyxin was only 21% effective.[3]

Mupirocin (Bactroban, pseudomonic acid A) is an antibiotic derived from the *Pseudomonas fluorescens* capsule and inhibits isoleucyl t-RNA synthetase and thus bacterial protein synthesis.[61] It is the topical treatment of choice for MRSA infections, gram-positive microbes, and intranasal carriage.[62] Mupirocin inhibits wound healing by a half-life of 2 days compared to controls, but the breaking strength of the wound is significantly enhanced.[63] Due to rapid development of resistance, mupirocin should not be used for longer than 10 days.

Nystatin (Mycostatin, Nilstat) is an antifungal antibiotic produced by *Streptomyces noursei*. Nystatin is the highly potent topical equivalent of Amphotericin-B; both exert antifungal activity by binding to ergosterol and lysing fungal cell membranes. Low-dose applications of 100,000u/g as creams, lotions, or ointments are used as prophylaxis against fungal growth. Treatment with pure nystatin powder at a concentration of 6,000,000 U/g on burn wounds has proved effective in eradicating invasive fungal infections. This novel application is not only effective superficially but also eradicates invasive clusters of fungi in deep wound tissues, as documented by pathological examination.[64] The application of the powder is easy and does not produce pain, discomfort, or impair wound healing. All previously autografted areas heal uneventfully.[64] Liquid nystatin 'swish and swallow' is used prophylactically to prevent the oral or perineal overgrowth of yeast and fungi in patients receiving multiple systemic antibiotics.[64]

SYSTEMIC ANTIMICROBIALS IN BURN PATIENTS

Long maligned, routine prophylactic use of antibiotics is well indicated for select burn patients. Whereas prophylactic antibiotics may be warranted for patients arriving from endemic areas, with penetrating traumas, open fractures, or from highly contaminated scenes, no prophylactic antibiotic treatments are typically initiated at admission or for routine perioperative prophylaxis. This is principally to avoid creation of antibiotic resistances with more difficult subsequent treatment. Additionally thermal wounds are normally aseptic in the first hours following injury as the burn sterilizes the wound surfaces.[65,66]

Empiric antibiotics are indicated in the setting of clinically suspected invasive wound infections, suspected sepsis, or septic shock. These antibiotics should broadly cover

all likely infecting organisms and be instituted as a component of multimodal critical and surgical care of the burned patient. Clinical response should be followed to ensure adequate treatment and antibiotics de-escalated as soon as possible based on culture findings. After time and culture data allow definitive diagnosis of infection, culture-directed treatment antibiotics should be continued for a finite treatment course, until cultures return negative or the wounds close.[67]

Greatly altered in burn patients, pharmacokinetics and pharmacodynamics require regular evaluation by a skilled clinical pharmacologist to ensure safe and effective drug dosing.[68] During the resuscitative phase of burn injury, which occurs within the first 48 hours post-trauma, burn shock can decrease blood flow to organs and tissues.[68] Drug treatments during this phase result in a slower distribution rate, slower renal and hepatic elimination, and delayed absorption of enteral, subcutaneous, and intramuscular drugs. After 24–48 hours, the patient enters the hypermetabolic phase, discussed extensively in Chapters 29 and 32 covering the hypermetabolic response, endocrine function, and critical care. During this period, burn patients exhibit increased blood flow to organs and tissues, an increased internal core temperature, and hypoproteinemia and edema formation.[68] Intravenous drugs have a shorter half-life due to the enhanced glome rular filtration rate and elimination of renally excreted drugs. Antibiotic treatments in these patients must be administered at higher doses and/or frequency. Time-dependent, renally excreted antibiotics, such as vancomycin, must be carefully monitored to ensure they exceed the MIC of the bacteria. Oral drugs will also exhibit greater absorption from the gastrointestinal tract and a faster onset of action.[68] The hypermetabolic phase causes hypoalbuminemia and raises the levels of acute-phase proteins.[68] Albumin binds to acidic and neutral drugs, such as aminoglycosides, vancomycin, aztreonam, and cefotetan; consequently in hypoalbuminemia more free drugs are circulating so a lower dose will be required for therapeutic effect. Conversely acute-phase proteins bind tightly to basic drugs, such as penicillins and cephalosporins, resulting in less free drug and necessitating higher drug dosages to produce a therapeutic effect. The hepatic response occurring during the hypermetabolic phase will present as a decrease in phase 1 metabolism, such as oxidation, reduction, or hydroxylation of a drug by the cytochrome P450 system, affecting many antibiotics, such as the quinolones and the macrolides. The decreased activity of these hepatic drug–metabolizing enzymes, as well as their decreased hepatic clearance and prolonged half-life, may produce systemic toxicity. However, phase 2 metabolism in the liver, such as conjugation reactions between the drug and the endogenous substrate, will not be impaired.[68] In light of the myriad of changes, care in the modern burn unit is greatly enhanced by the active participation of a pharmacist familiar with systematic drug level monitoring in burn patients.

Selection of systemic antibiotics is based on the likely etiologic organism, local antibiogram, and systemic toxicity. In the setting of an outpatient with cellulitis around a burn wound, empiric gram-positive coverage to include MRSA is indicated. We routinely cover these outpatients with rifampin, a bactericidal antibiotic inhibiting RNA synthesis by binding to the β-subunit of the DNA-dependent RNA polymerase and blocking RNA transcription.[69] Due to its high resistance pattern when employed alone, rifampin must be used in conjunction with other antiinfectives, such as sulfamethoxazole-trimethoprim (Bactrim) or levofloxacin, in the treatment of MRSA. Linezolid is a bacteriostatic synthetic antibacterial agent of a newer class of antibiotics, the oxazolidinones, developed for MRSA, methicillin-resistant *S. epidermidis*, enterococci, and staphylococci. Linezolid inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit to prevent translation.[69] Adverse effects of linezolid include myelosuppression (e.g., anemia, leukopenia, pancytopenia, and thrombocytopenia), which is generally reversible on discontinuation of the drug, and *Clostridium difficile* colitis. A weak, nonselective, and reversible inhibitor of monoamine oxidase, linezolid may cause increased serotonin serum levels and serotonin syndrome in patients on various serotonin reuptake inhibitors, such as fluoxetine and sertraline. Prolonged use also carries a risk of polyneuropathy.

Invasive wound infections, graft loss, sepsis, and septic shock from suspected gram-positive bacteria should be treated empirically with intravenous vancomycin until culture-directed de-escalation can occur. Vancomycin is bactericidal, preventing gram-positive bacterial cell wall glycopeptide polymerization thereby producing immediate inhibition of cell wall synthesis and lysing the cytoplasmic membrane.[69] As a time-dependent antimicrobial, serum levels of this drug must unceasingly exceed the MIC to provide sufficient bactericidal activity. Due to the wide variability in vancomycin elimination among burn patients, the dosage must be individualized to optimize serum concentrations by serially following trough levels, with a typical goal of 10–15 μg/mL for most burn wound infections. Due to poor penetration, certain compartments, such as the lungs and central nervous system, require higher trough concentrations to achieve therapeutic levels of vancomycin; in cases of pneumonia or meningitis, concentrations of 15–20 μg/mL are recommended.[70]

Alarmingly, gram-positive strains resistant to vancomycin, such as vancomycin-resistant *Enterococcus* (VRE) and vancomycin-intermediate *S. aureus* (VISA), have emerged. These bacteria are often susceptible to linezolid, as discussed earlier, as well as to tigecycline, daptomycin, quinupristin-dalfopristin, and dalbavancin, which have been developed specifically to tackle this problem. Working closely with a clinical pharmacist who can help establish an antibiotic and dosing regimen best fitting the specific resistance pattern in a given patient is critical.

Gram-negative infections more frequently require admission and intravenous antibiotics. While empiric therapy should be directed by local antibiogram, consideration must also be given to additive toxicity when combined with empiric gram-positive agents. In our hospital, we empirically use imipenem/cilastatin due to their low nephrotoxicity when used in conjunction with vancomycin.[71] De-escalation and discontinuation of antibiotics should occur as soon as cultures, wounds, and physiology warrant. Because gram-negative bacteria frequently become multidrug-resistant, testing for synergy between different classes of antibiotics is advisable.

Third- and fourth-generation cephalosporins and extended-spectrum penicillins are the antibiotics of choice

for many burn centers for empiric coverage of gram-negative infections due to their broad coverage and low toxicity. Fourth-generation cephalosporins (e.g., cefepime), extended-spectrum β-lactamase inhibitor penicillins (e.g., piperacillin-tazobactam and ticarcillin-clavulanate), and most importantly the carbapenems (e.g., imipenem/cilastatin, meropenem, and ertapenem) are important tools in eradicating gram-negative infections. Newer fifth-generation cephalosporins were developed to treat resistant *Pseudomonas*; unfortunately novel resistance patterns are already emerging.[72] These antibiotics are time-dependent and most efficacious when serum concentrations between dosing intervals are maintained at 1–2 times the MIC; thus extended infusions over 3–4 hours or continuous infusion may be necessary to keep concentrations above MIC, particularly when a pathogen is near the resistance threshold.[72] In perforating the cell wall, penicillins are often synergistic with intracellular antibiotics, such as aminoglycosides, and testing is warranted in the setting of highly or pan-resistant organisms.[73,74]

Aminoglycosides remain effective for significant susceptible gram-negative infections. Much of critical care has moved to once-daily dosing of these concentration-dependent antibiotics since it is as effective and less toxic than conventional dosage intervals. Pooled data from randomized controlled studies in adults showed that once-daily administration of aminoglycosides is associated with similar or greater efficacy (e.g., bacteriologic and/or clinical cure), less nephrotoxicity, and no greater risk of ototoxicity than administration of multiple daily doses.[69] Some clinicians remain concerned that traditional dosing intervals may be preferable in severe infections or in patients with unpredictable pharmacokinetics, as described in burn patients.[75] Therefore monitoring aminoglycoside serum concentrations and/or the peak serum concentration to MIC ratio in burn patients with life-threatening infections, suspected toxicity or nonresponse to treatment, decreased or varying renal function, and increased aminoglycoside clearance is well indicated.

Multidrug-resistant (MDRO) and pan-drug-resistant (PDRO) gram-negative organisms are increasingly prevalent. Many of these islets have sensitivities to polymyxins, a class of cell-wall intercalating antibiotics that includes the topical agent polymyxin-B and its intravenous analogue colistimethate sodium (colistin, polymyxin-E).[71] These antibiotics were largely abandoned in the 1970s due to concerns of toxicity when Kunin and Bugg showed polymyxin accumulation highest in the kidney and brain tissues, followed by liver, muscle, and lung. It was also reported that colistimethate appeared to increase the incidence of *C. difficile* colitis, renal dysfunction, and neuropathies proportionately to the duration of its use.[76,77] However, colistimethate use against MDRO has surged due to a lack of other systemic options. Branski et al. reported that, in 118 patients with life-threatening MDRO gram-negative infections, colistimethate provided an important salvage option for burn patients with otherwise incompletely treated infections. They further found that hepato-, neuro-, and nephrotoxicity were no different in matched patients treated with or without colistimethate, indicating concerns from 40 years ago might be unfounded with modern critical care.[71]

Antifungal treatment is complicated by the limited number of agents and their relative toxicities. The most commonly used antifungal agent, fluconazole, has excellent activity against *C. albicans* and low toxicity. However, non-albicans *Candida* spp. are increasingly frequent causes of invasive candidiasis, and these are resistant to fluconazole.[78] The Infectious Disease Society of America advocates echinocandins as the best empiric treatment for yeast infections, as most yeast are susceptible to them.[79] However, these are recommended only until cultures become available. Cultures should be performed frequently in these patients since resistance can develop quickly.[80,81] There is an increased prevalence of *Candida* spp. with greater antimicrobial resistance and higher mortality rates than *C. albicans*, such as *C. tropicalis* and *C. krusei*.[82,83] Ponziconazole and voriconazole, both azoles, are the treatment of choice for invasive *Aspergillus* and *Fusarium*. They are also effective against infections caused by *Candida* spp., including fluconazole-resistant ones. However, azoles have unpredictable, nonlinear pharmacokinetics with extensive interpatient and intrapatient variation in serum levels. Due to this and numerous drug–drug interactions, therapeutic drug monitoring is crucial.[84,85]

For decades Amphotericin B dexolate (AmBd), an intravenous polyene analogue of nystatin, has been the standard choice for intravenous treatment of life-threatening invasive molds. This drug is associated with significant toxicity, including infusion-related events and dose-limiting renal dysfunction.[86] Three new lipid formulations of amphotericin B (AmB lipid complex [ABLC], AmB colloidal dispersion, and liposomal AmB [AmB-L]) offer several advantages over AmBd, including increased daily doses of the parent drug (up to 10–15-fold), high tissue concentrations in reticuloendothelial organs, a decrease in infusion-related events (especially with ABLC and AmB-L), and a marked decrease in nephrotoxicity.[86] These lipid drugs are more expensive, but their enhanced safety profiles make them the new standard for treating invasive molds, particularly *Mucor*. The most successful treatment for fungal infection is prevention via swift removal of all burned tissue and closure of wounds with autografts. In the presence of active mold infections, voriconazole is the first-line treatment, followed by ABLC. An echinocandin, such as caspofungin, can be considered for combination treatment of *Aspergillus* and *Fusarium*.[71] *Fusarium* spp. have demonstrated innate resistance to Amphotericin.[87]

Pathogens will continue to evolve novel resistance mechanisms more rapidly than researchers can develop antibiotics. In the dire case where no antibiotic susceptibility exists for an infecting pathogen, it is important to remember excision of infected tissue, graft coverage of wounds, and topical care remain effective treatment plans. Barret and Herndon noted that aggressive, early surgical treatment reduced wound culture counts from greater than 10^5/g to less than 10^4/g and yielded excellent skin graft take. In contrast, poorer skin graft take occurred in patients with initial counts of greater than 10^6/g, but were reduced to 10^4/g only after delayed surgical excision, thus underscoring the correlation between early and aggressive wound excisions and better patient outcomes in the treatment of severe burns.[8,15] While infections can become overwhelming, there is no bacterial resistance mechanism to the surgeon's knife.

Specific Pathogens in Burn Wounds

Staphylococcus aureus, gram-positive cocci in clusters, remains the chief cause of burn wound infection and is a well-documented opportunistic pathogen in humans.[18,88] Colonization with these bacteria in an uninjured individual is usually asymptomatic, but they are a source of opportunistic infection that can lead to severe illness and death, especially in burn patients.[89] *Staphylococcus* produces virulence factors, such as proteinases, coagulases, and hyaluronidases, that enable it to invade local tissues and disseminate hematogenously, causing generalized systemic infection and sepsis.[90] The most common infections of *Staphylococcus* spp. are septicemia, cellulitis, impetigo, scalded skin syndrome, and postoperative wound infections. However, puerperal sepsis, pneumonia, osteomyelitis, endocarditis, and burn wound infection are the most grave. Exotoxins, which are produced by pathogenic strains of staphylococci, include a pyrogenic toxin, a dermonecrotizing toxin, and leukocidin. In addition to the exotoxin TSST-1, these organisms can produce enterotoxins A, B, and C, risk factors for TSS in susceptible patients.[91] *Staphylococcus* spp. generally produce penicillinases that make natural penicillins ineffective and thus require treatment with penicillinase-resistant penicillins, such as oxacillin. MRSA is now the predominant isolate, with rates of infection greater than 50% in burn units.[92,93] Empiric coverage should be vancomycin for intravenous therapy or Bactrim and rifampin orally, as detailed earlier, based on the local antibiogram and patient cultures.

Streptococci were once the leading cause of burn wound infection but are now less prevalent. Arranged in chains, these gram-positive cocci are particularly virulent when infecting a burn wound and quantitatively do not require less than 10^5 CFU/g tissue to prevent wound closure. A mere few β-hemolytic streptococci can cause wound infection, failure of a primary closure, and loss of a skin graft.[9] The major infecting species are *Streptococcus pyogenes* (also referred to as group A streptococci and the most problematic) and *S. agalactiae* (group B streptococci).[94] Natural penicillins, such as penicillin G and penicillin V, and first-generation cephalosporins are bactericidal to these species. While resistance to these penicillins or cephalosporins has not yet emerged, culture and antibiotic sensitivity data should be followed.

Enterococci are important inciters of gram-positive burn wound infection. Encouragingly a recent review comparing sepsis mortality between consecutive decades (1989–1999 and 1999–2009) found a steep decline in the rate of infection with enterococci (25% to 2%, respectively), perhaps stemming from the more liberal use of vancomycin of recent years.[2] However, with the increasing prevalence of vancomycin-resistant enterococci, VRE mortality rates are now greater than those of MRSA (58% and 33%, respectively).[95] While most *Enterococcus* spp. respond to vancomycin, VRE is treated with linezolid, a combination of ampicillin and aminoglycosides, or quinupristin/dalfopristin (Synercid). De-escalation is advised as soon as indicated by culture data.

Pseudomonas is not just the most ubiquitous gram-negative burn wound pathogen, but also the most likely to be responsible for sepsis leading to burn-related death.[2,18] Both local environments and gastrointestinal tracts (via translocation of endogenous gastrointestinal flora) are believed to be the primary sources of this bacterium. This species has a predilection for moist environments, and human burn wound exudates have been shown to stimulate the expression of virulence factors of *P. aeruginosa*, the pathogen chiefly responsible for nosocomial respiratory tract infections.[96] Additionally it breeds invasive and troublesome wound infections in burn patients. A superficial wound infection caused by *P. aeruginosa* typically will have a yellow-green color and noxious fruity smell.[97] This may become an invasive infection, ecthyma gangrenosum, causing purplish-blue ''punched-out'' lesions in the skin, and, if local thrombosis of vessels is present, the wound requires immediate dif local t to remove newly necrotic tissues (Fig. 11.8). Empiric treatment for *P. aeruginosa* infection has evolved from aminoglycosides to antipseudomonal β-lactams, such as piperacillin/tazobactam, cefepime, and carbapenems.[98] The increasing prevalence of MDRO *P. aeruginosa* requires the expanding use of antibiotics based on culture data, employment of fifth-generation cephalosporins, use of synergistic antibiotic coverage, and use of colistimethate, as discussed in the systemic antimicrobial section. This rapidly evolving and virulent pathogen is best eradicated by rapidly closing wounds to deny the bacterium access to any susceptible wound surface.

Acinetobacter spp. are gram-negative rods used commercially to convert wine to vinegar and are native flora of the respiratory tract, skin, gastrointestinal tract, and genitourinary tract. This organism may lead to numerous opportunistic infections, including pneumonia and infections of the surgical site and urinary tract.[99] Second only to *P. aeruginosa* in prevalence, this pathogen has an enhanced capacity for transfer between patients due to its ability to survive in both dry and wet conditions and equally on animate and inanimate objects, whether metal or plastic, making nosocomial transmission a major concern.[100,101] *Acinetobacter* spp. have been isolated from diverse clinical sources, including the upper and lower respiratory tracts, the urinary tract, and surgical and burn wounds, as well as in bacteremias secondary to intravenous catheterization. An agent of low virulence, it has a predilection for infecting patients with dysfunctional host defense mechanisms. Although traditionally susceptible to ceftazidime and ciprofloxacin, *Acinetobacter* has developed resistance to such an extent that only carbapenems (e.g., imipenem and meropenem) can now be relied on to treat these infections. In cases of MDRO *Acinetobacter*, colistin has become the rescue treatment, as with *Pseudomonas* infections.[71,102]

Stenotrophomonas maltophilia (also known as *P. maltophilia* or *Xanthomonas maltophilia*) is an aerobic gram-negative bacillus responsible for nosocomial infections in immunocompromised patients.[103] Increasingly reported in burn patients, this pathogen causes life-threatening infections which are very difficult to clear due to the particularly obturant biofilm *Stenotrophomonas* produces.[104] Additionally *S. maltophilia* is inherently resistant to a variety of antimicrobial agents, such as aminoglycosides, β-lactam agents, and carbapenems. The most common types of infections caused by *S. maltophilia* are wound and bacteremia; pneumonia and generalized infections associated with this

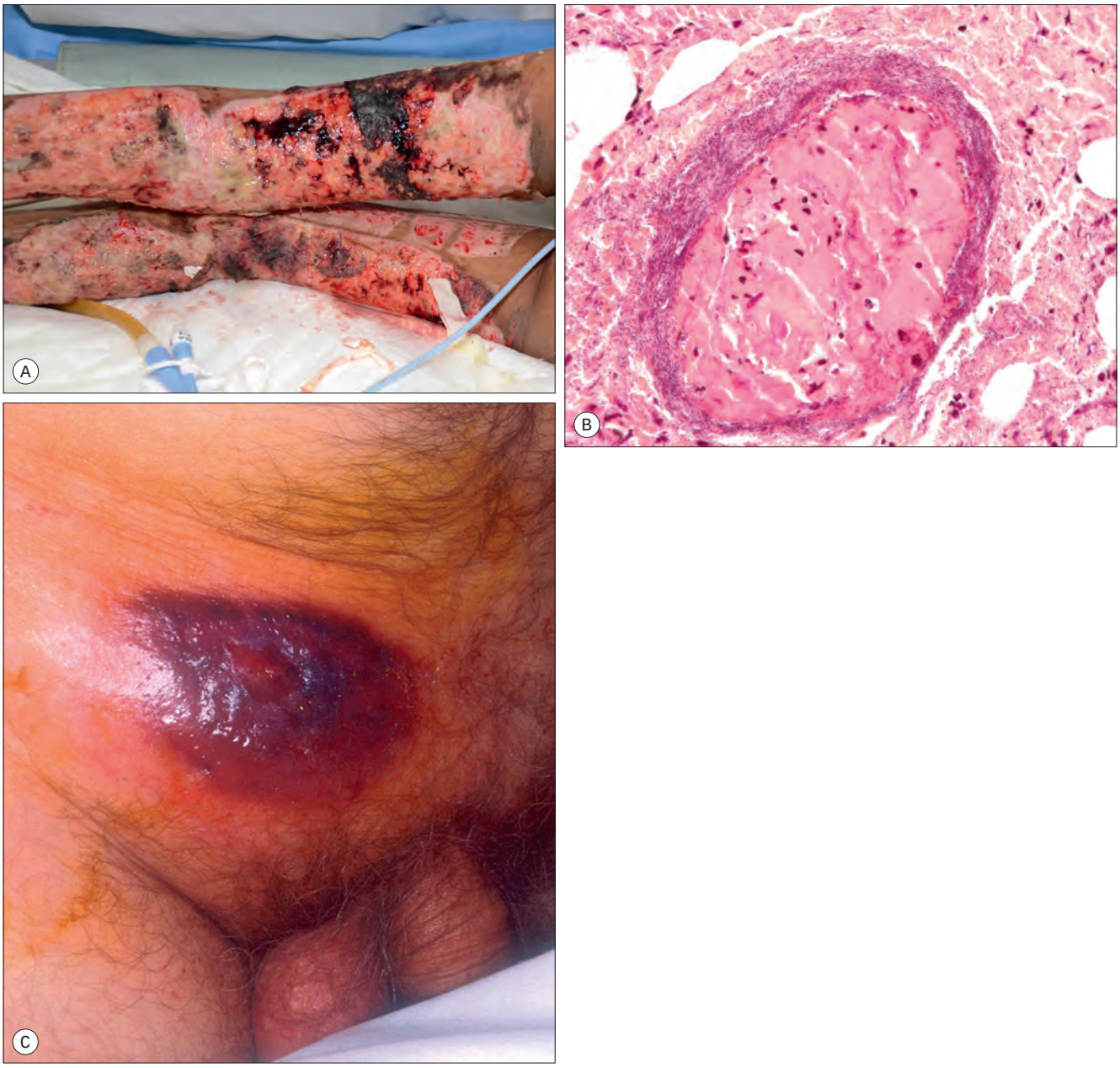

Fig. 11.8 Ecthyma gangrenosa. A tissue-invasive burn wound infection here seen in a 7-year-old girl transferred to our hospital after a 6-week treatment at another hospital. Note the (A) extensive greenish and slime-coated wound consistent with an invasive wound infection. The patient died subsequently from an overwhelming hematogenously spread pneumonia. (B) The vessel wall at 40× magnification micrograph shows a clear bacterial infiltration. (C) A typical purplish ecthyma gangrenosa lesion in a 35-year-old man. (C courtesy of Omar P. Sangüeza, MD; Professor and Director of Dermatopathology, Wake Forest University School of Medicine, North Carolina.)

pathogen are less common.[105,106] Infections are sensitive to trimethoprim-sulfamethoxazole alone or used with levofloxacin, and sensitivities should be monitored. Aggressive surgical dulfamethox and assiduous washing technique with soap and water are vital to combat the resultant biofilm.

Enterobacteriaceae, such as *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., *Serratia marcescens*, and *Proteus* spp., are often revealed as the cause of burn wound infections and other nosocomial infections in burn patients.[107] Although these pathogens have greater sensitivity to antibiotics than other gram-negative bacteria, emerging resistance patterns to carbapenems and fourth-generation cephalosporins led to a larger array of MDRO and PDRO.[108] Carbapenem-resistant Enterobacteriaceae (CRE) are increasing in incidence and in many cases require treatment with colistin.

Anaerobic bacteria, such as *Bacteroides* spp. and *Fusobacterium* spp., are rarely a cause of invasive burn infection. These bacteria are normal flora from the oropharyngeal cavity to the gastrointestinal tracts. Anaerobic flora are responsible for 2%–5% of surgical wound infections in the oropharyngeal area[109,110] and 10%–15% of wound infections in the gastrointestinal and urogenital tracts.[111] In burn patients, anaerobic infections are usually associated with avascular myonecrosis secondary to electrical injuries,

frostbite, or cutaneous flame burns with concomitant crush-type injuries.[112] With the advent of early excision and grafting, the incidence of anaerobic infections in thermal injury has been reduced significantly. If anaerobic infection is suspected, it is vital that collected specimens be placed in appropriate transport tubes void of oxygen. In these cases, broad-spectrum antibiotics covering anaerobes should be given until sensitivities are available to ensure the administration of the appropriate drug.[113,114]

Fungal wound infection and colonization have become increasingly prevalent following the introduction of topical antibacterials and liberal use of broad-spectrum antibiotics.[115] This has resulted in a surge in invasive fungal infection linked to higher death rates, regardless of the extent of the burn, coincident inhalation injury, or patient age.[116] In a recent review of 15 burn units, fungi were isolated at least once from 6.3% (435/6,918) of patients,[117] with positive cultures being most commonly obtained from the wound itself followed by (in order of decreasing frequency) respiratory, urine, and blood specimens.[118] Yeasts are identified primarily on the basis of specific biochemical tests, but both macroscopic and microscopic morphologies are also used to make final identification (Fig. 11.9). Mold identification is based on growth rate, colony structure, microscopic/microscopic appearance, dimorphism at different incubation temperatures, and inhibition of growth by cycloheximide, as well as various biochemical tests (Fig. 11.10).[119]

Early diagnosis of fungal infection can be difficult because clinical symptoms frequently mimic low-grade bacterial infections. Routine culture techniques may require 7–14 days to identify fungal contaminants, delaying initiation of treatment.[118] In contrast to bacterial sepsis, venous blood cultures might not reflect the causative fungal organism.[120] For this reason, arterial blood cultures and retinal examination for characteristic candidal lesions can be useful. *Candida* spp. are the most common fungal colonizers of the burn wound, although fungi like *Aspergillus* spp., *Penicillium* spp., *Rhizopus* spp., *Mucor* spp., *Rhizomucor* spp., *Fusarium* spp., and *Curvularia* spp. can also be present, and they have a vastly greater invasive potential than yeasts.[110,115] *Candida albicans* is the fourth most frequently identified pathogen in blood cultures from ICU patients; however, invasive infection with molds such as *Aspergillus* is correlated more closely with death.[121] Candidemia warrants retinal examination for retinal plaques, as further discussed in Chapter 43 on burn injuries of the eye (Fig. 11.11)

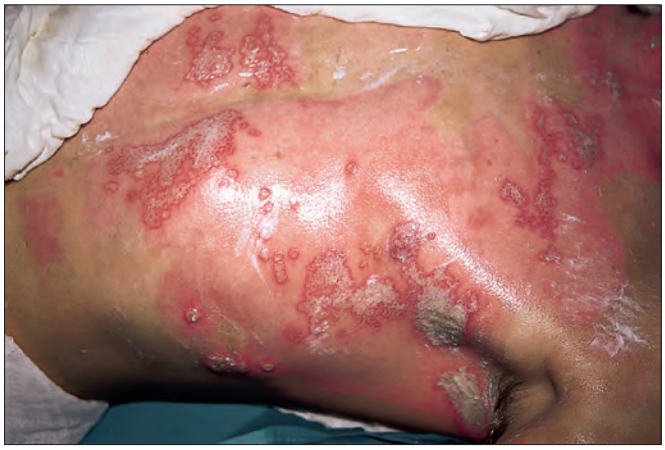

Fig. 11.9 *Candida* Infection in a healing second-degree burn wound. Pain and itch is usually present in this kind of infection. Treatment with silver sulfadiazine mixed with Mycostatin was effective in controlling *Candida* in this patient.

Most patients infected with molds are exposed to spores in the environment at the time of injury, from either rolling on the ground or extinguishing flames in contaminated surface water. Other environmental foci have been cited as the source of nosocomial mold infection, including bandaging supplies left open to the air, heating and air-conditioning ducts, and floor drains.[110,115] Once colonized, hyphae extend into subcutaneous tissue, stimulating an inflammatory response. This phenomenon is diagnostic of mold wound infection. Vascular invasion and systemic dissemination are common and often accompanied by thrombosis and avascular necrosis, clinically observed as rapidly advancing dark discolorations of the wound margins or well-described lesions[120] (Fig. 11.10). Treatments for yeasts and molds vary greatly due to the vastly different pathogenicities of these organisms. Yeasts found in burn wounds are more often associated with colonization and do not represent infection. Treatment is usually considered when the same yeast is identified at multiple sites, and topical treatment is applied liberally; if invasive infection is considered systemic, antifungals are administered. In contrast, the identification of mold in a burn wound is a very serious condition. Often invasive, infection with mold requires radical débridement including amputation and high-dose topical and systemic antifungals, such as 6,000,000 U/g nystatin powder.[64] Hyphae invading live tissues and blood vessels should be considered a surgical emergency and treated aggressively. It is essential to work closely with a pathologist to make rapid diagnosis of invasive mold and ensure complete surgical resection at the margin, as one would resect a malignant cancer.

Viral infections, particularly Herpesviridae, have become more significant causes of morbidity. Prospective and retrospective assays of sera have documented a large incidence of subclinical viral infections. In one of the first large retrospective studies from the 1980s, Linnemann et al. found a fourfold increase in anti-cytomegalovirus (CMV) antibodies in 22% of patients, increased herpes simplex virus (HSV) in 8%, and a rise in varicella-zoster (VZV) titers in 5%.[122] The study continued in a prospective manner, with 33% of the children developing CMV infection, 25% developing herpetic infection, and 17% developing adenovirus infection.[122] The most common cause of viral infection is reactivation of latent infection due to the debilitated, immunosuppressed state of the patient after a substantial injury. Herpes viruses, especially HSV and VZV, have by far the greatest occurrence, but CMV is not unusual.

CMV infection frequently occurs concurrently with bacterial and fungal infections but rarely alters the patient's clinical course. Kealey and coworkers showed that, in addition to blood transfusions, cadaver skin is a principal source of CMV infections in burn patients.[123] Overall seroprevalence in burn patients ranges between 37% and 73%.[124,125] Gong and coworkers studied the reactivation rate and found 108 of 180 patients to be positive at admission.[126] Linnemann and colleagues determined that primary infection or reactivation of CMV was reported with an overall

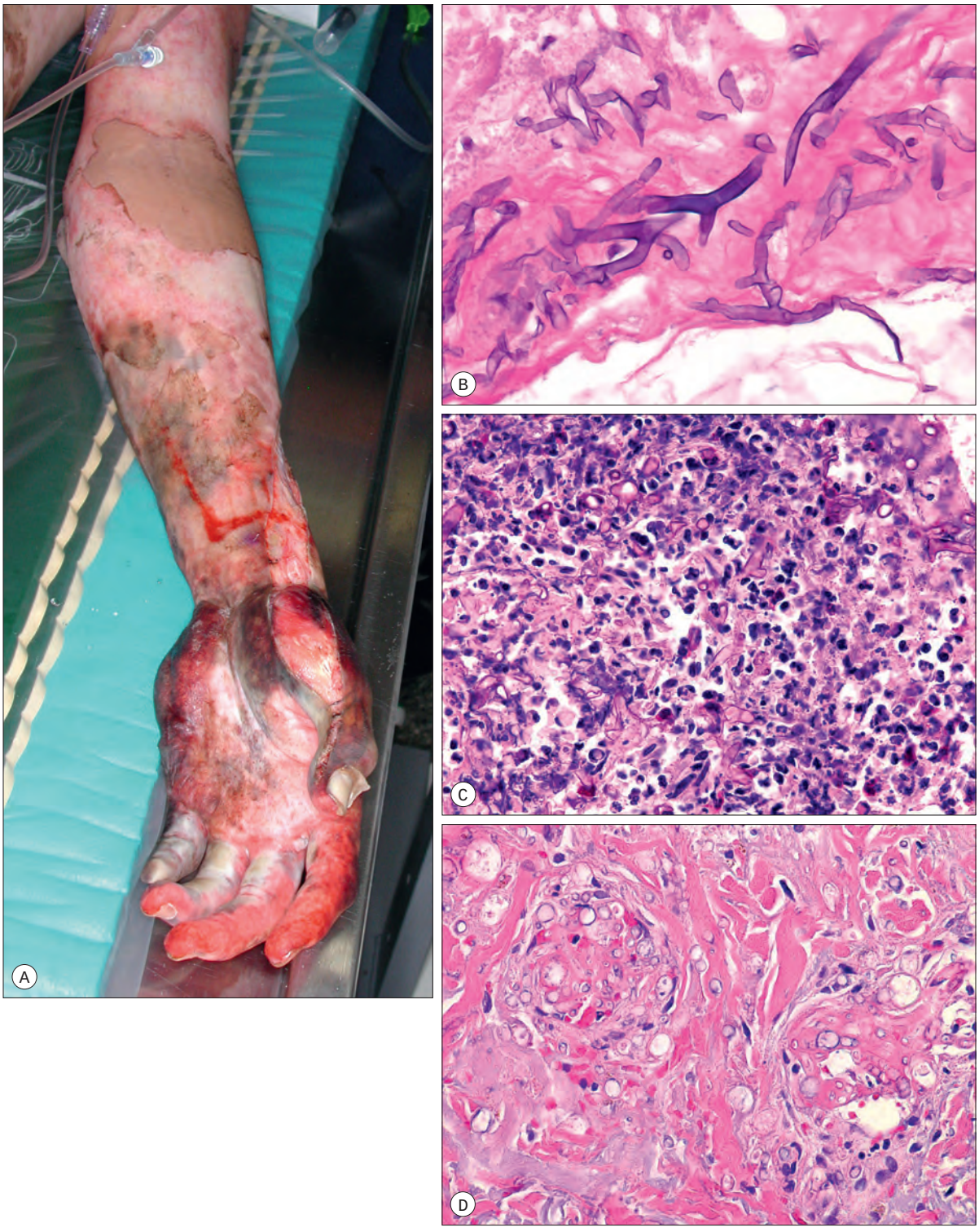

Fig. 11.10 Diagnosis of invasive mold infection. Invasive mold infection carries a significant increase in morbidity and mortality. Physical examination reveals (A) a left forearm and hand wound with macroscopical fungal growth (a white, fluffy appearance) and necrotic borders before repeated surgical débridement. Diagnosis on histological examination is critical to guide both surgical treatment as well as selection of antifungal therapy. Below are 40× magnification micrographs of (B) *Aspergillus*, (C) *Mucor*, and (D) *Fusarium* findings. (B, C, D courtesy of Omar P. Sangüeza, MD; Professor and Director of Dermatopathology, Wake Forest University School of Medicine, North Carolina.)

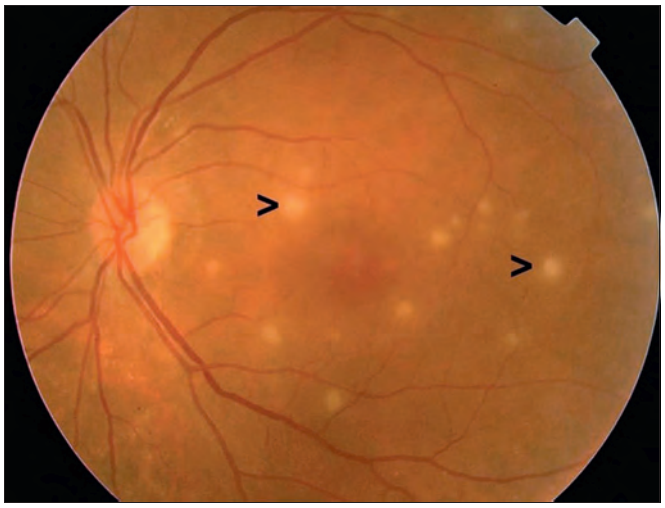

Fig. 11.11 Candidal retinopathy. Yeasts are an increasingly common infectious agent in burn patients. Funduscopic examination is critical to diagnose candidal retinal implants and determine the length and success of antifungal treatment. The picture reveals the typical multiple creamy white intra retinal lesions with hemorrhage.

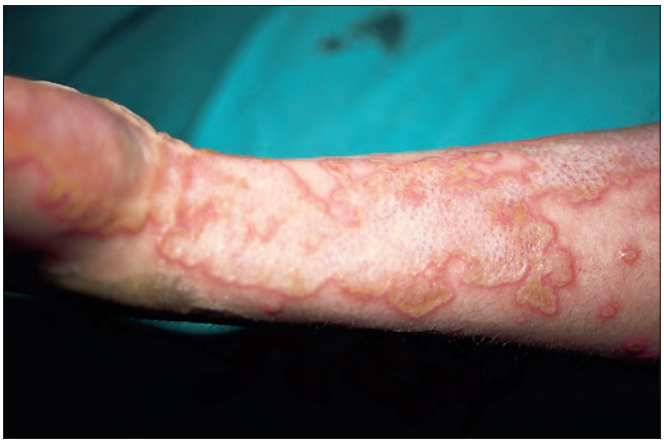

Fig. 11.12 Herpetic wound infection. Herpes simplex virus type I infection in a patient with 35% partial-thickness and full-thickness burns. Extreme pain and itching are typical of this infection.

frequency of 33%.[122] In this study, prospective analyses "directly correlated CMV infection with more severe burns, more skin grafts, and subsequent higher numbers of blood transfusions." In contrast Rennekapff and coworkers found in 2007 a seroconversion rate between 18% and 22% for burn patients seronegative for CMV prior to burn injury.[127] CMV inclusions may be identified in the cells of multiple organs but have not been reported in the burn wound.[128] Immunocompromised patients have a higher frequency of CMV infection, resulting in a broad range of adverse conditions from febrile illness to systemic infections with organ involvement.[129] CMV infection has also been associated with unexplained fever and lymphocytosis, as seen by a concomitant rise in specific antibodies.[122,128] Systemic CMV disease is an unusual occurrence; the majority of patients who demonstrate increased CMV-specific antibody sustain more limited CMV infections. The absence of reports of severely burned patients with increased CMV antibodies suggests that most of these infections are subtle and have been overlooked by past studies. Nevertheless a higher number of CMV copies per milliliter of blood is associated with a higher rate of major infections, more ventilator days, and longer hospitalizations.[130,131]

Generalized, nonhealing burn wounds have been associated with CMV-related pathological changes in endothelial and periendothelial cells.[124] Inclusion bodies consistent with CMV infection, as well as CMV antigens, have been detected by immunohistochemical staining of a skin biopsy from a transplanted cadaver allograft (from a CMV-positive donor) on a severely burned adult male; however, the relationship of the CMV infection to necrosis, inflammation, and increased vascularity evident in infected skin is unknown.[132] Severe burn injury has been shown to predispose experimental animals to murine CMV infection, which is associated with greater susceptibility to sepsis.[133,134]

Tennenhaus and colleagues surveyed and evaluated U.S. and German burn centers for awareness, perception, diagnosis, and treatment of CMV in patients with burn injury.[135] CMV infection incidence was reported at 1 : 280 and 1 : 870 in German and U.S. burn centers, respectively. When testing, 70% of German and 19% of U.S. burn centers used serology, 52% German and 25% U.S. centers used body fluid viral isolation, and 43% German and 6% U.S. centers used leukocyte CMV-DNA analysis. Two-thirds of the German and half of the U.S. centers distinguished infection from disease. A total of 43% German and 19% U.S. centers would subsequently treat the established disease; however, no differences were observed in mortality.[136] CMV infection is an undesirable outcome and should always be considered in cases of unexpected fever and hepatitis, especially in burned children.[122]

Treatment of CMV infection is commonly initiated with intravenous acyclovir or its longer-acting oral prodrug valacyclovir, despite both demonstrating only moderate anti-CMV activity. This is because they are inexpensive and readily available in most hospitals. Less obtainable intravenous ganciclovir, a medication designed for CMV, is the agent of choice for treatment of patients with symptoms of significant CMV infection.[137] Valganciclovir, the longer acting oral prodrug of ganciclovir, has similar efficacy to intravenous ganciclovir but does not require a chemotherapy hood for preparation by the pharmacy. Thus valganciclovir has emerged as the drug of choice whenever oral therapy is possible.[138–140] Prophylactic therapy against CMV is not recommended in burned patients.

Viral infections arising in healing burn wounds are often attributed to HSV, particularly on the face and genitals. These infections most commonly manifest as vesicles in healing partial-thickness burns or split-thickness donor sites (Fig. 11.12). Partial-thickness burns and donor sites infected with herpes may convert to full-thickness injuries requiring skin grafting for ultimate closure. Skin graft donor sites can convert to full-thickness injury, also requiring grafting to close.[8] In the immunocompromised burn patient, the infection usually starts with the formation of vesicles at the edge of the wound, with these vesicles then coalescing into a confluent raw area. A near-total loss of epidermal coverage can occur (Fig. 11.13). Other epithelial surfaces, such as oral or intestinal mucosa, can also be involved, potentially causing erosion and perforation.

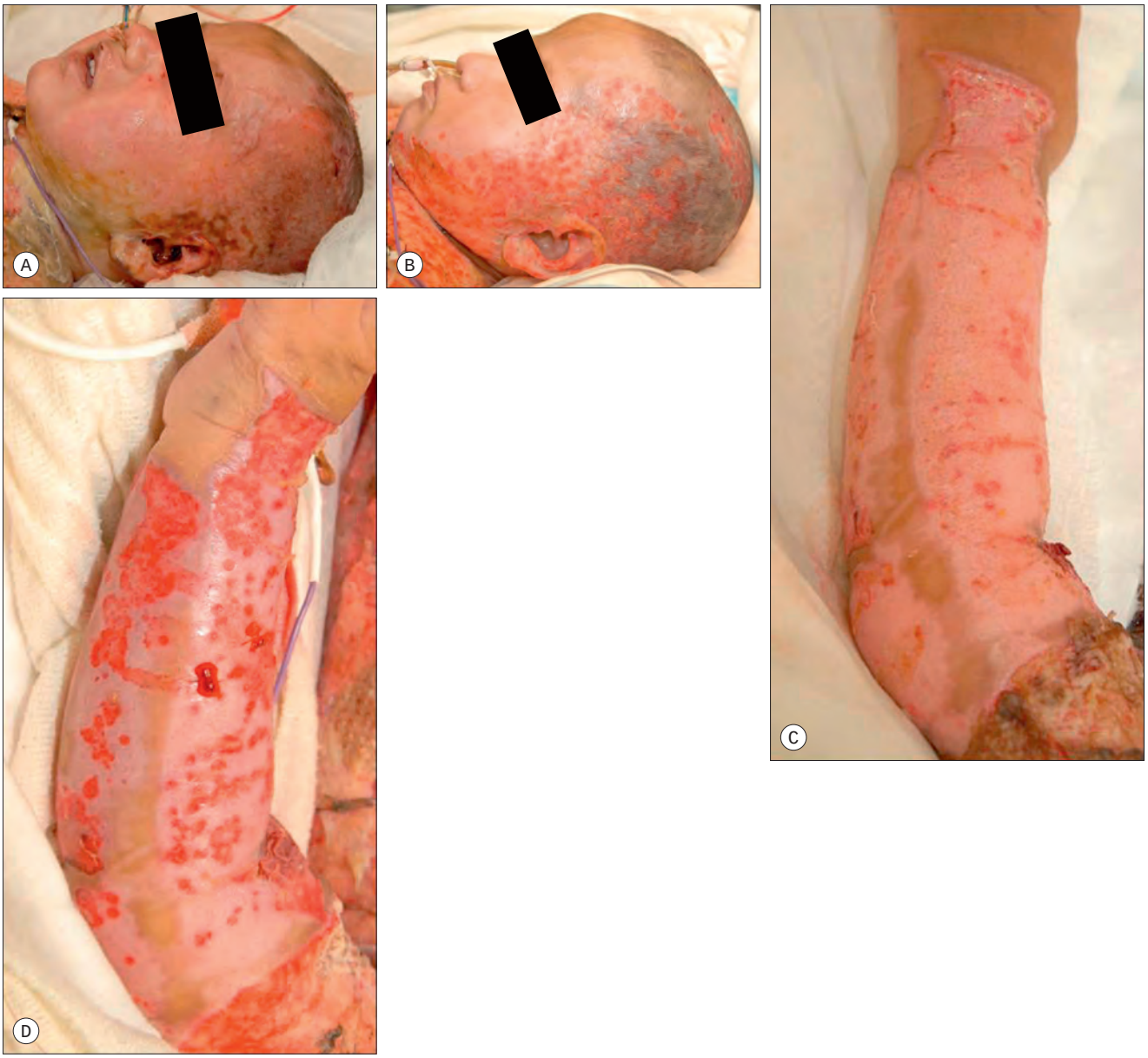

Fig. 11.13 Fulminant herpetic infection. A 13-month-old girl with 80% TBSA scald burn who developed a fulminant herpes simplex II infection 2 weeks after admission. (A) Ten days post-burn, prior to clinical manifestation of infection. (B) Post-burn day 18. Full manifestation of herpetic lesions that affect the entire body surface area and convert previously healed areas into open wounds. (C) The left arm, which was used twice as a donor site for split-thickness skin graft (days 4 and 11) prior to herpetic infection. The image is from day 17, with initial manifestation of herpetic infection with red macules. (D) Day 18 post burn; 30 hours later, conversion to confluent defects with near total loss of epidermis.

The clinical manifestations of lesions may be preceded by unexplained fever unresponsive to routine antibiotic coverage.[141]

Tzanck smears, viral cultures, and polymerase chain reaction (PCR) are the methods of choice to diagnose herpetic infections. Tzanck smears are a rapid, inexpensive, and minimally invasive tool used to detect infections by cytology over the course of the past last century (Fig. 11.14). While they lack the diagnostic precision necessary to discriminate between different types of Herpesviridae or even primary versus recurrent infections, they can reveal active infections that warrant treatment.[142] Viral cultures are effective means of diagnosis, but they take several days and are expensive. More sensitive than smears and quicker than cultures, PCR has thus become the standard in our burn center.

Increased mortality, extensive visceral involvement, and necrotizing tracheobronchitis have become associated with herpetic infections post-burn in recent years. Fidler and colleagues performed a retrospective study characterizing the incidence, presentation, and outcome of 14 patients with facial herpes rashes out of 95 severely burned intubated adults. Rashes attributed to herpetic infections were found to be present in at least 15% of patients, but no difference in mortality or length of stay between patients with or without the infection was detected.[143] Necrotizing hepatic and adrenal lesions may lead to multisystem organ failure. Mortality in patients with disseminated infection is

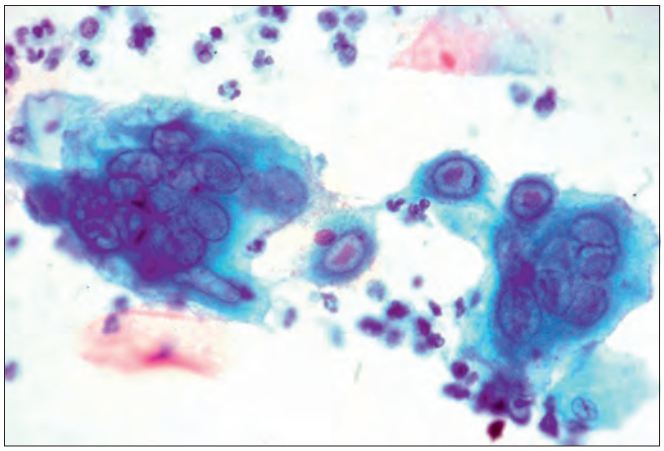

Fig. 11.14 Tzanck smear. This cytology can be performed rapidly as a touch prep or as a scraping smear of a suspicious lesion. The Tzanck smear should be performed on a fresh blister. Once identified: 1. Gently deroof the lesion with a scalpel. 2. Scrape the base of the lesion. 3. Smear the tissue onto a clean microscope slide. 4. Allow it to dry in the air. 5. Fix the specimen with preservatives. 6. Stain the slide and analyze it under microscope. Pathognomonic multinucleated giant cells are diagnostic of a herpetic infection. While not determinant of the type of herpes simplex virus, a test can be performed in minutes inexpensively, and a positive result indicates treatment.

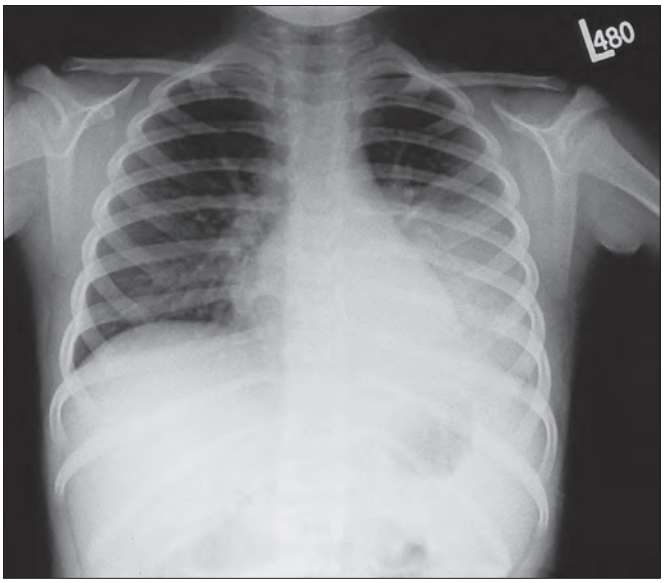

Fig. 11.15 Left lower pneumonia. Burn patient with typical radiographic picture of lobar pneumonia. The diagnosis of pneumonia in patients with inhalation injury and respiratory distress syndrome is still arduous.

approximately twice that expected for patients of similar age and burn size.

Split-thickness grafts provide adequate coverage of previously infected herpetic wounds,[144] but the coverage is frequently associated with secondary graft loss and the need for reoperation and patch grafting. Furthermore skin graft donor sites can convert to full-thickness injuries due to active herpetic infection. As such, skin donor sites should not be harvested for grafting for 10–14 days following infection resolution.[145] In burn patients with active herpetic infection, intravenous acyclovir or valacyclovir should be administered systemically for no less than 10 days and often longer.[146] Recent studies indicate that valacyclovir has greater bioavailability and steadier plasma concentration than acyclovir. While the best treatment remains controversial, both are acceptable for herpetic infection.[147]

VZV infection (chickenpox) is prevalent among school-aged children and rapidly spreads through inhalation of the virus. While rare in burned patients, VZV infections can be life-threatening in immunocompromised hosts, and small epidemics have occurred within pediatric burn units.[144] In the nonimmunized pediatric population, acute VZV infection directly correlates with morbidity and mortality.[148] Characteristic fluid-filled lesions appear in healed or healing partial-thickness burns, as well as in uninjured epithelium and mucous membranes. Owing to the fragility of newly healed or healing skin, the vesicles are much more destructive in injured than uninjured skin and may present as hemorrhagic, oozing pockmarks prone to secondary infection and subsequent scarring. Neovascularized skin grafts may be lost, and further grafting procedures should be delayed until the lesions are quiescent. Antiviral treatment with acyclovir is indicated in case of infection and, as suggested by Sheridan and colleagues, should be given prophylactically to nonimmunized pediatric patients.[148] The therapeutic effect of antiviral agents administered post-burn remains to be fully elucidated, as recently elaborated by Wurzer and Lee.[149]

Infections From Sources Other Than Wounds in the Burn Patient

Pneumonia is a leading cause of morbidity and mortality in burn patients.[1] Inciting infectious organisms can enter the lung either through direct contamination of the airway or hematogenously. Mechanical ventilation increases the risk of pneumonia; patients should be extubated as soon as clinically possible to prevent ventilator-assisted pneumonia (VAP), as discussed in Chapter 32 on critical care. Inhalation injury further increases the risk of VAP. Carrying a worse prognosis than pneumonias originating in the airways, the hematogenous etiology of pneumonia presents later in the hospital course and is often bilateral. Etiological organisms typically match those colonizing or infecting the burn wounds. Centers for Disease Control clinical diagnostic criteria of pneumonia are as follows: (1) chest X-ray revealing a new and persistent infiltrate, consolidation, or capitation[3,95] (Fig. 11.15); (2) sepsis (as defined for burn patients); and (3) a change or purulence in expectorated or aspirated sputum. If two of these criteria are found, a clinical diagnosis of pneumonia is then made, and, prior to the start of antimicrobial treatments, specimens should be collected for microbial analysis.

Tracheal aspirate, bronchoalveolar lavage (BAL), or protected bronchial brush (PBB) is performed to obtain a specimen. In burn patients, the possibility exists to use surface quantitative wound cultures (QWC) to predict pathogens found in VAP. Ramzy et al. investigated the relationship between burn wound flora and microbial pathogens in the tracheobronchial tree and found a 48% match. However, when strict quantitative criteria were applied, the match

rate fell to 14%. Burn size and inhalation injury had no significant effect on match rate.[150] The difference between qualitative and quantitative match rates suggests cross-colonization between the burn wound and tracheobronchial tree but little to no cross-infection. Thus both QWC and BLF cultures must be performed when determining antimicrobial specificity in the burned patient. However, wound cultures can be helpful in guiding empiric treatment for VAP and should be covered until BAL or PBB samples allow for culture-directed therapy.

BAL and PBB are recommended over tracheal aspirate for definitive diagnosis and treatment of VAP.[151] Positive microbiological results are tracheal aspirate showing 10^5 or more colony-forming units (CFU); BAL, 10^4 or more organisms; and PBB, 10^3 or more organisms. The data subsequently modify the clinical diagnosis in one of three ways:

- If a pathogen is isolated in sufficient quantities, then the clinical diagnosis is confirmed.
- If the clinical diagnosis was strong but the microbiologic data fail to confirm, then the diagnosis is probable.
- With low or moderate clinical suspicion, but with the presence of a positive specimen, the pneumonia diagnosis is possible.

In many quality assurance programs, a clinical diagnosis cannot be vacated by a lack of confirmation by the microbiology report, often resulting in inappropriately diagnosed and treated VAP.[3] In a 2005 study, Wahl and colleagues reported that negative BAL results ($<10^4$ CFU) reduced the clinical VAP diagnosis rate by 21%. Negative BAL results prompted the discontinuation of antibiotics administered based on clinical suspicion of VAP. In this study, none of the patients whose antibiotics were discontinued had antibiotics restarted based on clinical grounds.[152]

Regardless the tenets of pneumonia treatment remain consistent with standard critical care. Broad-spectrum antibiotics are instituted empirically to cover all likely etiologic agents. Utilization of ventilator support allows the patient to oxygenate and ventilate. Clinical diagnosis is made and confirmed with tracheal or bronchial cultures. Antibiotics are changed to treat the identified etiologic pathogen and discontinued after a finite course or when cultures are negative and the clinical condition resolved.[67]

Bloodstream infections in burn patients develop from a myriad of sources: burn wounds, urinary tract infections, pneumonias, translocation from the gut, or from the intravenous and intra-arterial lines essential to their care. Treatment of bloodstream infections is the same as for all infections: source control by removal of possible etiological causes, early institution of broad-spectrum antibiotics covering likely organisms, cultures of the blood and potential sources to make a definitive diagnosis, tailoring antimicrobials to the cultures, and discontinuation of the antibiotics following the course of treatment.[67] In most major burn patients, vascular access devices are requisite for treatment. Many central venous catheters (CVCs) must be placed through burned tissue or cannot have standard dressings applied due to poor skin quality or wound therapy. These limitations are known to increase central line–associated bloodstream infection (CLABSI) risk but are required for care. If burn patients demonstrate symptoms of SIRS or sepsis, their catheters should be removed or changed. Cultures should be performed of both the blood and catheters for evaluation as potential causes of sepsis. When there is concern of sepsis, dogmatic culturing of removed vascular access devices and blood is crucial to proper burn critical care. Rates of catheter-associated infection and septic thrombophlebitis in burn patients are as high as 57%.[153–155] One of the following two criteria must be met to diagnose a bloodstream infection: (1) the patient has two or more positive blood cultures for a known pathogen or one positive blood culture in the presence of sepsis, or (2) the patient has a common skin contaminant cultured from two or more blood cultures on separate occasions, as well as sepsis.[3] The bloodstream infection is considered primary if the same organism has not been cultured at another site. If the same organism is cultured at an alternate location, the bloodstream infection is considered secondary. A catheter-related bloodstream infection is present if a patient has sepsis and no other source of infection and if the signs of sepsis resolve within 24 hours of catheter removal. Unfortunately these administrative definitions do not often comport with the patient's clinical course and, generally, CLABSI is overdiagnosed. However, it is imperative to place the concerns of proper patient care and diagnosis exemplified by potential source control, early empiric antibiotics, and liberal use of cultures above inaccurate administrative definitions that fail to improve patient health.

Franchesi and coworkers[156] reported a 50% correspondence between the organisms cultured from the tip and connectors of the catheter within 2 days of placement. Furthermore, they found that a negative correlation existed between the frequency of catheter infection and the distance separating the point of catheter insertion from the burn wound. These data support the hypothesis that catheter infections arise primarily from burn wound contamination migrating to the catheter tip. Serious complications can often be avoided by following strict aseptic techniques. General guidelines for protecting against catheter-related infections are[157]: training health care staff on the correct procedures for inserting and maintaining catheters, including indications and suitable infection control practices; use of a mask, hat, gown, sterile gloves, and drapes during placement of CVCs; use of 2% chlorhexidine to prevent infection; and avoiding routine CVC changes. In the event that infection continues despite adhering to the guidelines, use short-term CVCs coated with an antibiotic, antiseptic, or both.

Suppurative thrombophlebitis should be suspected in patients with persistent positive blood cultures in the absence of signs of local infection. Often suppuration can occur subsequent to catheter removal, so cultures at the time of removal may be unreliable predictors of infection. Gross clinical signs of suppurative thrombophlebitis are frequently not present.[158] Upon confirmation of the diagnosis, immediate operative excision is essential to prevent progressive sepsis. Entire excision of a vein to the port of entry into the central circulation may be necessary because phlebitis tends to migrate to vein valves, leaving an apparently normal vein between infected foci. The subcutaneous tissue and skin should be packed open where a grossly purulent vein is removed and allowed to granulate and close by secondary intention (Fig. 11.16).

Gastrointestinal infections can limit clinical examination, thereby complicating burn care. Like all patients,

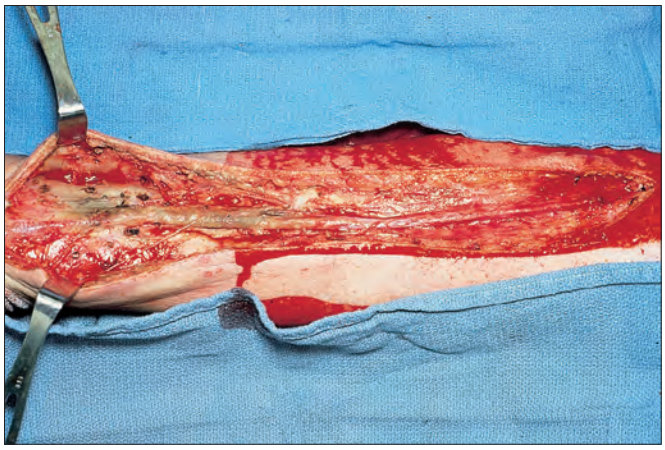

Fig. 11.16 Suppurative thrombophlebitis. Infection was noted along the length of vein. Proper treatment is total excision of the vein from the site of infection to the point of entry into central circulation.

those burned can develop conditions such as appendicitis, intussusception, ileus, and bowel obstruction. Ascetic fluid or peritoneal dialysis fluid can also become infected. Larger burns are associated with episodes of hypoperfusion, leading to sloughing of intestinal mucosa. Heme-positive mucoid, watery stools, abdominal distension, and diminished bowel sounds often characterize this condition. Diarrhea is a common issue, and osmotic causes from feeds should be excluded by testing for reducing substances. *C. difficile* is a well-known entity in critically ill patients, especially those with a history of antibiotic use and in immunocompromised patients. Current guidelines for the treatment of the first episode of *C. difficile* include oral or intravenous metronidazole, oral or rectal vancomycin, and fidaxomicin.[159] Possible complications due to *C. difficile* infections can be pseudomembranous colitis with the potential to progress to fulminant toxic colitis and bowel perforation. Should any of these develop, subtotal or total abdominal colectomy with an ileostomy may be required.[160] A loop ileostomy with colonic lavage using postoperative vancomycin colonic flushes via the ileostomy is an alternative surgical approach with perhaps lower morbidity and mortality.[161]

Necrotizing enterocolitis can occur in patients severely granulocytopenic from any cause, including burn. Splenic enlargement and tenderness are often present, along with high fever. Chest X-ray may reveal an elevated left hemidiaphragm, basilar pulmonary infiltrates, atelectasis, or a left pleural effusion, while abdominal X-rays can demonstrate a shift of the colon and stomach down and to the right, extraintestinal or bowel wall gas, or air–fluid levels in the upper left quadrant. Ultrasonography and computed tomography (CT) are the preferred diagnostic techniques for the determination of suspected splenic abscess and necrotizing enterocolitis. As with all infections, initial antibiotic therapy should have a broad spectrum of activity. A combination of antibiotics with activity against both aerobic and anaerobic gram-negative bacilli would be most appropriate. Free air or suspected necrotic bowel due to an unresolving lactic acidosis are indications for a laparotomy.[162]

Genitourinary infections occur from indwelling urinary catheters or hematogenous dissemination of bacteria. Fungi can lead to urinary tract infections in burn patients. These organisms are often introduced via the prolonged or unnecessary use of urinary catheters. This underlines, once again, the importance of infection prevention following the guidelines repeated earlier (e.g., aseptic techniques, catheter care, routine urine monitoring, and early removal). In some burn patients, especially those with genital burns or protracted shock, a prolonged catheterization may be well indicated, balancing the elevated risk of infection against the care benefit. If infection develops, patients should have their catheters removed or changed, urine cultured, appropriate empiric antibiotics administered, and then culture-directed antimicrobials utilized. In cases of highly resistant pathogens, urinary catheters may need to be discontinued, with the patient only intermittently catheterized.[163]

Chondritis typically occurs in full-thickness injuries to the ear resulting in infection of the auricular cartilage. The auricles have a comparatively low blood supply, and chondritis frequently follows tissue ischemia. Chondritis usually presents 3–5 weeks after thermal injury but may be seen earlier and may develop following partial-thickness injuries. Mafenide acetate cream has become the topical agent of choice for burned cartilaginous surfaces like the ear because it coats and adheres to the irregular surfaces well while deeply penetrating the wound and saturating the cartilage to prophylactically guard it against infection. With its use, the incidence of suppurative chondritis has significantly decreased[164] (Fig. 11.17). Chondritis presents with dull pain and a warm, red, tender, and edematous ear. Appropriate antibiotics should be immediately administered, and, if there is an identifiable site, the abscess immediately excised and drained, with culture and sensitivity obtained. Should induration and tenderness persist, a more extensive débridement is imperative. Generally the helix is bivalved at the posterior helical margin and all necrotic cartilage débrided. Difficulty may arise in distinguishing between viable and necrotic tissue, and normal cartilage is frequently sacrificed to ensure débridement. However, infected cartilage is usually soft, whereas normal cartilage will feel granular on curettage. If appropriate and sufficient excision of the necrotic tissue is not performed, the auricle can auto-amputate and suppurative chondritis can invade the mastoid bone, potentiating the formation of intracranial abscesses.[165]

Ophthalmic infections occur from injuries suffered in the initial trauma, from corneal exposure due to poor lid function due to edema or facial burns, herpetic reactivation, or hematogenous spread of infection. Corneal injury can lead to bacterial infection with subsequent corneal perforation and loss of the eye. The cornerstone of treatment is prevention through treatment of abrasions with topical antimicrobial agents, early eyelid release, and vigilance in protecting against risk of exposure trauma.[166] In incapacitated patients, the entire burn team must be vigilant and monitor the eye for injuries and infection. This topic is discussed in depth in Chapter 43 on burn injuries of the eye.

Suppurative sinusitis is an uncommon infection but can cause ICU sepsis. In patients with no identifiable source of sepsis, diagnosis can be made based on X-rays or CT scans. Therapy with broad-spectrum antibiotics and promotion of drainage should be initiated immediately. Surgical drainage of the involved sinuses may be necessary if the infection is

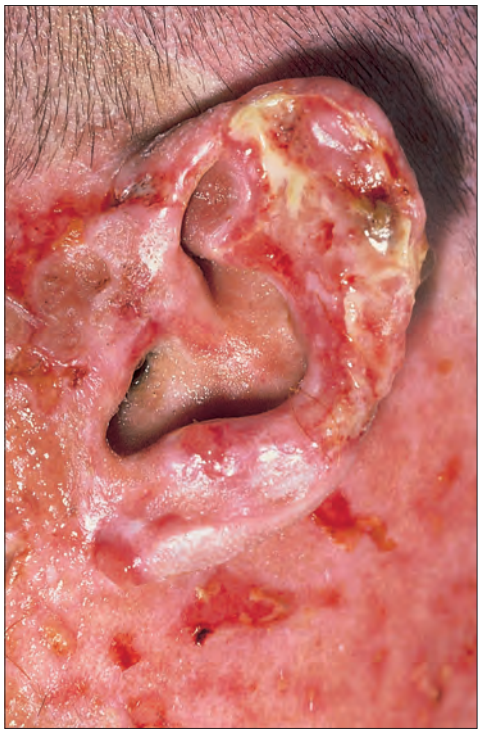

Fig. 11.17 Left ear with suppurative chondritis. Chondritis seen 3 weeks after flame burn to the left ear. Note the erythema and drainage from the helical rim.

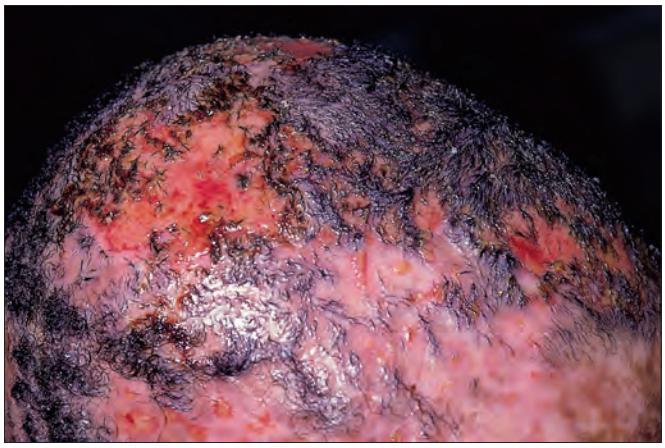

Fig. 11.18 Chronic folliculitis of the scalp. Hairs from hair-bearing areas are embedded in the granulation tissue of converted second-degree burns and donor sites, and microorganisms are entrapped, prolonging the healing process. Shaving of the affected area, topical treatment with mupirocin, and cleansing with soap and water typically resolve this problem in several days to a week.

unresponsive to the antibiotics. In the ICU, transnasal intubation and the use of nasogastric or nasoduodenal tubes for enteral feeding are considered risk factors. However, in 25 years of routine nasotracheal intubations and routine prolonged nasojejunal and nasogastric tube placements, we have not encountered a single case of suppurative sinusitis in Galveston. Oral intubation and nasogastric feeding may be employed as temporary measures, but if sinusitis becomes complicated and prolonged treatment is necessary, then a tracheostomy and/or orogastric feeding is indicated.

Folliculitis is an infection commonly occurring on the scalp, male face, and scalp skin graft donor sites. As in the case of impetigo, cultures commonly reveal *S. aureus*, particularly MRSA (Fig. 11.18). Treatment consists of twice-daily cleansing with soap and water, unroofing any abscesses, and twice-daily application of mupirocin. Shaving the hair is helpful both prophylactically and for treatment. Keratinocytes in the viable hair shafts allow rapid reepithelialization once bacterial counts are brought under control. Excision and grafting is rarely required.

Tetanus is a rare complication of burn wounds in the developed world. Routine prophylaxis at admission with 0.5 mL tetanus toxoid is given, if it has not been administered in the previous 3 years.[167,168] In addition, if the patient's last booster was more than 10 years prior, 250 U of tetanus antitoxin is also administered. Should *Clostridium tetani*, an anaerobic gut flora of ruminants, colonize or infect a burn wound in an unvaccinated individual, the resulting intoxication can lead to a horrific and easily avoided mortality.

HIV infection is endemic in areas such as sub-Saharan Africa; some countries have rates of 35%–39% in the total adult population. In the United States, the incidence is much lower, but since people with HIV do get burned, care of this disease in the burn unit is worth consideration. HIV seems to have an additive effect on the immunosuppression of the burn, as reflected in the CD4/CD8 cell counts. In a 2003 prospective study from Zimbabwe, Mzezewa and colleagues found that graft survival after split-thickness skin grafting of burn wounds in HIV-infected patients was impaired and hospital stay was prolonged, with significant alterations in the levels of pro- and antiinflammatory cytokines.[169] The authors concluded that HIV infection results in immune dysregulation, which might be related to impaired skin graft survival. Recent data have emerged describing a substantial burden of sepsis in the infected population receiving highly active antiretroviral therapy, in addition to a much poorer prognosis in this group compared with the uninfected population. Although there is a lack of literature regarding the implications of antiretroviral medications on burned patients and the effect on wound healing and graft take, using antiretroviral therapy to reduce septic incidences should be considered.[170]

Conclusion

Treatment of infection in the burn patient follows the same algorithm dominating treatment of all infections in every critically ill patient: (1) early source control, (2) culture identification of infecting microbes, (3) early institution of empiric antimicrobials with subsequent transition to culture-directed antibiotics when sensitivities are ascertained, and (4) discontinuation of antimicrobials following the administration of a sufficient course or when the wounds are closed. The considerations specific to burn care are (1) source control is determined by excising the burn wound and covering it with skin graft, (2) aggressive use of quantitative wound cultures guides antimicrobial selection, and (3) careful and frequent evaluation to diagnose sepsis and treatment with empiric antibiotics when indicated.

All eschar must be excised as quickly as possible, ideally within the first 48 hours post-burn, because eschar provides an ideal microbial culture medium. Burn wounds should be closed as rapidly as feasible with autograft. The tenet, "every donor, every time" should be employed in all large burns: every area of donor skin should be harvested and autograft applied at every operation. When insufficient autograft is available to cover the wounds, homograft should be used to temporize wounds. Homograft overlay of widely expanded autograft, in the methodology of Alexander, is an effective way to limit the wound surface area available to pathogens and maximize utilization of finite donor areas, as detailed in Chapter 12 on operative wound management. Every moment a burn wound lacks a complete epithelial surface, there is a cumulative risk for wound infection and resistant organisms to take hold. Source control is also obtainable by assiduous washing and débriding in hydrotherapy, which has been demonstrated to be an indispensible component of modern burn care. High concentrations of antimicrobials can and should be delivered topically to burn wounds for colonization and infection treatment and for prophylaxis.

Aggressive use of quantitative wound cultures is the standard of care in modern burn wound management, and sensitivities determined from these studies direct effective tailoring of antimicrobials to the patient's infecting microbiota, thereby reducing toxicity from superfluous antibiotics. All vascular access devices removed from a burn patient should be cultured to ensure that any colonizing or infecting bacteria are identified, correct diagnoses are made, and antimicrobial sensitivities are monitored.

Due to their hypermetabolic states, determining when a burn patient is septic is complicated. When a presumptive diagnosis of sepsis is made, broad-spectrum coverage should be instituted to cover all likely pathogens. The choice of initial agent is based on the local antibiogram; in many burn centers, carbapenems and vancomycin are appropriate choices. Once sensitivities return, empiric antibiotics should be de-escalated.

The ultimate infection control method in burn care is closing the burn wound with skin. In the setting of pan-resistant organisms, this is the only treatment. Every time the patient has skin available for grafting, this opportunity must be exploited to reduce the wound surface area available to pathogens and provide definitive prophylaxis and treatment of burn wound infections.

Complete references available online at
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References

1. National Burn Repository Chicago 2015.
2. Williams FN, Herndon DN, Hawkins HK, et al. The leading causes of death after burn injury in a single pediatric burn center. *Crit Care*. 2009;13(6):R183.
3. Greenhalgh DG, Saffle JR, Holmes JHT, et al. American Burn Association consensus conference to define sepsis and infection in burns. *J Burn Care Res*. 2007;28(6):776-790.
4. Teplitz C, Davis D, Mason AD Jr, Moncrief JA. *Pseudomonas* burn wound sepsis. I Pathogenesis of experimental *Pseudomonas* burn wound sepsis. *J Surg Res*. 1964;4:200-216.
5. Robson MC, Krizek TJ, Heggers JP. Biology of surgical infection. *Curr Probl Surg*. 1973;1–62.
6. Pruitt BA Jr, McManus AT, Kim SH, Goodwin CW. Burn wound infections: current status. *World J Surg*. 1998;22(2):135-145.
7. Robson MC. Bacterial control in the burn wound. *Clin Plast Surg*. 1979;6(4):515-522.
8. Barret JP, Herndon DN. Effects of burn wound excision on bacterial colonization and invasion. *Plast Reconstr Surg*. 2003;111(2):744-750, discussion 751-752.
9. Altoparlak U, Erol S, Akcay MN, Celebi F, Kadanali A. The time-related changes of antimicrobial resistance patterns and predominant bacterial profiles of burn wounds and body flora of burned patients. *Burns*. 2004;30(7):660-664.
10. Rutala WA, Weber DJ. Are room decontamination units needed to prevent transmission of environmental pathogens? *Infect Control Hosp Epidemiol*. 2011;32(8):743-747.
11. Trick WE, Vernon MO, Hayes RA, et al. Impact of ring wearing on hand contamination and comparison of hand hygiene agents in a hospital. *Clin Infect Dis*. 2003;36(11):1383-1390.
12. Karabay O, Kocoglu E, Tahtaci M. The role of mobile phones in the spread of bacteria associated with nosocomial infections. *J Infect Dev Ctries*. 2007;1:72-73.
13. Snyder GM, Thom KA, Furuno JP, et al. Detection of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci on the gowns and gloves of healthcare workers. *Infect Control Hosp Epidemiol*. 2008;29(7):583-589.
14. Taddonio TE, Thomson PD, Smith DJ Jr, Prasad JK. A survey of wound monitoring and topical antimicrobial therapy practices in the treatment of burn injury. *J Burn Care Rehabil*. 1990;11(5):423-427.
15. Kwei J, Halstead FD, Dretzke J, Oppenheim BA, Moiemen NS. Protocol for a systematic review of quantitative burn wound microbiology in the management of burns patients. *Syst Rev*. 2015;4:150.
16. Miles AA, Misra SS, Irwin JO. The estimation of the bactericidal power of the blood. *J Hyg (Lond)*. 1938;38(6):732-749.
17. Steer JA, Papini RP, Wilson AP, McGrouther DA, Parkhouse N. Quantitative microbiology in the management of burn patients. II. Relationship between bacterial counts obtained by burn wound biopsy culture and surface alginate swab culture, with clinical outcome following burn surgery and change of dressings. *Burns*. 1996;22(3):177-181.
18. Mayhall CG. The epidemiology of burn wound infections: then and now. *Clin Infect Dis*. 2003;37(4):543-550.
19. White MC, Thornton K, Young AE. Early diagnosis and treatment of toxic shock syndrome in paediatric burns. *Burns*. 2005;31(2):193-197.
20. Pruitt BA Jr, Foley FD. The use of biopsies in burn patient care. *Surgery*. 1973;73(6):887-897.
21. Robson MC, Krizek TJ. Predicting skin graft survival. *J Trauma*. 1973;13(3):213-217.
22. Napolitano LM. Severe soft tissue infections. *Infect Dis Clin North Am*. 2009;23(3):571-591.
23. Heggers JP, Sazy JA, Stenberg BD, et al. Bactericidal and wound-healing properties of sodium hypochlorite solutions: the 1991 Lindberg Award. *J Burn Care Rehabil*. 1991;12(5):420-424.
24. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101(6):1644-1655.
25. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31(4):1250-1256.
26. Calandra T, Cohen J. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. *Crit Care Med*. 2005;33(7):1538-1548.
27. Greenhalgh DG. Topical antimicrobial agents for burn wounds. *Clin Plast Surg*. 2009;36(4):597-606.
28. Glasser JS, Guymon CH, Mende K, et al. Activity of topical antimicrobial agents against multidrug-resistant bacteria recovered from burn patients. *Burns*. 2010;36(8):1172-1184.
29. Dai T, Huang YY, Sharma SK, et al. Topical antimicrobials for burn wound infections. *Recent Pat Antiinfect Drug Discov*. 2010;5(2):124-151.
30. Burmolle M, Thomsen TR, Fazli M, et al. Biofilms in chronic infections – a matter of opportunity – monospecies biofilms in multispecies infections. *FEMS Immunol Med Microbiol*. 2010;59(3):324-336.
31. Bianchi T, Wolcott RD, Peghetti A, et al. Recommendations for the management of biofilm: a consensus document. *J Wound Care*. 2016;25(6):305-317.
32. Kennedy P, Brammah S, Wills E. Burns, biofilm and a new appraisal of burn wound sepsis. *Burns*. 2010;36(1):49-56.
33. Wilkins RG, Unverdorben M. Wound cleaning and wound healing: a concise review. *Adv Skin Wound Care*. 2013;26(4):160-163.
34. Dusane DH, Rajput JK, Kumar AR, et al. Disruption of fungal and bacterial biofilms by lauroyl glucose. *Lett Appl Microbiol*. 2008;47(5):374-379.
35. Seo Y, Bishop PL. Influence of nonionic surfactant on attached biofilm formation and phenanthrene bioavailability during simulated surfactant enhanced bioremediation. *Environ Sci Technol*. 2007;41(20):7107-7113.
36. Eginton PJ, Holah J, Allison DG, Handley PS, Gilbert P. Changes in the strength of attachment of micro-organisms to surfaces following treatment with disinfectants and cleansing agents. *Lett Appl Microbiol*. 1998;27(2):101-105.
37. Fader RC, Maurer A, Stein MD, Abston S, Herndon DN. Sodium hypochlorite decontamination of split-thickness cadaveric skin infected with bacteria and yeast with subsequent isolation and growth of basal cells to confluency in tissue culture. *Antimicrob Agents Chemother*. 1983;24(2):181-185.
38. Cotter JL, Fader RC, Lilley C, Herndon DN. Chemical parameters, antimicrobial activities, and tissue toxicity of 0.1 and 0.5% sodium hypochlorite solutions. *Antimicrob Agents Chemother*. 1985;28(1):118-122.
39. Smith RA. Clorpactin XCB: its use in urology in the surgical treatment of malignant neoplasms. *J Urol*. 1959;81(4):554-557.
40. Castigliano SG, Shigeoka EH. Incidence of skin graft "takes" after clorpactin XCB wound irrigation in cancer surgery. A preliminary study on acceptance of human skin grafts. *Arch Surg*. 1960;81:992-996.
41. Wang L, Bassiri M, Najafi R, et al. Hypochlorous acid as a potential wound care agent: Part I. Stabilized hypochlorous acid: a component of the inorganic armamentarium of innate immunity. *J Burns Wounds*. 2007;6:e5.
42. Robson MC, Payne WG, Ko F, et al. Hypochlorous acid as a potential wound care agent: Part II. Stabilized hypochlorous acid: its role in decreasing tissue bacterial bioburden and overcoming the inhibition of infection on wound healing. *J Burns Wounds*. 2007;6:e6.
43. Gelmetti C. Local antibiotics in dermatology. *Dermatol Ther*. 2008;21(3):187-195.
44. Georgiade NG, Harris WA. Open and closed treatment of burns with povidone-iodine. *Plast Reconstruct Surg*. 1973;52(6):640-644.
45. Nagoba BS, Selkar SP, Wadher BJ, Gandhi RC. Acetic acid treatment of pseudomonal wound infections—a review. *J Infect Public Health*. 2013;6(6):410-415.
46. Phillips I, Lobo AZ, Fernandes R, Gundara NS. Acetic acid in the treatment of superficial wounds infected by *Pseudomonas aeruginosa*. *Lancet*. 1968;1(7532):11-14.
47. Sloss JM, Cumberland N, Milner SM. Acetic acid used for the elimination of *Pseudomonas aeruginosa* from burn and soft tissue wounds. *J R Army Med Corps*. 1993;139(2):49-51.
48. Nagoba BS, Deshmukh SR, Wadher BJ, Patil SB. Acetic acid treatment of pseudomonal postoperative wound infection. *J Hosp Infect*. 1997;36(3):243-244.
49. Duc Q, Breetveld M, Middelkoop E, et al. A cytotoxic analysis of antiseptic medication on skin substitutes and autograft. *Br J Dermatol*. 2007;157(1):33-40.
50. Duran N, Duran M, de Jesus MB, et al. Silver nanoparticles: a new view on mechanistic aspects on antimicrobial activity. *Nanomedicine (Lond)*. 2016;12(3):789-799.
51. Politano AD, Campbell KT, Rosenberger LH, Sawyer RG. Use of silver in the prevention and treatment of infections: silver review. *Surg Infect (Larchmt)*. 2013;14(1):8-20.

52. Heggers J. The use of antimicrobial agents. *Clin Plast Surg*. 1979;6(4):545-551.
53. Aziz Z, Abu SF, Chong NJ. A systematic review of silver-containing dressings and topical silver agents (used with dressings) for burn wounds. *Burns*. 2012;38(3):307-318.
54. Chattopadhyay A, Chang K, Nguyen K, et al. An inexpensive bismuth-petrolatum dressing for treatment of burns. *Plast Reconstr Surg Glob Open*. 2016;4(6):e737.
55. Diggle FH. The value of "Bipp" in primary operations for gunshot wounds of joints. *Br Med J*. 1919;1(3045):572-573.
56. Nigam A, Allwood MC. BIPP: how does it work? *Clin Otolaryngol Allied Sci*. 1990;15(2):173-175.
57. Atwal A, Cousin GC. Bismuth toxicity in patients treated with bismuth iodoform paraffin packs. *Br J Oral Maxillofac Surg*. 2016;54(1):111-112.
58. Ovaska H, Wood DM, House I, et al. Severe iatrogenic bismuth poisoning with bismuth iodoform paraffin paste treated with DMPS chelation. *Clin Toxicol (Phila)*. 2008;46(9):855-857.
59. Mendelson JA. Topical mafenide hydrochloride aqueous spray in initial management of massive contaminated wounds with devitalized tissue. *Prehosp Disaster Med*. 2001;16(3):172-174.
60. Mulcahy LR, Isabella VM, Lewis K. *Pseudomonas aeruginosa* biofilms in disease. *Microb Ecol*. 2014;68(1):1-12.
61. Denning DW, Haiduven-Griffiths D. Eradication of low-level methicillin-resistant *Staphylococcus aureus* skin colonization with topical mupirocin. *Infect Control Hosp Epidemiol*. 1988;9(6):261-263.
62. Strock LL, Lee MM, Rutan RL, et al. Topical Bactroban (mupirocin): efficacy in treating burn wounds infected with methicillin-resistant staphylococci. *J Burn Care Rehabil*. 1990;11(5):454-459.
63. Tao L, Zhou J, Gong Y, et al. Risk factors for central line-associated bloodstream infection in patients with major burns and the efficacy of the topical application of mupirocin at the central venous catheter exit site. *Burns*. 2015;41(8):1831-1838.
64. Barret JP, Ramzy PI, Heggers JP, et al. Topical nystatin powder in severe burns: a new treatment for angioinvasive fungal infections refractory to other topical and systemic agents. *Burns*. 1999;25(6):505-508.
65. White CE, Renz EM. Advances in surgical care: management of severe burn injury. *Crit Care Med*. 2008;36(7 suppl):S318-S324.
66. Enoch S, Roshan A, Shah M. Emergency and early management of burns and scalds. *Br Med J*. 2009;338:b1037.
67. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med*. 2004;32(3):858-873.
68. Martyn J. Clinical pharmacology and drug therapy in the burned patient. *Anesthesiology*. 1986;65(1):67-75.
69. McEvoy GK. *AHFS Drug Information Essentials*. Bethesda, MD: American Society of Health-System Pharmacists; 2004.
70. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. *Clin Infect Dis*. 2006;42(suppl 1):S35-S39.
71. Branski LK, Al-Mousawi A, Rivero H, et al. Emerging infections in burns. *Surg Infect (Larchmt)*. 2009;10(5):389-397.
72. Arizpe A, Reveles KR, Patel SD, Aitken SL. Updates in the management of cephalosporin-resistant gram-negative bacteria. *Curr Infect Dis Rep*. 2016;18(12):39.
73. Vigliarolo L, Ramirez MS, Centron D, Lopardo H. Influencia de la concentracion inhibitoria minima de penicilina en la accion sinergica de su combinacion con gentamicina frente a estreptococos del grupo viridans. [Influence of penicillin minimum inhibitory concentration in the synergy between penicillin and gentamicin in viridans-group streptococci]. *Rev Argent Microbiol*. 2007;39(2):107-112.
74. Liao CH, Huang YT, Tsai HY, Hsueh PR. In vitro synergy of ampicillin with gentamicin, ceftriaxone and ciprofloxacin against *Enterococcus faecalis*. *Int J Antimicrob Agents*. 2014;44(1):85-86.
75. Roberts DM. The relevance of drug clearance to antibiotic dosing in critically ill patients. *Curr Pharm Biotechnol*. 2011;12(12):2002-2014.
76. Kunin CM, Bugg A. Recovery of tissue bound polymyxin B and colistimethate. *Proc Soc Exp Biol Med*. 1971;137(3):786-790.
77. Kunin CM, Bugg A. Binding of polymyxin antibiotics to tissues: the major determinant of distribution and persistence in the body. *J Infect Dis*. 1971;124(4):394-400.
78. Leroy O, Mira JP, Montravers P, Gangneux JP, Lortholary O. Comparison of albicans vs. non-albicans candidemia in French intensive care units. *Crit Care*. 2010;14(3):R98.
79. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(5):503-535.
80. Pappas PG, Kauffman CA, Andes DR, et al. Executive summary: Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):409-417.
81. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):e1-e50.
82. Alangaden GJ. Nosocomial fungal infections: epidemiology, infection control, and prevention. *Infect Dis Clin North Am*. 2011;25(1):201-225.
83. Hope W, Morton A, Eisen DP. Increase in prevalence of nosocomial non-*Candida albicans* candidaemia and the association of *Candida krusei* with fluconazole use. *J Hosp Infect*. 2002;50(1):56-65.
84. Malani AN, Kerr LE, Kauffman CA. Voriconazole: how to use this antifungal agent and what to expect. *Semin Respir Crit Care Med*. 2015;36(5):786-795.
85. Boucher HW, Groll AH, Chiou CC, Walsh TJ. Newer systemic antifungal agents: pharmacokinetics, safety and efficacy. *Drugs*. 2004;64(18):1997-2020.
86. Saliba F, Dupont B. Renal impairment and amphotericin B formulations in patients with invasive fungal infections. *Med Mycol*. 2008;46(2):97-112.
87. Ellis D. Amphotericin B: spectrum and resistance. *J Antimicrob Chemother*. 2002;49(suppl 1):7-10.
88. Murray PRBE. *Manual of Clinical Microbiology*. 8th ed. Washington, DC: American Society for Microbiology; 2003.
89. Cook N. Methicillin-resistant *Staphylococcus aureus* versus the burn patient. *Burns*. 1998;24(2):91-98.
90. de Macedo JL, Rosa SC, Castro C. Sepsis in burned patients. *Rev Soc Bras Med Trop*. 2003;36(6):647-652.
91. Edwards-Jones V, Greenwood JE. What's new in burn microbiology? James Laing Memorial Prize Essay 2000. *Burns*. 2003;29(1):15-24.
92. Prasanna M, Thomas C. A profile of methicillin resistant *Staphylococcus aureus* infection in the burn center of the Sultanate of Oman. *Burns*. 1998;24(7):631-636.
93. Thabet L, Turki A, Ben Redjeb S, Messadi A. Profil bacteriologique et resistance aux antibiotiques des bacteries isolees dans un service de reanimation des brules durant deux ans. [Bacteriological profile and antibiotic resistance of bacteria isolates in a burn department]. *Tunis Med*. 2008;86(12):1051-1054.
94. Wilson GR, French GW, Sully L. Loss of split thickness skin grafts due to non-group A beta-haemolytic streptococci. *Ann R Coll Surg Engl*. 1988;70(4):217-219.
95. von Baum H, Ober JF, Wendt C, Wenzel RP, Edmond MB. Antibiotic-resistant bloodstream infections in hospitalized patients: specific risk factors in a high-risk population? *Infection*. 2005;33(5-6):320-326.
96. Gonzalez MR, Fleuchot B, Lauciello L, et al. Effect of human burn wound exudate on *Pseudomonas aeruginosa* virulence. *mSphere*. 2016;1(2).
97. McManus AT, Mason AD Jr, McManus WF, Pruitt BA Jr. Twenty-five year review of *Pseudomonas aeruginosa* bacteremia in a burn center. *Eur J Clin Microbiol*. 1985;4(2):219-223.
98. Walton MA, Villarreal C, Herndon DN, Heggers JP. The use of aztreonam as an alternate therapy for multi-resistant *Pseudomonas aeruginosa*. *Burns*. 1997;23(3):225-227.
99. Zarrilli R, Crispino M, Bagattini M, et al. Molecular epidemiology of sequential outbreaks of *Acinetobacter baumannii* in an intensive care unit shows the emergence of carbapenem resistance. *J Clin Microbiol*. 2004;42(3):946-953.
100. Chim H, Tan BH, Song C. Five-year review of infections in a burn intensive care unit: high incidence of *Acinetobacter baumannii* in a tropical climate. *Burns*. 2007;33(8):1008-1014.
101. Corbella X, Montero A, Pujol M, et al. Emergence and rapid spread of carbapenem resistance during a large and sustained hospital outbreak of multiresistant *Acinetobacter baumannii*. *J Clin Microbiol*. 2000;38(11):4086-4095.
102. Albrecht MC, Griffith ME, Murray CK, et al. Impact of Acinetobacter infection on the mortality of burn patients. *J Am Coll Surg*. 2006;203(4):546-550.
103. Friedman ND, Korman TM, Fairley CK, Franklin JC, Spelman DW. Bacteraemia due to *Stenotrophomonas maltophilia*: an analysis of 45 episodes. *J Infect*. 2002;45(1):47-53.

104. Dalamaga M, Karmaniolas K, Chavelas C, et al. *Stenotrophomonas maltophilia*: a serious and rare complication in patients suffering from burns. *Burns*. 2003;29(7):711-713.
105. Sanyal SC, Mokaddas EM. The increase in carbapenem use and emergence of *Stenotrophomonas maltophilia* as an important nosocomial pathogen. *J Chemother*. 1999;11(1):28-33.
106. Hanes SD, Demirkan K, Tolley E, et al. Risk factors for late-onset nosocomial pneumonia caused by *Stenotrophomonas maltophilia* in critically ill trauma patients. *Clin Infect Dis*. 2002;35(3):228-235.
107. Patel JAW-BN. Infections in burn patients. In: Feigin RD, ed. *Feigin & Cherry's Textbook of Pediatric Infectious Diseases*. Amsterdam: Elsevier; 2009.
108. Guggenheim M, Zbinden R, Handschin AE, et al. Changes in bacterial isolates from burn wounds and their antibiograms: a 20-year study (1986–2005). *Burns*. 2009;35(4):553-560.
109. Woods GL. *Diagnostic Pathology of Infectious Diseases*. Philadelphia: Lea & Febiger; 1993:xiv.
110. Becker WK, Cioffi WG Jr, McManus AT, et al. Fungal burn wound infection. A 10-year experience. *Arch Surg*. 1991;126(1):44-48.
111. William M, Procop GW. *Koneman's Color Atlas and Textbook of Diagnostic Microbiology*. Winn MD, Koneman EW, (eds). 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2006.
112. Desai MH, Herndon DN, Abston S. Candida infection in massively burned patients. *J Trauma*. 1987;27(10):1186-1188.
113. Church D, Elsayed S, Reid O, Winston B, Lindsay R. Burn wound infections. *Clin Microbiol Rev*. 2006;19(2):403-434.
114. Murray PM, Finegold SM. Anaerobes in burn-wound infections. *Rev Infect Dis*. 1984;6(suppl 1):S184-S186.
115. Pruitt BA. Phycomycotic infections. *Prob Gen Surg*. 1984;1:664-678.
116. Horvath EE, Murray CK, Vaughan GM, et al. Fungal wound infection (not colonization) is independently associated with mortality in burn patients. *Ann Surg*. 2007;245(6):978-985.
117. Ballard J, Edelman L, Saffle J, et al. Positive fungal cultures in burn patients: a multicenter review. *J Burn Care Res*. 2008;29(1):213-221.
118. Sheridan RL. Sepsis in pediatric burn patients. *Pediatr Crit Care Med*. 2005;6(3 suppl):S112-S119.
119. Woods GL. *Diagnostic Pathology of Infections Diseases*. Philadelphia: Lea & Febiger; 1993.
120. Spebar MJ, Lindberg RB. Fungal infection of the burn wound. *Am J Surg*. 1979;138(6):879-882.
121. Wisplinghoff H, Bischoff T, Tallent SM, et al. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis*. 2004;39(3):309-317.
122. Linnemann CC Jr, MacMillan BG. Viral infections in pediatric burn patients. *Am J Dis Child*. 1981;135(8):750-753.
123. Kealey GP, Aguiar J, Lewis RW 2nd, et al. Cadaver skin allografts and transmission of human cytomegalovirus to burn patients. *J Am Coll Surg*. 1996;182(3):201-205.
124. Kealey GP, Bale JF, Strauss RG, Massanari RM. Cytomegalovirus infection in burn patients. *J Burn Care Rehabil*. 1987;8(6):543-545.
125. Seeman J, Konigova R. Cytomegalovirus infection in severely burned patients. *Acta Chir Plast*. 1976;18(3):142-151.
126. Gong F, Ding L, Jiang D, et al. Association of human leukocyte antigen E polymorphism with human cytomegalovirus reactivation in Chinese burn patients. *Acta Biochim Biophys Sin (Shanghai)*. 2013;45(11):982-984.
127. Rennekampff HO, Hamprecht K. Cytomegalovirus infection in burns: a review. *J Med Microbiol*. 2006;55(Pt 5):483-487.
128. Deepe GS Jr, MacMillan BG, Linnemann CC Jr. Unexplained fever in burn patients due to cytomegalovirus infection. *JAMA*. 1982;248(18):2299-2301.
129. Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. *Clin Infect Dis*. 2002;34(8):1094-1097.
130. Bordes J, Maslin J, Prunet B, et al. Cytomegalovirus infection in severe burn patients monitoring by real-time polymerase chain reaction: a prospective study. *Burns*. 2011;37(3):434-439.
131. Gibbs JT, Zieger M, Sood R. Cytomegalovirus colitis in a burn patient. *J Burn Care Res*. 2016;37(3):e298-e300.
132. Bale JF Jr, Kealey GP, Ebelhack CL, Platz CE, Goeken JA. Cytomegalovirus infection in a cyclosporine-treated burn patient: case report. *J Trauma*. 1992;32(2):263-267.
133. Hamilton JR, Overall JC Jr. Synergistic infection with murine cytomegalovirus and *Pseudomonas aeruginosa* in mice. *J Infect Dis*. 1978;137(6):775-782.
134. Bale JF Jr, Gay PE, Madsen JA. Monitoring of serum amylase levels during valproic acid therapy. *Ann Neurol*. 1982;11(2):217-218.
135. Tenenhaus M, Rennekampff HO, Pfau M, Hamprecht K. Cytomegalovirus and burns: current perceptions, awareness, diagnosis, and management strategies in the United States and Germany. *J Burn Care Res*. 2006;27(3):281-288.
136. Kagan RJ, Naraqi S, Matsuda T, Jonasson OM. Herpes simplex virus and cytomegalovirus infections in burned patients. *J Trauma*. 1985;25(1):40-45.
137. Biron KK. Antiviral drugs for cytomegalovirus diseases. *Antiviral Res*. 2006;71(2-3):154-163.
138. Paya C, Humar A, Dominguez E, et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant*. 2004;4(4):611-620.
139. Cvetkovic RS, Wellington K. Valganciclovir: a review of its use in the management of CMV infection and disease in immunocompromised patients. *Drugs*. 2005;65(6):859-878.
140. Gandhi MK, Khanna R. Human cytomegalovirus: clinical aspects, immune regulation, and emerging treatments. *Lancet Infect Dis*. 2004;4(12):725-738.
141. Goodwin CW, McManus WF. Viral infections in burned patients. *Immunology*. 1985;12(3-4):8-9.
142. Kelly B, Shimoni T. Reintroducing the Tzanck smear. *Am J Clin Dermatol*. 2009;10(3):141-152.
143. Fidler PE, Mackool BT, Schoenfeld DA, et al. Incidence, outcome, and long-term consequences of herpes simplex virus type 1 reactivation presenting as a facial rash in intubated adult burn patients treated with acyclovir. *J Trauma*. 2002;53(1):86-89.
144. Edgar P, Kravitz M, Heggers JP. Herpes simplex in pediatric burn patients. *Proc Am Burn Assoc*. 1990;22:56.
145. Sen S, Szoka N, Phan H, Palmieri T, Greenhalgh D. Herpes simplex activation prolongs recovery from severe burn injury and increases bacterial infection risk. *J Burn Care Res*. 2012;33(3):393-397.
146. Bourdarias B, Perro G, Cutillas M, et al. Herpes simplex virus infection in burned patients: epidemiology of 11 cases. *Burns*. 1996;22(4):287-290.
147. Guo A, Hu P, Balimane PV, Leibach FH, Sinko PJ. Interactions of a nonpeptidic drug, valacyclovir, with the human intestinal peptide transporter (hPEPT1) expressed in a mammalian cell line. *J Pharmacol Exp Ther*. 1999;289(1):448-454.
148. Sheridan RL, Weber JM, Pasternak MM, Mulligan JM, Tompkins RG. A 15-year experience with varicella infections in a pediatric burn unit. *Burns*. 1999;25(4):353-356.
149. Wurzer P, Guillory A, Parvizi D, et al. Human herpes viruses in burn patients: a systematic review. *Burns*. 2017;43(1):25-33.
150. Ramzy PI, Herndon DN, Wolf SE, et al. Comparison of wound culture and bronchial lavage in the severely burned child: implications for antimicrobial therapy. *Arch Surg*. 1998;133(12):1275-1280.
151. Rogers AD, Deal C, Argent AC, Hudson DA, Rode H. Ventilator associated pneumonia in major paediatric burns. *Burns*. 2014;40(6):1141-1148.
152. Wahl WL, Ahrns KS, Brandt MM, et al. Bronchoalveolar lavage in diagnosis of ventilator-associated pneumonia in patients with burns. *J Burn Care Rehabil*. 2005;26(1):57-61.
153. Samsoondar W, Freeman JB, Coultish I, Oxley C. Colonization of intravascular catheters in the intensive care unit. *Am J Surg*. 1985;149(6):730-732.
154. Maki DG, Jarrett F, Sarafin HW. A semiquantitative culture method for identification of catheter-related infection in the burn patient. *J Surg Res*. 1977;22(5):513-520.
155. O'Neill JA Jr, Pruitt BA Jr, Foley FD, Moncrief JA. Suppurative thrombophlebitis—a lethal complication of intravenous therapy. *J Trauma*. 1968;8(2):256-267.
156. Franceschi D, Gerding RL, Phillips G, Fratianne RB. Risk factors associated with intravascular catheter infections in burned patients: a prospective, randomized study. *J Trauma*. 1989;29(6):811-816.
157. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. MMWR Recommendations and reports. *MMWR Recomm Rep*. 2002;51(RR-10):1-29.
158. Pruitt BA Jr, Stein JM, Foley FD, Moncrief JA, O'Neill JA Jr. Intravenous therapy in burn patients. Suppurative thrombophlebitis and other life-threatening complications. *Arch Surg*. 1970;100(4):399-404.

159. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol*. 2013;108(4):478-498, quiz 499.
160. Nassour I, Carchman EH, Simmons RL, Zuckerbraun BS. Novel management strategies in the treatment of severe *Clostridium difficile* infection. *Adv Surg*. 2012;46:111-135.
161. Neal MD, Alverdy JC, Hall DE, Simmons RL, Zuckerbraun BS. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated *Clostridium difficile* associated disease. *Ann Surg*. 2011;254(3):423-427, discussion 427-429.
162. Anderson DK, Dunn DL, Hunter JG, Matthews JB. *Schwartz's Principles of Surgery*. New York: McGraw-Hill; 2015.
163. Chenoweth C, Saint S. Preventing catheter-associated urinary tract infections in the intensive care unit. *Crit Care Clin*. 2013;29(1):19-32.
164. Leon-Villapalos J, Jeschke MG, Herndon DN. Topical management of facial burns. *Burns*. 2008;34(7):903-911.
165. Templer J, Renner GJ. Injuries of the external ear. *Otolaryngol Clin North Am*. 1990;23(5):1003-1018.
166. Reim M, Redbrake C, Schrage N. Chemical and thermal injuries of the eyes. Surgical and medical treatment based on clinical and pathophysiological findings. *Arch Soc Esp Oftalmol*. 2001;76(2):79-124.
167. Sherman RT. The prevention and treatment of tetanus in the burn patient. *Surg Clin North Am*. 1970;50(6):1277-1281.
168. Larkin JM, Moylan JA. Tetanus following a minor burn. *J Trauma*. 1975;15(6):546-548.
169. Mzezewa S, Jonsson K, Sibanda E, Aberg M, Salemark L. HIV infection reduces skin graft survival in burn injuries: a prospective study. *Br J Plast Surg*. 2003;56(8):740-745.
170. Moreira J. The burden of sepsis in critically ill human immunodeficiency virus-infected patients—a brief review. *Braz J Infect Dis*. 2015;19(1):77-81.

12 Operative Wound Management

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Introduction

Surgery for burn injury is a key component to the multidisciplinary care of the burn patient. It usually involves early procedures such as escharotomy and fasciotomy when indicated, followed by burn excision. Early intervention in the form of early burn wound excision and grafting has dramatically changed the outcome and survival of the burn patient.[1]

Following burn injuries, tissues affected, including skin, promote an inflammatory response at the junction between the eschar and the underlying viable tissue. The presence of microorganisms within the eschar attracts polymorphonuclear leukocytes that release large amounts of proteolytic enzymes and inflammatory mediators. Subsequent enzymatic action results in separation of the eschar, leaving granulation tissue. In large surface area burns, the inflammatory response at the burn injury site develops into a systemic response.

Mediators such as prostanoids, thromboxane, histamine, cytokines, and tumor necrosis factor are produced and released from the burn site. The serum levels of these mediators increase proportionally to the skin surface area of the burn. The hypermetabolic response with increased protein catabolism, increased energy expenditure, weight loss, poor wound healing, and immune depression continues until the outpouring of mediators abate.[2,3]

Advantages of Operative Wound Management

Early excision and skin grafting to achieve wound closure have been shown to reduce infection rates, reduce length of hospital stay, and improve survival in burn patients. Pediatric burn patients in particular have benefited from timely surgical intervention.[4,5] There has been a remarkable increase in the total burn surface area (TBSA) associated with a 50% mortality risk over recent decades. It is now fairly unusual for a child to succumb to burn injuries of any size, even in association with an inhalation injury (Tables 12.1 and 12.2). Early prompt fluid resuscitation, appropriate critical care, nutritional support, and treatment of infections have also played a major role in this achievement.

Early operative intervention, however, remains the major contributor to this major advance in burn care. In 1974, Burke and colleagues reported on the results of total excision of full-thickness burns where allografts were applied to cover burn wounds following excision; allograft rejection was controlled using immunosuppressants.[6]

Improved mortality, shorter hospital length of stay, and fewer metabolic complications were noted when early excision was retrospectively compared with late excision.[7] In another study, 32 children with an average age of 7 years and mean burn size of 65% (TBSA) who underwent either total excision or serial debridement were studied. Mortality, overall blood loss, and cumulative operating time were equivalent.[8] The early excision group, however, had their length of hospital stay almost halved (97 ± 8 days vs. 57 ± 5 days). Since then, hundreds of children with burns of more than 30% TBSA treated with early excision have demonstrated a hospital length of stay of less than 1 day/% TBSA burned.[9]

Tompkins et al. demonstrated that mortality of adult burn patients at Massachusetts General Hospital improved from 24% in 1974 to 7% in the time period from 1979 to 1984 after implementation of prompt eschar excision and immediate wound closure.[10] This study was later expanded to include 85 patients aged 17–55 years.[11] Those patients aged 17–30 years without inhalation injury showed significantly reduced mortality of 9% if treated by early excision, compared to 45% when treated conservatively. Patients with a concomitant inhalation injury or aged over 30 years, however, had no survival benefit from early excision.

In children with burn injuries, Xiao-Wu et al. showed that delays in the excision of extensive burn were associated with longer hospitalization, delayed wound closure, increased rates of invasive wound infection, and increased incidence of sepsis.[12]

Munster et al. demonstrated a statistically significant decrease in hospital length of stay correlating with a decrease in the interval between surgical interventions over a 14-year period.[13] Other variables such as burn size, inhalation injury, and age remained unchanged during the same time period; mortality rate decreased significantly.

Elderly burn patients have also been shown to benefit from early excision. Deitch et al. demonstrated that early surgical excision in patients with an average age of 68 led to 40% reduction in mean hospital length of stay compared to the national average and reduced mortality.[14] Many studies show that early excision can be safely performed in the elderly with clear benefits of reducing hospital length of stay and the number of septic episodes.[15–19]

Hypertrophic scar formation is common following burn injuries, with dark-skinned patients more prone to hypertrophic scar development. However the most important factor in the development of hypertrophic burn scars is delayed wound healing. Deitch et al. demonstrated that in wounds requiring more than 10 days to heal, the risk of hypertrophic scarring is significant and rises to 80% if healing is delayed beyond 21 days.[20] Operative treatment also limits the duration of pain caused by the burn wound.

In conclusion, early burn wound excision is lifesaving, offers improved cosmetic and functional outcomes, and is cost-effective.

Techniques of Burn Wound Excision

EXCISION OF A SMALL BURN

Operative intervention is indicated without delay once the burn injury is determined to be a "deep" injury. Deep burn injuries are clearly either full-thickness or deep partial-thickness burns that are unlikely to heal within 3 weeks and are typically flame or contact burns. Heimbach et al. noted that deep partial-thickness burns did not convert to full-thickness burns when topical antimicrobials were used to control infection.[21] Although these wounds eventually healed after several weeks, they showed persistent blistering, pruritus, hypertrophic scar formation, and poor functional outcomes. These observations prompted a prospective trial of early excision and grafting versus nonoperative treatment of indeterminate depth in burns of less than 20% TBSA.[22] Shorter hospitalization, lower cost, and reduced time away from work, but greater use of blood products were seen in patients treated with early excision. Those patients treated nonoperatively required more late skin grafting to achieve wound closure and developed more hypertrophic scars.

Table 12.1 Mortality Following Burn Over Time for Different Age Groups, Shown as the Burn Size at Which 50% Live or Die

	LA50 (% TBSA)		
Age [years]	**1942–1952**	**1980–1991**	**1992–2004**
0–14	49	98	99
15–44	46	70	88
45–64	27	46	75
>65	10	19	33

TBSA, Percentage of total body surface area burned; *LA50,* lethal burn area for a 50% mortality.
From Branski LK, Barrow RE, Herndon DN, unpublished data, 1992–2004.

TANGENTIAL EXCISION

Tangential excision, as a technique, is the meticulous removal of burned skin while preserving underlying viable tissue. Body contours are better preserved with tangential excision than with fascial-level excision, which removes underlying subcutaneous fat; hence, it is the standard excision technique for burns.

Tangential excision was originally described by Janzekovic, who observed that deep skin graft donor sites could be grafted with thinner split-thickness skin grafts taken from another area.[23] Later she extended this concept to partial-thickness burns by repeatedly excising thin layers of the burned skin until viable tissue was reached (Fig. 12.1). Then split-thickness skin grafts were immediately applied.

The technique of tangential excision and autografting of partial-thickness burns was a major advance in burn care at the time. Prior to its introduction, only full-thickness burns were excised, including subcutaneous fat and accompanying lymphatics down to the underlying layer of investing fascia (Fig. 12.2). Janzekovic analyzed the results of the use of tangential excision in more than 2000 patients. She found that, compared to fascial excision, hospital length of stay, pain, and reconstructive procedures were decreased.[24]

A number of different instruments can be used to perform tangential excision of the burn wound. The Goulian knife, Watson knife, and the Versajet Hydrosurgery System are used for tangential excision (Fig. 12.3).[25] Deep partial-thickness burns are debrided down to white, viable dermis with punctate bleeding. In full-thickness burns, excision continues layer by layer until viable subcutaneous tissue with a yellow glistening appearance is encountered. Dull yellow color, purple discoloration, or thrombosed vessels indicate nonviable tissues that are not suitable for grafting and require deeper excision (Fig. 12.4). When excision is performed on limbs with a pneumatic tourniquet, these features are particularly important.

There are noninvasive imaging tools available for predicting burn depth and healing time in adult burns. These include laser Doppler imaging (LDI), which is the current gold standard; infrared thermography (IRT); and spectrophotometric intracutaneous analysis (SIA). LDI uses a low-intensity laser beam to scan across the tissue surface. Laser is both absorbed and scattered by tissue matrix and the blood flow in the vessels. Flux is then determined by processing the photocurrent resulting from both absorbed and scattered light. The device generates a colored map of the

Table 12.2 Pediatric-Specific Mortality Rates Over Time; Near-Total Early Excision Is the Basis of These Excellent Results.

	MORTALITY SORTED BY BURN SIZE (% TBSA)							
Years	**<20%**	***n***	**21%–40%**	***n***	**41%–60%**	***n***	**61%–100%**	***n***
1980–1985	<0.1%	889	1%	230	8%	105	33%	95
1986–1990	<0.1%	571	1%	224	4%	117	19%	88
1991–1995	<0.1%	522	2%	192	8%	94	20%	78
1996–2000	<0.1%	635	1%	222	3%	133	19%	114
2001–2004			2%	83	2%	121	26%	91

n, Total number of patients admitted with respective burn size in given period.
Mortality and pediatric burn patients, Shriners Burn Institute, Galveston, Texas.

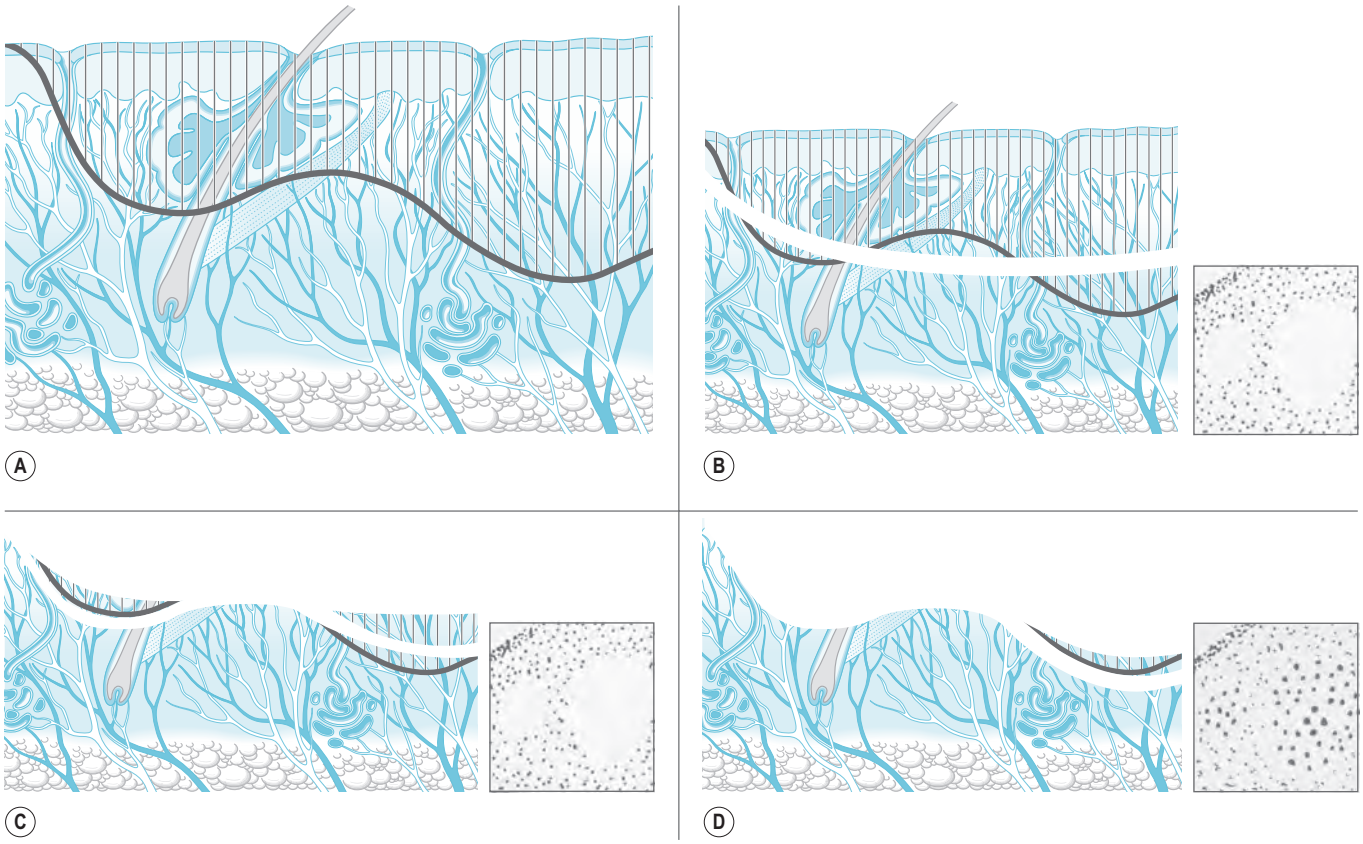

Fig. 12.1 (A–D) Schematic representation of tangential excision; sequential slices are taken until punctate hemorrhage is evident (From Janzekovic Z. A new concept in the early excision and immediate grafting of burns. *J Trauma.* 1970 Dec;10(12):1103–1108.)

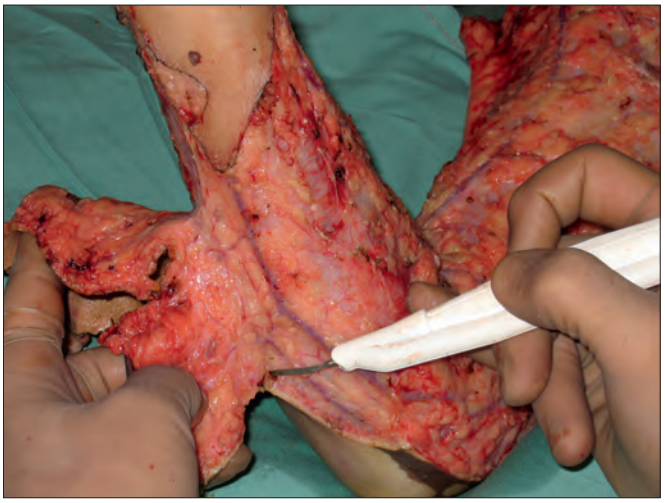

Fig. 12.2 Fascial-level excision using cutting diathermy and an incorporated smoke evacuator.

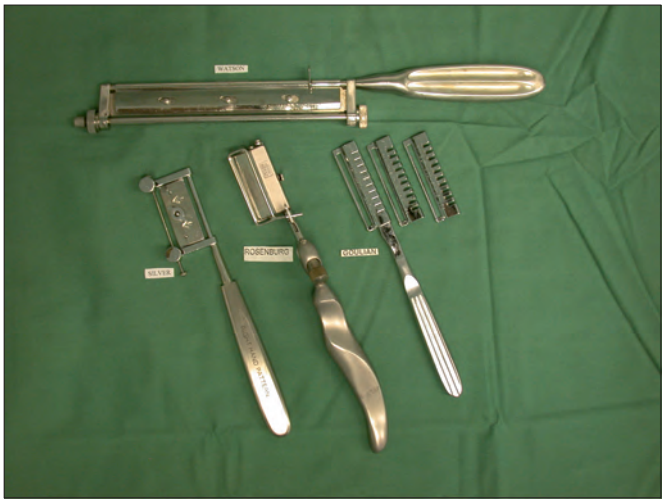

Fig. 12.3 A selection of hand-cutting dermatomes available for use for tangential excision. Most have the ability to set the aperture to the desired depth, while the Goulian has a large series of blade changeable guards.

wound correlating with the extent of the injury. LDI can be a useful tool in surgical decision-making in indeterminate-depth burns.[26]

IRT uses the heat signature resulting from tissue perfusion to predict the depth of burn injury. Superficial burns retain a bright color compared to the surrounding normal tissue due to increased perfusion, whereas deeper burns appear darker in color due to decreased or lack of perfusion.[27,28] SIA is used in the diagnosis of pigmented skin lesions such as melanoma. It uses spectrally filtered images using polarized light ranging from 400 to 1000 nm. A complex set of mathematical algorithms determines the melanin and hemoglobin content of the epidermis and papillary dermis, then presents them in high-resolution images.

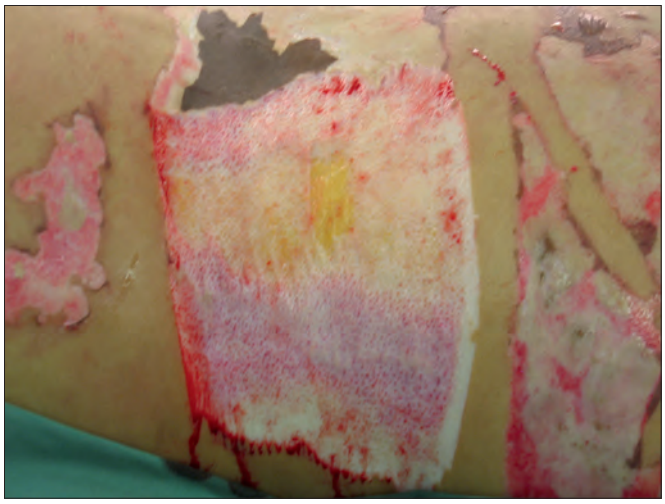

Fig. 12.4 A deep flame burn on the left thigh that is in the process of being debrided. The wound has been tumesced with 1 : 1 000 000 epinephrine in normal saline and shows minimal bleeding. The lower part of the wound demonstrates residual dead dermis with dull appearance and staining from lyzed cells. The area just above demonstrates shiny yellow, living fat and (mostly) surviving shiny white dermis with a few patches needing another slice.

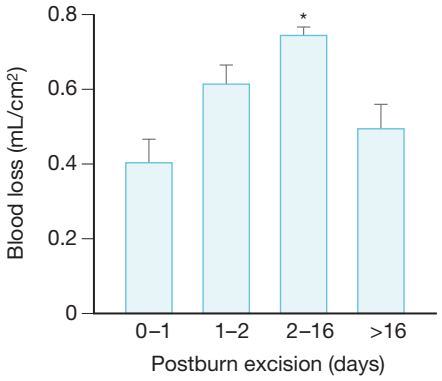

Fig. 12.5 Blood loss is almost halved by operating within 24 hours of injury. (From Desai MH, Herndon DN, Broemeling L, Barrow RE, Nichols RJ Jr, Rutan RL. Early burn wound excision significantly reduces blood loss. *Ann Surg.* 1990 Jun;211(6):753–759; discussion 759–762.)

The additional analysis of pigment available using SIA may more accurately indicate the depth of burn compared with perfusion alone.[29]

Ultrasounds with frequencies higher than 20 MHz have shown promising results in quantitative assessment of burn depth in animal models.[30] Currently only LDI has been validated for use in burn depth assessment.[29] It has been shown to reduce wound healing time in patients requiring surgery with a potential cost saving of about $1200 per patient.[31] Unfortunately LDI costs in excess of $70,000 in addition to annual servicing costs.

FASCIAL EXCISION

Skin and subcutaneous tissue are excised en-bloc using electrocautery in fascial excision. This involves excision of the full thickness of the integument, including all subcutaneous tissues down to the investing deep fascia. It is usually performed to reduce blood loss in extensive burns or in cases of severe infection to control the source of infection.

Fascial excision can limit the amount of blood loss because control of the deeper perforating vessels is achieved during the excision, bypassing the extensive capillary network present in the skin and subcutaneous tissue. Fascial excision is also required for areas where subcutaneous tissue has been involved in the burn injury. The advantages of this technique include improved graft take on fascia and reduced blood loss.

Fascial excision is also indicated in cases of life-threatening invasive wound infection or sepsis, particularly fungal infections such as *Aspergillus* and *Mucor*, and in cases of failed graft take in extensive burns in critically ill patients. Episodes of sepsis lead to ischemic necrosis of the subcutaneous fat due to poor peripheral perfusion and microvascular stasis. This represents a considerable problem in patients with extensive burns leading to late graft loss, and the ischemic areas are transformed into portals for invasive wound infection. The disadvantages of fascial excision are lymphedema due to the interruption of the subcutaneous lymphatics and contour deformities due to the loss of subcutaneous fat.

CONTROLLING BLOOD LOSS DURING BURN EXCISION

Excision of large burns can result in considerable, if not massive, blood loss. Tangential excision can lead to large blood loss unless measures are taken to limit hemorrhage. The simplest measure is to operate within 24 h of the burn injury. Vasoactive metabolites, in particular the potent vasoconstrictor thromboxane, are in abundance during this time to limit blood loss.[32] Desai et al. demonstrated in a prospective trial of 318 pediatric patients with burns of more than 30% TBSA that early excision of burns is associated with an overall reduction in blood loss. The average blood loss per surface area excised (mL/cm^2) was compared at various post-burn excision time points. The total blood loss during excision performed within the first 24 hours after burn was 0.4 mL/cm^2 excised, compared to 0.75 mL/cm^2 excised if performed between days 2 and 16 post burn. The blood loss dropped to 0.49 mL/cm^2 excised if the procedure was performed after the 16th day. Overall mortality was 5% for an average burn size of 60% TBSA. Early excision had no adverse effect on mortality. Very early excision led to a halving of blood loss for both large and small burns[32,33] (Fig. 12.5).

Other factors associated with increased blood loss during excision of burns are old age, male gender, larger body size, large full-thickness burns, high wound bacterial count, total area excised, and operative time.[33]

Several techniques to reduce blood loss during burn wound excision can be employed in the operating room. Adjunctive measures to limit blood loss include tourniquets for the extremities, pre-debridement tumescent infiltration with epinephrine solutions, topical application of epinephrine 1: 10 000–1: 20 000, fibrin sealant, autologous platelet

gel, calcium-enriched alginate sheets, and immediate bandaging with delayed grafting.

The application of tourniquets to the extremities is a very effective method of minimizing blood loss, especially for excision of burns involving hands and digits. As with tumescent infiltration, the absence of bleeding can make the estimation of the right depth of excision difficult. To counteract this, the tourniquet can be released briefly to check the adequacy of excision and then reinflated. The larger vessels are controlled by electrocautery or ligation and the wound is covered with sheets of calcium alginate or sponges, which are soaked in epinephrine solution. Following the release of the tourniquet, the limb should be elevated for about 10 min prior to graft application.

Tumescent solution made of epinephrine containing saline can be injected into the burn wound prior to excision. This technique is particularly useful for burn excision of areas such as the trunk, scalp, and face; 1.6 mL of 1 : 1000 epinephrine (0.8 mL in pediatric patients) is added to 500 mL of 0.45% normal saline solution. The resulting local vasoconstriction will minimize blood loss, and one-way syringes, such as the Multi-Ad Fluid Dispensing System or a pneumatic infuser, can make the injection process easier (Fig. 12.6).

Monitoring the patient's hemodynamics is necessary because epinephrine may cause tachycardia and hypertension, which can worsen bleeding. Another drawback of this technique is that the lack of bleeding from the wound bed may make the adequacy of excision difficult to assess.

When dealing with large areas of disrupted capillaries, one of the most effective ways to safely limit blood loss is rapid excision followed by coverage with epinephrine-soaked sponges or gauze and compressive bandages.

Delayed grafting after excision is used in some centers to limit blood loss. In case of delayed skin grafting, the wound bed needs to be kept moist and clean prior to skin grafting. The wound can be covered with bulky cotton dressings with tubes through the dressing to the wound surface for continuous or intermittent irrigation with antibiotic solution. The patient returns to the operating room within 24 h and undergoes a second procedure of procurement and application of skin grafts. This may be a practical approach in cases of large surface area excision, where coagulopathy can develop due to large blood loss or hypothermia. The authors of this chapter adhere to a hemoglobin (Hgb) threshold of 7 for transfusion. One study suggested a possible decrease in infection rate when compared to a more liberal transfusion strategy.[34]

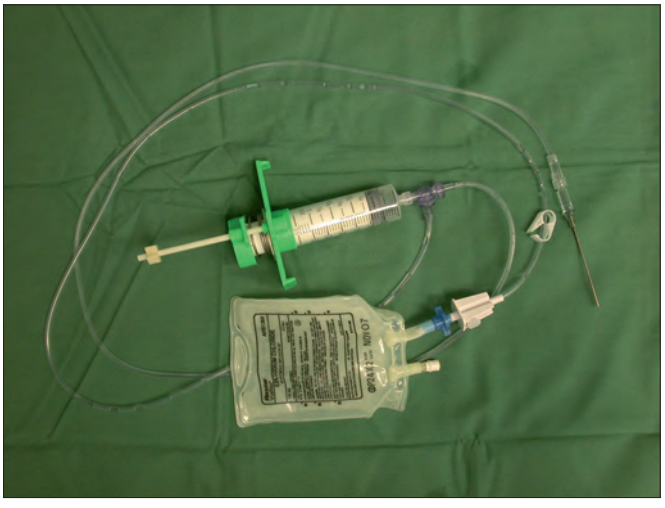

Fig. 12.6 An infuser device.

TECHNIQUES OF WOUND CLOSURE

Once procured, the autograft skin can be used in different ways depending on the size of body surface area burned that requires grafting.

Autografts are classified as full- or split-thickness depending on the depth of dermal layer included when harvesting the skin. Full-thickness autografts have better cosmetic results and reduced scarring compared to split-thickness autografts because the dermis provides flexibility and elasticity. The main caveat is that the increased amount of dermis in the full-thickness autograft can compromise its own viability during the imbibition, inosculation, and neovascularization phases of graft take. The donor site completely devoid of dermis must be closed primarily or grafted. Therefore, split-thickness skin grafts are mainly used in the treatment of extensive burn injuries.

If the burn is small, skin grafts can be applied without meshing as a "sheet." The advantage of nonmeshed skin is better cosmetic outcomes. The disadvantage is the possible accumulation of seroma or hematoma underneath the skin graft that can compromise the apposition of the skin graft to the wound bed. Seroma or hematoma should be identified and removed by aspiration with a 25- or 27-gauge needle. The skin graft can be secured to the wound bed with quilting sutures or the application of a bolster dressing, which can reduce shearing of the skin graft. These grafts are best laid perpendicular to the long axis of limbs, particularly across joint flexural creases, which is in line with the general rule of placing potential scars perpendicular to the dominant muscle contraction in the area, thus reducing the degree of contracture if it occurs. Possible exceptions are the dorsum of the hand and forearm, where one may contend that longitudinally placed grafts are cosmetically superior.

In large burns where donor sites are limited, autografts are usually meshed. This allows the autograft skin to be expanded to cover a wider area compared to its original size. The most commonly utilized mesh ratios are 2 : 1 and 4 : 1, although other ratios of expansion can be employed. The main advantages of 2 : 1 meshed autograft skin is the ease of handling and application and the extensive network of slits that allows drainage of seroma or hematoma. The main disadvantage is that the interstices leave a visible pattern once healed. Much larger areas can be covered when autografts are meshed 4 : 1 or greater and widely expanded. This widely meshed skin graft requires an overlay coverage of nonexpanded allograft skin to decrease the risk of graft loss, and this is applied over the autograft skin in a sandwich pattern (Fig. 12.7).[35] The large interstices, which require a considerable amount of time to heal by epithelialization; the need for an allograft skin overlay; and the less desirable cosmetic result limit the use of 4 : 1 meshed autograft skin to massively burned patients. Even in massive

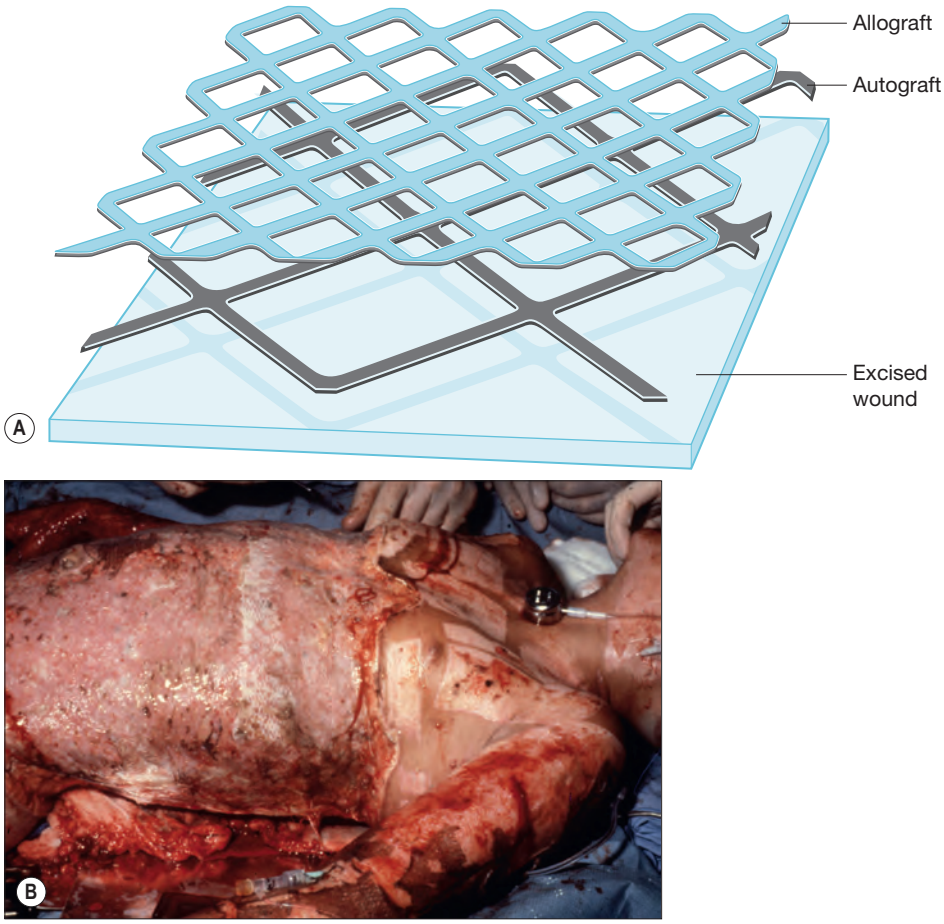

Fig. 12.7 (A) Schematic representation of "sandwich" technique of allograft overlay. (B) Sandwich technique on the chest of a boy with massive deep burn having a return surgery a week after sandwich grafting. Most of the (fresh) allograft has vascularized with one piece obviously whiter than the rest. The mesh pattern of the underlying widely meshed autograft is visible. (From Alexander JW, MacMillan BG, Law E, Kittur DS. Treatment of severe burns with widely meshed skin autograft and meshed skin allograft overlay. *J Trauma.* 1981 Jun; 21(6): 433–438.)

burns, the face, neck, and hands are still grafted with nonmeshed split-thickness skin graft due to the unacceptable outcome of using widely meshed skin grafts in these areas.

The Meek technique, which was later modified by Kreis et al., is another tool to cover extremely large burn surface areas.[36,37] It uses autografts cut into small squares with the aid of a dermatome and a cork board. The squares are then pressed onto prefolded pleated gauze that is expanded in all four directions, leaving uniformly distributed islands of autograft skin that are then applied to the wound bed. Ratios of expansion can vary from 3 : 1 to 9 : 1. This technique has similar disadvantages to 4 : 1 meshed autografts.

Advances in Wound Closure

DERMAL REPLACEMENT

The flexibility, elasticity, and strength of normal skin are provided mainly by the dermis. Excision of full-thickness burn removes the entire dermis, and the lack of the dermal layer prevents the healed skin from having the properties of normal skin. The use of dermal replacements in the treatment of burns can provide the highly desired characteristics of normal dermis. Integra is a dermal substitute composed of a porous matrix of cross-linked bovine collagen and glucosaminoglycans providing a scaffold for cellular invasion and capillary growth. It is applied to the wound bed following burn excision, and the matrix is fully incorporated into the wound bed in 2–3 weeks; then, thin split-thickness autograft skin is applied. Except for a possible increased risk of infections, the use of Integra is safe and effective.[38] Skin graft take is usually aided by the use of negative-pressure wound therapy such as VAC Therapy (Fig. 12.8).[39]

Another dermal analog available for the treatment of full-thickness burns is Alloderm, consisting of cadaveric dermis devoid of cells and epithelial elements. Its applications are similar to other dermal analogs, and it has shown favorable results.[40]

CULTURED EPIDERMAL AUTOGRAFTS

Cultured epidermal autografts (CEA) remain an important tool in the management of patients with massive burns. In full-thickness burns involving more than 90% TBSA, it may be the only treatment available, given that procurement of

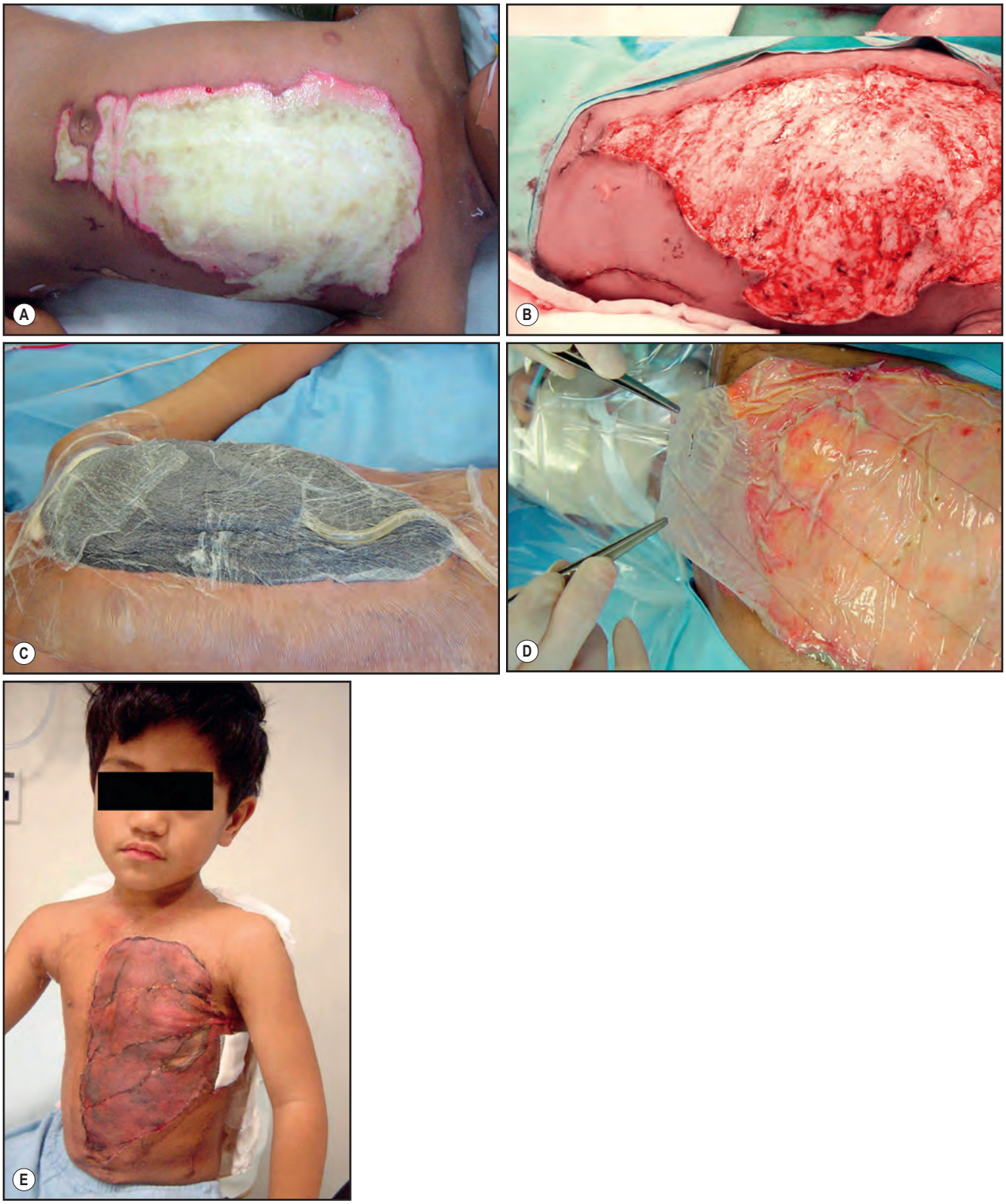

Fig. 12.8 (A–C) Deep flame burn on a boy's chest treated with early excision and Integra with VAC. (D) The silicone layer being removed on day 12 ready for thin grafting with well-vascularized dermal template underneath. (E) The pleasing final result.

the unburned skin will not be sufficient to cover the patient's wounds.

Munster has shown that the use of CEA in the massively burned patient reduced mortality.[41] CEA requires two 2 × 6-cm full-thickness unburned skin specimens. The skin is processed and cultured in vivo in the presence of murine fibroblasts to promote growth. The culture is expanded over a period of 3 weeks until thin sheets of keratinocytes, 2–8 cells thick, are available for grafting. Shearing and blistering are common problems for many months following application. The long-term survival of CEA in extensively burned patients has been reported at between 5% and 50% in the literature, and CEA applied to areas such as the back, buttocks, and posterior lower extremities are prone to shearing and graft loss. Barret et al. compared the use of CEA with widely meshed autograft skin and allograft skin overlay in a group of children with more than 90% TBSA.[42] Once healed, the CEA has a better cosmetic result than healed 4:1 meshed autograft skin but is associated with longer hospital length of stay and increased number of reconstructive procedures. Despite these limitations, including substantial cost, series from different burn centers have shown promising results when used in conjunction with allograft dermis. Sood et al. reported a graft take rate of greater than 72%.[43]

Tissue engineering technology is a rapidly advancing field where fetal skin constructs have been successfully introduced [44] and reproduced in vitro using genetic replication.[45] Bilaminar cultured skin substitutes showed promising results,[46] and, recently autologous engineered skin substitutes reduced mortality and requirements for donor skin in full-thickness burns of greater than 50% TBSA.[47]

SKIN PROCUREMENT

Many factors are considered when choosing the best donor site for skin grafting. Donor sites represent new wounds that would add significant morbidity to the patient; patients usually complain of more pain at the donor site compared to the burn wound or graft site. Whenever possible, skin grafts should be obtained from donor sites matching the color of the recipient area. The face and neck should be grafted with skin obtained from the area above the line of the nipple for the best color match. Thigh, hip, and back are commonly used as donor sites because the skin is flat for easy procurement, and scars are easily covered under clothing. The scalp may represent an ideal donor site because it is associated with less pain and faster healing, given the rich blood supply. The subsequent scar can be hidden after the regrowth of hair.

Good quality skin grafts of consistent depth are obtained using an electric or pneumatic-powered dermatome. The depth of the skin harvest can be precisely adjusted, with thickness usually between 0.006 and 0.018 inches.

Patients with extensive burns have few potential available donor sites. Anatomical regions that are usually spared and represent viable options for skin graft are the axilla, the mons pubis, and the scrotum. Given the irregular topography, tumescent fluid can be infiltrated to facilitate skin graft procurement.

In extensively burned patients, multiple operations are required to achieve complete wound coverage since donor sites are limited. A limiting factor to repeat grafting is the healing time of the donor sites. Donor site healing is a result of migration and proliferation of the epithelial cells from hair follicles, sweat glands, and sebaceous glands within the dermis. Early re-epithelialization after a week can allow reprocurement of thin split-thickness skin grafts from donor sites.

MANAGEMENT OF DONOR SITE

Careful management of the donor site is required to expedite wound healing. Smaller donor sites can be treated with occlusive or adherent dressings such as Opsite or Biobrane. Another technique is the use of alginate sheets or hydrocolloid dressings, which produce a moist environment that promotes healing and diminishing pain. The wounds can be also covered with gauze impregnated with an oil-based ointment. The most common examples are Xeroform or locally prepared dressing containing olive oil, petrolatum, lanolin, and the chemotactic agent "Sudan red." Silver-impregnated dressings such as Acticoat, Mepilex Ag, or Aquacel Ag seem to diminish bacterial overgrowth and can be used directly on the donor site. The healing time of donor sites depends on the depth of skin graft, vascularity of the donor site, wound management, and general condition of the patient.

DRESSINGS

After burn excision and skin grafting, the grafts are covered with nonadherent dressings. At our institution, gauze impregnated with a petrolatum-based ointment and a mixture of an antibacterial (Polymyxin/Bacitracin) and an antifungal (Mycostatin) is used. This is followed by the placement of a layer of fluff gauze and an elastic bandage. With areas of the body prone to shearing, such as the back and axilla, the application of a bolster dressing to protect the skin grafts can be beneficial. The application of negative-pressure wound therapy can also be useful in splinting and protecting the grafts. Dressings are usually removed on postoperative day 3. This time frame is normally sufficient to allow for adherence of the skin graft to the wound bed.

TEMPORARY SKIN SUBSTITUTES

Providing wound coverage with skin substitutes, even if it is temporary, has many advantages. Wound coverage prevents water and electrolyte losses as well as tissue desiccation, therefore maintaining a moist environment that allows faster epithelial cell migration and proliferation. Other benefits include reducing pain, creating a barrier to bacterial contamination, and preventing protein loss. Available temporary skin substitutes are either biological, such as allografts, xenografts, or amniotic membrane, or artificial, such as Biobrane.

Allografts remain an effective temporary burn wound coverage after excision if autograft skin is not available.[48] Allograft skin can be stored in a cryopreserved state for an extended period of time and become adherent and vascularized when applied to a viable wound bed. This process can also serve as a test for wound bed viability after burn excision, with immune rejection occurring

3–4 weeks after application. When allografts are used as a temporary coverage to the face and hands, they should be applied as sheet grafts. This prevents the formation of granulation tissue between the interstices, which can cause scarring and poor cosmetic outcome following definitive autografting.

Xenografts are another option for temporary wound coverage. Only porcine xenograft skin is currently available for clinical use.[49] Their main application is on partial-thickness burns following superficial debridement, as well as on donor sites. As with allografts, xenografts become adherent and provide the benefits of temporary wound coverage, such as pain control, while the underlying wound re-epithelializes, but the xenograft does not vascularize.

Amniotic membrane can also be used to provide temporary coverage to superficial burns. Given its flexibility and pliability, amniotic membrane is useful for application on irregular surfaces such as the face. Despite not reducing healing time or scarring, it provides some of the benefits of wound coverage and reduces the number of dressing changes required until healing is achieved.[50]

Management of Specific Types of Burns

SCALD BURNS

Small or moderate size scald burns have been shown to be the exception to the general rule of early excision. Young children who had scald burns up to 20% TBSA required less area to be excised and had smaller blood loss if operated on in the second or third week post burn.[51]

A subsequent prospective trial randomized 24 children to early or late excision if their scald burn was of clinically indeterminate depth.[52] There was no significant wound infection or sepsis resulting from late excision. Only half of the delayed excision group ultimately required surgical intervention, and a significantly smaller area of excision was necessary.

In light of the previous evidence, children with scald burns of less than 20% TBSA can be appropriately treated with a topical antimicrobial such as silver sulfadiazine for about 2 weeks. This approach needs to be balanced with the knowledge that the longer a wound remains open, the greater the inflammatory response and subsequent scar formation. A number of techniques are available to cover the partial-thickness burn. When successful, they have the advantage of reducing the pain associated with frequent dressing changes. Biobrane is a useful dressing for smaller and more superficial wounds.[53]

At the time of the first wound dressing application, all loose skin and blisters are removed to leave a clean, moist surface. Biobrane is a nylon/silicone bilaminated composite skin substitute that becomes adherent to the exposed dermis, thereby acting as a neo-epidermis. Lal et al. reported no increase in infection rates using Biobrane.[54] Infections occur rarely as a result of nonadherence and accumulation of fluid. Other alternatives include the use of silver-impregnated dressings such as Acticoat, allografts, and xenografts.

EXTENSIVE BURNS

Patients with burns of greater than 40% TBSA pose unique challenges with increased demands for donor sites, which are of limited availability. Ideally, near-total excision should be completed as soon as possible in the first few days following injury, definitely within a week. The back, buttocks, and posterior thighs are covered with autograft skin taken at thickness between 0.008 and 0.010 inch and meshed at an expansion ratio of 4:1. Allografts are the best option to apply as an overlay to protect widely meshed autografts.

Consideration needs to be given to the use of dermal replacement therapies (e.g., Integra). Dermal replacements are an expensive option but produce good results in relation to scarring. Integra is a bilaminar composite that has a neo-dermis of bovine collagen held in a matrix pattern of shark cartilage chondroitin-6-sulfate. A layer of rubberized silicone is press sealed as a top layer. The abdomen, anterior thigh, forearm, leg, and male chest are sites where Integra can be easily applied (Fig. 12.9).

. The neo-dermis is vascularized from the underlying wound bed, and the process takes 2–3 weeks to complete. The neo-dermis often develops a pink or plum color due to staining of the matrix during the vascularization process. If hematoma or seroma develops, it can be aspirated with a 27-gauge needle, or the overlying Integra is incised, the hematoma removed, and the edges are stapled down.

The neo-dermis is "ready" or adequately vascularized when it has a straw color. Close inspection under magnification will reveal widespread telangiectasia. The second-stage operation involves gentle removal of the silicone layer and application of 0.006-inch autograft skin, which can be meshed up to an expansion ratio of 3 :1. CEA has been used as epidermal cover for vascularized Integra neo-dermis.[55]

Debate continues regarding the role of Integra in wound coverage of patients with burns of greater than 70% TBSA. The incidence of failure due to infection rises dramatically as the burn size approaches greater than 75% TBSA. The first priority remains excision of all the burn wounds, wound coverage with autografts, and application of allografts to the remaining areas, with a return to the operating room planned once used donor sites are healed.

The Operating Room

The burn operating room is usually an extension of the burn intensive care unit. Large, heated, humid, and well-lit rooms are ideal for burn surgery. The procedures are long, intense, and require multiple individual setups for different types of equipment and instrumentation.

A very important perioperative issue for safe management of a patient undergoing extensive burn excision is the maintenance of body temperature. The patient is usually completely exposed with little intact skin, particularly after procurement of donor skin, leading to rapid heat loss. A number of strategies can be used to counteract heat loss and maintain normothermia. The operating room should be warmed to 32°C, since the latent heat of water evaporation is 31.5°C. Above this temperature, the energy source for evaporation will come from the environment rather than the patient. Radiant heaters are useful in perioperative thermoregulation. Other adjunctive measures include the use of space blankets, aluminum foil coverings, plastic

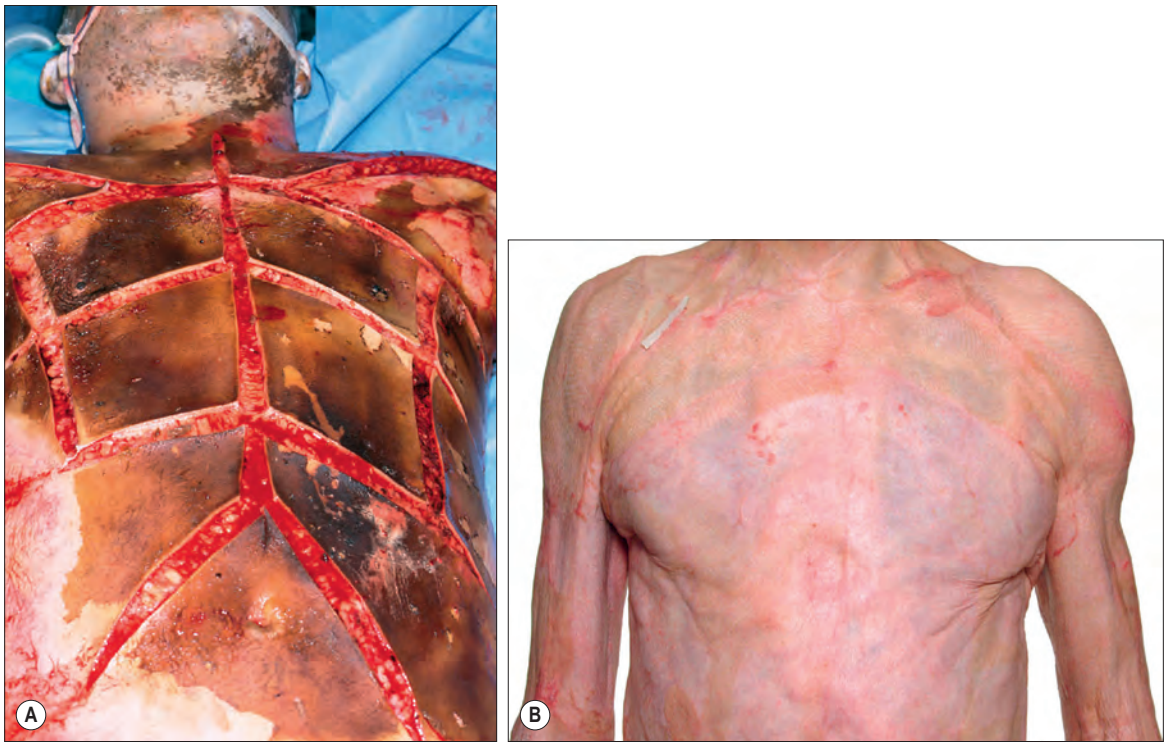

Fig. 12 9 (A,B) High-voltage electrical flash burn treated by fascial excision and Integra. Flat anterior surfaces are particularly amenable to use of Integra.

sheets over the head and face, and heated intravenous fluids at 38°C. Repeated applications of warm sterile blankets, forced air warming systems, warm irrigation fluids, and active heating via either infrared or ceramic heaters have also been used.

The ideal operating room environment should allow only minimal evaporative loss from the patient. Reliable vascular access is required, and the central access lines should be sutured securely to prevent dislodgment during patient positioning.

The Operation

At our institution, excision commences with the patient in the prone position, during which excision of the shoulders, back, buttocks, and upper thighs is performed. Wide-meshed autografts with allograft overlay are applied. If insufficient autografts are available, the excised wound is covered with allografts. Other alternatives include skin substitutes such as Integra, xenografts, or allografts. Dermal replacement materials are prone to failure due to increased rates of infection in extensive burns, particularly on dorsal surfaces, but can be applied selectively on ventral surfaces. Sutures are inserted in a row along the posterior axillary lines and tied over the bulky gauze dressing as a bolster to prevent shearing of skin grafts on the back and buttocks. The patient is then placed in the supine position

As soon as donor sites are healed, patients return to the operating room for further autografting and replacement of nonadherent allografts or infected skin substitutes. In children with considerably extensive burns, treatment with recombinant human growth hormone (GH) demonstrated donor site wound healing was accelerated by 25%. GH-treated patients required less infused albumin to maintain normal serum levels, and this was an indication of the net positive protein balance.[56] The usual hospital length of stay of 42 days for a 30 kg patient with a 60% TBSA burn was reduced to 32 days. This remarkable decrease in length of hospital stay produced a net saving of 15% in total hospital costs, and mortality was reduced from 45% to 8%.[57] Although it must be acknowledged that two European studies in critically ill adults of mixed etiology showed increased mortality among the GH-treated groups, this experience has not been repeated in the extensively burned pediatric population in North America.[58] Other anabolic agents have shown promise as a means of stimulating wound healing in severely injured catabolic burn patients.[59] Oxandrolone 20 mg/day has demonstrated a positive effect on protein kinetics and wound healing in clinical trials.[60,61] In oxandrolone-treated severely burned adults, donor site healing was accelerated by 20% compared to nontreated patients.[59] Although these pharmacological agents provide great support to the extensively burned patient, they are only an adjunct to early near-total excision and prompt wound coverage.

Operative Management of Burns Involving Special Areas

THE HAND

Survival after serious burns has improved dramatically over the past 30 years; however despite generally satisfactory long-term quality of life, many patients will have significant physical disabilities. Many of these disabilities can be traced to compromised hand function following severe burn

injuries. If optimal function is to be restored after extensive burn injuries, proper care of the injured hand is essential. These early efforts should be directed at preservation of tissue, maintenance of normal hand anatomy, and development of a strategy for wound closure.

Escharotomy and Fasciotomy

A critical part of the initial care of hand burn is to maintain soft tissue perfusion in the acute phase following the burn injury. Decompression of high compartment pressure caused by burned skin and tissue edema is an area in which early surgical intervention can produce a remarkable difference to the final outcome of hand function. Hands at risk of ischemia include circumferential or near-circumferential burns, very deep burns, and any electrical injuries involving high- or intermediate-range voltage. It is important to elicit clinical signs of ischemia subtler than the loss of palpable pulse at the wrist. Mean arterial pressure in the central vascular system is three times higher than capillary pressure, and blood flow can be maintained in these vessels despite impaired flow in distal soft tissues. If the hand is warm, soft, and has pulsatile flow detectable by Doppler in the palmar arch and the digital vessels, and it has a normal pulse oximetry signal at the tip of the digit, then flow is adequate. As flow becomes progressively impaired, the hand will become firm and cold, with decreased Doppler flow and loss of the pulse oximetry signal. Decompression should be performed to prevent otherwise avoidable ischemic injury as a result of compartment syndrome. Pressure measurement confirmation is generally not required if serial examinations suggest diminished tissue perfusion.

Escharotomy should be performed using electrocautery. Longitudinally oriented medial and lateral incisions are made through eschar on the arm and forearm, stopping at the metacarpophalangeal joints of the first and fifth digits (Fig. 12.10A).

The hand is then re-examined for perfusion prior to performing hand and digital escharotomies. If blood flow is restored adequately following arm and forearm decompression, additional escharotomy may be unnecessary.

The efficacy and safety of digital escharotomies are debatable. One study demonstrated a reduced incidence of amputation if digital escharotomies were performed on circumferentially burned digits.[62] However, particularly in small children, improperly performed digital escharotomies can result in significant injury, and therefore caution must be used. When digital perfusion remains inadequate despite decompression of the arm, forearm, and hand, escharotomies of full-thickness burns of the digits should be performed. Longitudinal incisions are carefully made with pinpoint electrocautery mid-laterally between the neurovascular bundle and the dorsal extensors, avoiding both structures. A single longitudinal incision is made on the radial aspects of the thumb and little finger and the ulnar aspects of the digits. This places the incisions on the side of the digit with the least functional importance should the digital nerve be exposed by separation of edematous tissue after escharotomy. The central digital incision can be extended proximally onto the dorsum of the hand between the metacarpals to enhance decompression (Fig. 12.10B).

The line of incision along a given digit can be found by putting the fingers in maximal flexion, marking the lateral extensions of the flexor wrinkles and completing them to a continuous line (Fig. 12.10C).[63] Meticulous hemostasis is maintained throughout the procedure, and the outcome of decompression is confirmed using Doppler.

Escharotomy can generally be performed at the bedside or in the emergency department under moderate sedation supplemented with sub-eschar injections of local anesthetic. Some patients will require general anesthesia in the operating room for the procedure to be performed appropriately.

Fasciotomy might be required for edema developing within the fascial compartments of the forearm and hand. Clinically this is often seen following high-voltage electrical injuries or exceptionally deep thermal injuries. Upper extremity fasciotomy may include volar and dorsal decompression, carpal tunnel release, and dorsal hand fasciotomy. A curvilinear incision is ideal for volar exposure of the compartments of the forearm. This approach allows access to all individual muscle bundles in the volar forearm. It also allows decompression of the carpal tunnel through a palmar extension of the incision, and creates a well-vascularized skin flap to cover the median nerve at the wrist

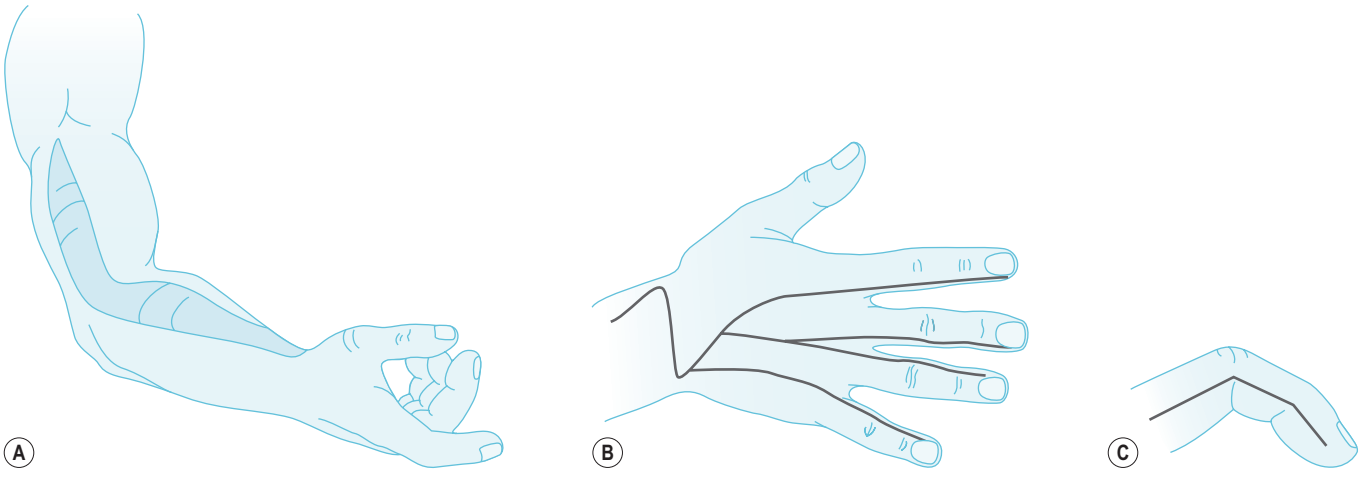

Fig. 12.10 (A) Arm escharotomy. (B) Hand escharotomy. (C) Finger escharotomy. (From fig. 61.6ABC in Green DP, Pederson WC, Hotchkiss RN, et al. ed. *Green's operative hand surgery*, Philadelphia: Elsevier/Churchill Livingstone; 2005:2164.)

upon completion of the fasciotomy. When needed, straight linear incisions are adequate for decompression of the dorsal aspect of the forearm, and inter-metacarpal incisions on the hand allow decompression of the intrinsic muscles of the hand.

Techniques of Excision and Grafting

It has become increasingly clear that allowing hand injuries to heal by secondary intention over the course of many weeks produces poor long-term aesthetic and functional results.[64] Usually surgery is indicated for any deep dermal or full-thickness hand burn that will not promptly heal within 3 weeks. This need is apparent to an experienced examiner within 5 days of the injury (Fig. 12.11).

The skin on the dorsum of the hand is much thinner than the palmar skin. There is a general consensus that earlier surgery is associated with a better functional outcome and a reduced need for reconstructive procedures in the future.

Different options for wound coverage include split-thickness autografts, full-thickness autografts, and groin or abdominal flaps. Split-thickness nonmeshed autograft is the optimal coverage for most hand burns. Full-thickness grafts are ideally reserved for palmar surface burns, particularly deep wounds of limited extent, or for reconstructive operations. Groin and abdominal flaps can be useful when managing isolated injuries with exposed tendons without paratenon, exposed bone without periosteum, or exposed neurovascular bundles.

Deep partial and full-thickness hand burns generally require tangential excision and autografting. These procedures are ideally performed under a pneumatic tourniquet to reduce blood loss, and tangential excision is performed until a bed of viable tissue is encountered. Viability is recognized by the appearance of a pearly white moist dermis, punctate bleeding, or the presence of bright yellow subcutaneous fat without thrombosed small vessels or extravascular blood staining. Recognition of viable tissue in an exsanguinated extremity under tourniquet is an acquired skill that greatly facilitates low-blood-loss excisions.

The hand is then wrapped in epinephrine-soaked gauze prior to deflation of the pneumatic tourniquet. After 5–10 min to allow for spontaneous hemostasis, definitive hemostasis is secured with careful use of pinpoint electrocautery. The hand is covered with sheet autograft skin. Finally grafted hands are covered with a gentle compressive gauze wrap and placed in a thermoplastic splint in position of function. Hands are elevated and immobilized for 3–4 days prior to reinstituting passive and active hand therapy.

Only about 15% of palmar burns require grafting. Because the palmar skin is much thicker than the dorsal skin, it is not uncommon to wait for 2–3 weeks before a decision to graft is made. Palmar burns that require skin grafting are usually covered with thick, split-thickness sheet autografts if the defect is large, and full-thickness autografts if the defect is small. In deep palmar burn injuries with loss of range of motion, the hand is splinted with metacarpophalangeal joints (MCPJ) in extension, both during topical care of the burn and following surgery. Skin grafts from the instep area have been advocated for aesthetic reasons, but functional results with full-thickness or thick split-thickness grafts are generally acceptable.

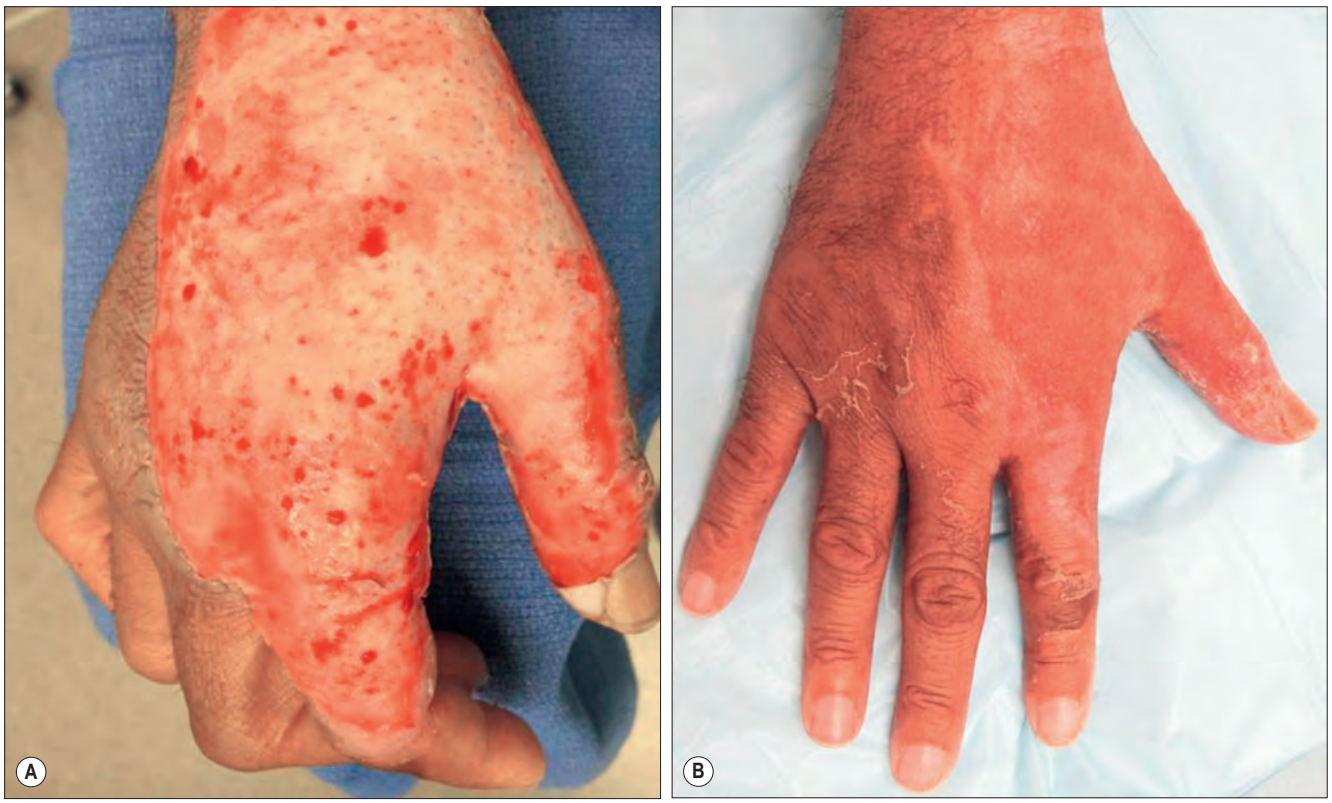

Fig. 12.11 Deep dermal burn of the dorsal hand that underwent excision and grafting. (A) Post-burn day 7. (B) 6 weeks post injury.

Hands are splinted in the position of function: the MCPJ at 70–90 degrees of flexion, the interphalangeal joints (IPJ) in extension, the wrist in 20 degrees of extension, and the thumb in palmar abduction and external rotation. Special attention should be given to the position of the fifth digit because it is particularly prone to flexion contractures resulting in fixed IPJ flexion. In the hand, failure of early wound closure may compromise the ability to participate in early physical therapy and possibly compromise long-term outcomes.

If the extensor mechanism is compromised by direct injury or subsequent desiccation and rupture, the dorsal collateral bands migrate volarly, and the proximal interphalangeal joint (PIPJ) develops a flexion contracture from which recovery might be impossible. In some cases, this unfortunate sequence of events can be prevented by ensuring prompt coverage of the PIPJ. If the depth of injury compromises the extensor mechanism, splinting in extension and inserting axial Kirschner wire (K wires) across the joint for 2–3 weeks may facilitate healing with improved stability. If the overlying extensor mechanism is damaged in an open PIPJ, a partially functional joint can sometimes be salvaged by K-wire fixation for 2–3 weeks, which may allow granulation tissue to bridge the open joint; this can subsequently be skin-grafted.

Techniques to Salvage Length in Fourth-Degree Hand Burns

In the presence of fourth-degree burns involving the underlying extensor mechanism, joint capsule, and bone, management can be more complex with less satisfactory outcomes. Patients with small surface area burns are candidates for early debridement with groin or abdominal flap coverage (Fig. 12.12).[65]

A common pattern is deep dorsal burn with exposure of the proximal interphalangeal joints, and dorsal phalanges with viable volar tissue. If these wounds are kept moist and

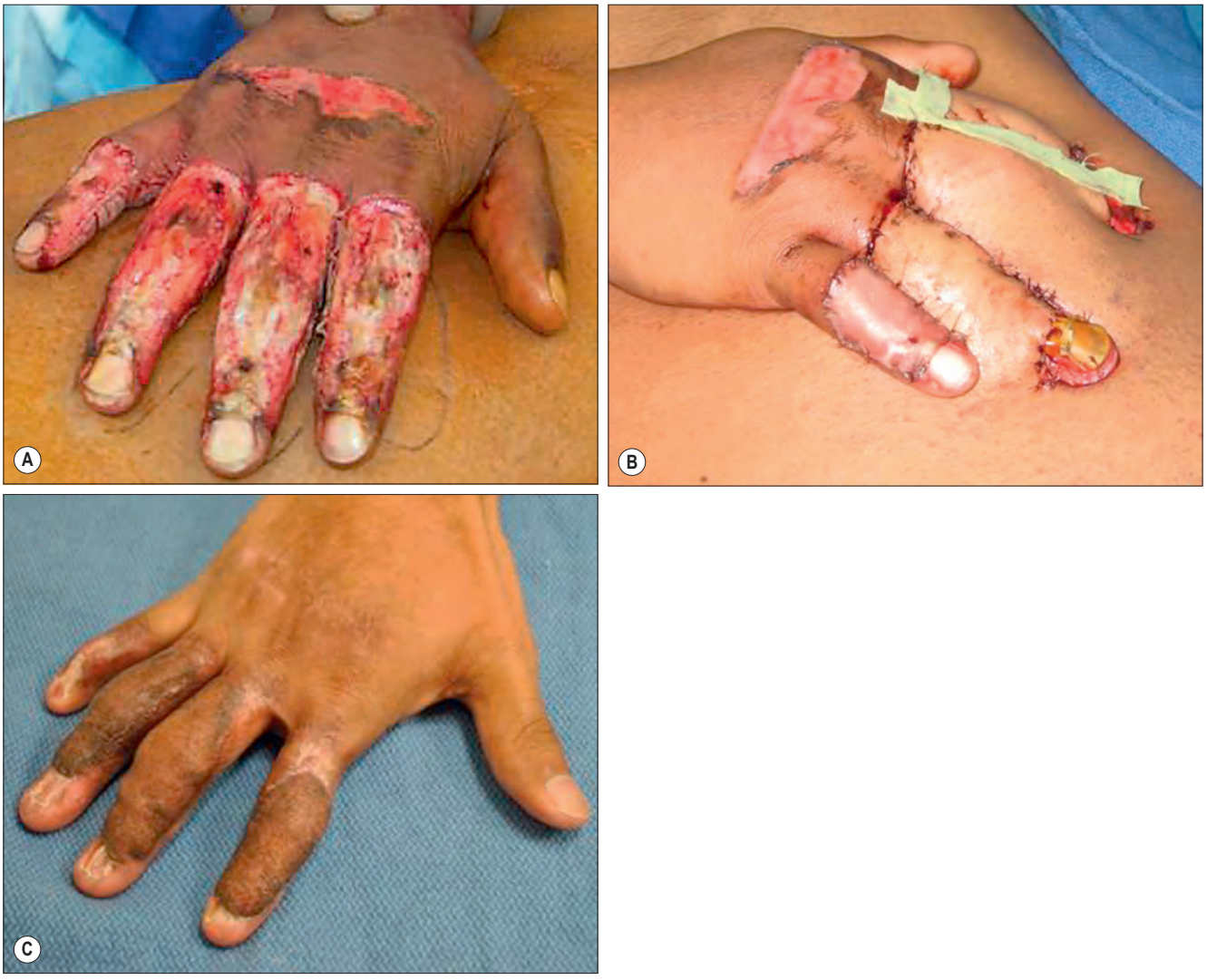

Fig. 12.12 Abdominal flap coverage of fourth-degree dorsal finger burns. (A) Deep dorsal burns and intraoperative positioning of the hand on the abdomen. (B) Flaps in position. (C) Final result.

clean, with position of function maintained, often the avascular tissue will granulate and can be skin grafted with an acceptable result.

When the extensor mechanism is exposed, maintaining the position of function during granulation tissue formation is critical to the final outcome. Granulation tissue formation may be facilitated by meticulously debriding remnants of burned cortical bone. Positioning may not be reliable when only splints are used, therefore K-wire insertion can be helpful to maintain the IPJ position while metacarpophalangeal joint flexion is maintained with the splints. Wires are passed axially from the tip of the finger proximally, stopping when the PIPJ is immobilized. Autografting is performed whenever possible, and exposed joints and bones are allowed to granulate and subsequently are covered with autograft skin (Fig. 12.13). Joints that remain unstable following coverage are fused by open arthrodesis at a later stage.

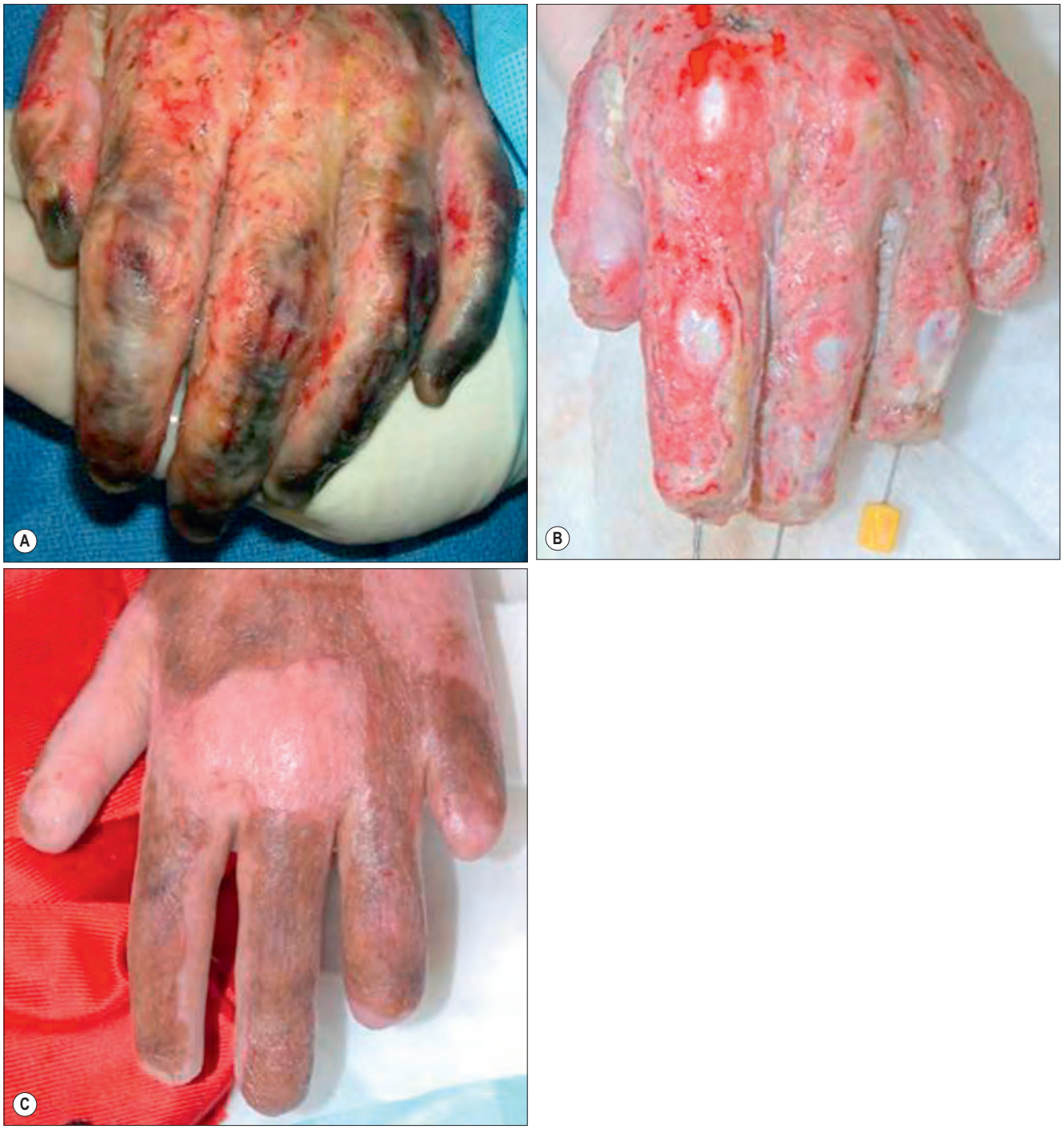

Fig. 12.13 Preservation of digital length in fourth-degree dorsal burn of the hand in a 9-year-old boy with 85% TBSA burn. (A) Day 7 post-burn. (B) Day 12 post-burn. (C) Day 61 post-burn.

THE SCALP

Scalp and skull burns are a major challenge due to the location of these injuries representing a complex wound with the possibility of injury to underlying structures. These injuries can be classified into two groups: injuries limited to soft tissue and injuries that involve the calvarium. Surgical management of the burned scalp can vary from simple soft tissue debridement and skin grafting to management of complicated calvarial bone injury.

Scalp burns without bony involvement are treated similarly to any other burn, with debridement and skin grafts or flap coverage.[66] There are several classifications for scalp burn wounds based on the depth and extent of the injury. Calvarial burn that does not involve the inner table can be managed by careful burring and skin grafting. The use of a fine diamond-tipped drill allows controlled layer-by-layer removal of nonviable bone without risking penetration into the intracranial cavity. Complex defects involving full-thickness bone loss with exposure of the dura will require reconstruction using local, regional, or free flaps.

The use of bone grafts or tissue expanders is deferred until after the acute burn phase. The priority is wound debridement and adequate coverage without compromising the underlying tissues. Surgical debridement includes the removal of necrotic soft tissue and bone, avoiding injury to the dura. Surgical excision stops at a viable layer to apply a skin graft.

Central nervous system infections are a possible complication, and antibiotic prophylaxis should be considered prior to the procedure.

THE FACE

Burns to the face can have potentially devastating consequences to the patient and can adversely impact the patient's return to premorbid activity. Attention to details, adequate excision, wound coverage and postoperative management are essential in the preservation of vital functions and cosmesis.[67] Facial burns can involve injuries to vital structures such as the upper airway and sensory organs such as the eyes and ears.

There have been no large randomized outcome trials comparing early excision and grafting of the face compared to grafting after eschar separation and granulation tissue formation. Most authors have applied the general principle of early excision to prevent contractures and provide the best aesthetic outcome, with a suggested maximal waiting period of 18 days.[68]

Once a decision has been made to proceed with excision and grafting, site and thickness of donor skin need careful consideration. If possible, the donor skin should be procured from the area above the line of the nipples for the best color match. Skin grafts from the scalp provide excellent color match but carry a risk of follicle transplantation if taken too deeply and subsequent hair growth of the recipient site and alopecia of donor site. An alternative site is the upper back.

Excision of facial burns can be performed using various methods; the mainstay of excision remains use of the Goulian/Weck knife. If there are any doubts regarding the depth of the burn, tangential excision using a Goulian knife is more appropriate to preserve viable dermis, which is essential for optimal results (Fig. 12.14).

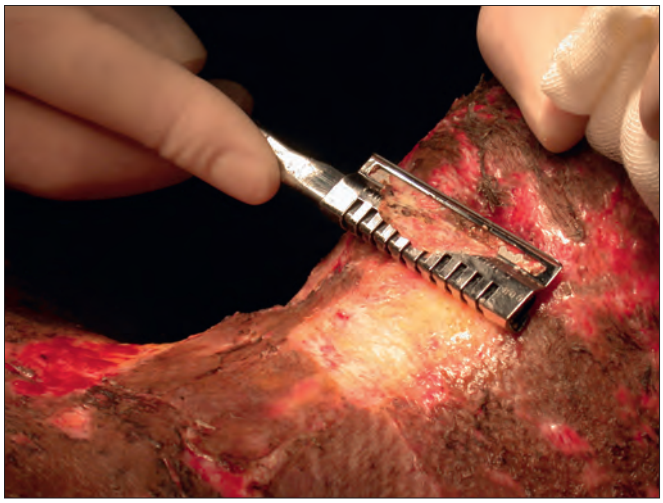

Fig. 12.14 Tangential excision being applied with a Goulian knife to the chin. Previous grafting had been largely successful. The instrument is useful for small and tricky areas.

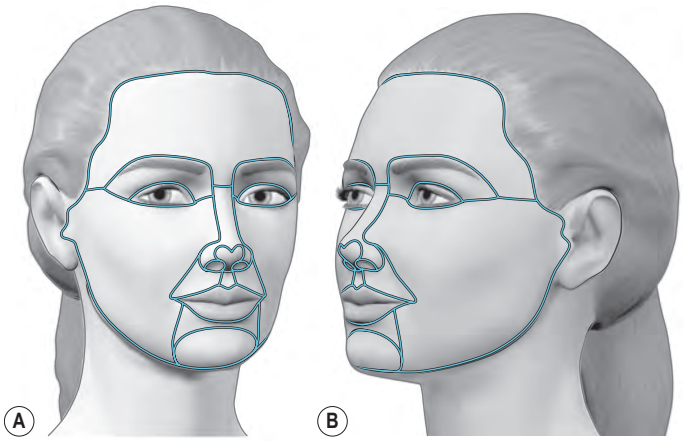

Fig. 12.15 Aesthetic units of the face. (A) Frontal view. (B) Lateral view. (From McCauley RL, Obeng MK. Reconstruction of cheek deformities. In: McCauley RL, ed., *Functional and aesthetic reconstruction of burned patients*. Boca Raton, FL: Taylor and Francis Group; 2005: 270.)

Previously described "water dissectors" such as the Versajet Hydrosurgery System can also be used in areas of contour for more controlled and precise excision, thus avoiding potential injuries to viable deeper layers.

Owing to the rich capillary networks in the face, large amounts of blood may be lost at the time of the excision. Epinephrine clysis is an appropriate pre-emptive measure to reduce blood loss during facial excision.[69,70] Epinephrine-moistened topical sponges are helpful, and electrocautery can be useful for accurate hemostasis.

Placement of skin grafts on the face should be carried out with respect to aesthetic units, where sheet autografts are placed to reconstruct an entire aesthetic unit. For aesthetic purposes the face is divided into cosmetic units (Fig. 12.15),[71] and the periorbital, nasal, and upper cheek areas

are grafted as a single aesthetic unit.[71] Grafts should be taken as widely as possible to reduce the number of seams between the grafts, then secured with sutures, glues, or fibrin sealant.

The use of fibrin sealant, a hemostatic adjunct and adhesive underlay, has been shown in studies to reduce seroma and hematoma formation as well as minimize the need for staples or sutures, producing equal or better outcome.[72] Medical-grade glue such as 2-cyano-butyl acrylate (Histoacryl) can be used to secure the edges of skin grafts.

Once the skin grafts are secured in place, tubes and lines should be positioned appropriately to avoid disruption of the grafts. Nasal septal ties can be used to secure the endotracheal tube and avoid facial ties that can disrupt the skin grafts.

Sheet grafts on the face should be evaluated frequently for fluid collection or hematoma, which can be drained with a small-gauge needle. Some centers delay autografting the face to reduce graft loss from hematoma formation. Temporary wound coverage with allografts remains a good option until definitive coverage.[73]

In areas of extensive soft tissue injury with no underlying bony injuries, such as the buccal area, acute reconstruction with regional or free tissue transfer can be considered. If the maxillary sinuses are exposed, the dead space may be filled using free vascularized omental transfers, as described in cases of facial trauma.[74]

EYELIDS

Deep burns to the eyelids should be excised and grafted early because they can result in cicatricial ectropion, leading to lagophthalmos, exposure keratitis, corneal ulceration, and, ultimately, perforation leading to blindness.[75] Post-burn cicatricial ectropion is a serious complication, with unconscious ventilated patients at particular risk. Release of burn scars and full-thickness skin grafts to the lower eyelids and split-thickness skin grafts to the upper lids should be undertaken as soon as the condition is diagnosed.[76]

Ophthalmic lubricant drops and ointments should be applied frequently to keep the eyes moist to avoid exposure keratitis, especially in unconscious patients. If post-burn ectropion develops, early tarsorrhaphy or release of the contracted eyelids may be necessary.

Tarsorrhaphy can be carried out at the bedside under local anesthesia. A U-stitch is placed using a fine nonabsorbable suture at the lid margin, anterior to the gray line to avoid corneal irritation. The upper and lower eyelids are approximated at their lateral and/or medial portions. Lateral tarsorrhaphy is more commonly used. The suture should be secured through material such as a rubber pledget to prevent the suture from being pulled through skin. The suture should incorporate the ridge of tarsus but not traverse it, and an adequate tarsorrhaphy will permit the passive closure of the eyelids to protect the cornea.

Upper and lower eyelid releases can be carried out using local flaps, full-thickness skin grafts, or split-thickness skin grafts. Full-thickness eyelid defects require layered reconstruction using hard palate mucosa or acellular dermis as the inner lamella and split skin grafts or local skin flaps as the outer lamella.[77]

GENITAL BURNS

Genital burns can produce significant morbidity and long-term consequences for mobility, urine elimination, and sexual function. Spontaneous epithelialization will likely occur with scald burns in this region owing to the rich supply of hair follicles and skin appendages.

Recommendations for acute management include selective urethral catheterization to allow urine collection and urethral stenting in the case of circumferential constricting burns.

Most partial-thickness burns of the scrotum will heal spontaneously because scrotal skin is thick and contains multiple hair follicles. Testicular function should be evaluated by measuring stimulated testosterone levels if testicular injury is suspected.[78]

Small full-thickness burns to the scrotum can be excised and closed primarily, and large full-thickness burns will require skin grafting. Along the shaft of the penis, full-thickness burns are excised using Goulian knife or Versajet and grafted using unmeshed split-thickness skin grafts. Full-thickness burns involving foreskin can be managed with circumcision because phimosis is a common sequela.

Scald burns to the genitalia are best managed conservatively because they are usually partial thickness and heal with acceptable outcomes. Deep burns to the glans penis may be allowed to demarcate and proceed to eschar separation, then the underlying granulation tissue is skin grafted later. Full-thickness burns to the labia majora should be excised and grafted as a delayed procedure to avoid scar contractures in the long term.

Perianal burns are seen in association with extensive burns in adults and in children with scald burns. Early excision and grafting is recommended to prevent bacterial colonization and infection from fecal contamination. Some centers recommend bowel diversion to aid healing and graft take.[79] If skin graft failure occurs, it is important to try regrafting because prolonged healing time by secondary intention can cause perianal circular contractures.

THE BREAST

The scarring and disfigurement associated with breast burns can be a source of significant psychological stress in developing girls and young women.[80] All efforts should be made to preserve the breast bud in prepubescent girls and the breast mound in a postpubertal women. Small burns, especially linear ones, may be excised and closed primarily or allowed to form scar and later excised.

The nipple-areola complex, especially in women, requires particular attention; it is best left un-excised because healing can occur from the deep glandular structures that are usually preserved.

Conclusion

One of the most important components of modern burn care is early operative wound management. The available evidence is clear that prompt burn wound excision and closure is lifesaving for massively burned patients. Skin substitutes and dermal replacement have made operative

wound care even more accessible in terms of providing temporary wound coverage. This offers an alternative to topical antimicrobial therapy and conservative management for full-thickness wounds.

Complete references available online at www.expertconsult.inkling.com

Further Reading

Desai MH, Herndon DN, Broemeling L, et al. Early burn wound excision significantly reduces blood loss. *Ann Surg*. 1990;211(6):753-759, discussion 759–762. (Paper on early burn excision and decreased blood loss.)

Heimback DM, Warden GD, Luterman A, et al. Multicenter postapproval clinical trial of Integra dermal regeneration template for burn treatment. *J Burn Care Rehabil*. 2003;24(1):42-48. (Paper on dermal regeneration template.)

Herndon DN, Barrow RE, Rutan RL, et al. A comparison of conservative versus early excision. Therapies in severely burned patients. *Ann Surg*. 1989;209(5):547-553, discussion 552–553.

Janzekovic Z. The burn wound from the surgical point of view. *J Trauma*. 1975;15(1):42-62. (Classic paper on early excision and immediate grafting.)

Sood R, Roggy D, Zieger M, et al. Cultured epithelial autografts for coverage of large burn wounds in eighty-eight patients: the Indiana University experience. *J Burn Care Res*. 2010;31(4):559-568. (Paper on cultured epithelia autografts.)

Supp DM, Boyce ST. Engineered skin substitutes: practices and potentials. *Clin Dermatol*. 2005;23(4):403-412.

References

1. Ong YS, Samuel M, Song C. Meta-analysis of early excision of burns. *Burns*. 2006;32(2):145-150.
2. Lee JO, Herndon DN. Modulation of the post-burn hypermetabolic state. *Nestle Nutr Workshop Ser Clin Perform Programme*. 2003;8:39-49, discussion 56.
3. Herndon DN, Tompkins RG. Support of the metabolic response to burn injury. *Lancet*. 2004;363(9424):1895-1902.
4. Bull JP, Fisher AJ. A study of mortality in a burns unit: a revised estimate. *Ann Surg*. 1954;139(3):269-274.
5. Muller MJ, Herndon DN. The challenge of burns. *Lancet*. 1994;343(8891):216-220.
6. Burke JF, Bondoc CC, Quinby WC. Primary burn excision and immediate grafting: a method shortening illness. *J Trauma*. 1974;14(5):389-395.
7. Pietsch JB, Netscher DT, Nagaraj HS, Groff DB. Early excision of major burns in children: effect on morbidity and mortality. *J Pediatr Surg*. 1985;20(6):754-757.
8. Herndon DN, Parks DH. Comparison of serial debridement and autografting and early massive excision with cadaver skin overlay in the treatment of large burns in children. *J Trauma*. 1986;26(2):149-152.
9. Herndon DN, Barrow RE, Rutan RL, et al. A comparison of conservative versus early excision. Therapies in severely burned patients. *Ann Surg*. 1989;209(5):547-552, discussion 552-553.
10. Tompkins RG, Burke JF, Schoenfeld DA, et al. Prompt eschar excision: a treatment system contributing to reduced burn mortality. A statistical evaluation of burn care at the Massachusetts General Hospital (1974–1984). *Ann Surg*. 1986;204(3):272-281.
11. Thompson P, Herndon DN, Abston S, Rutan T. Effect of early excision on patients with major thermal injury. *J Trauma*. 1987;27(2):205-207.
12. Xiao-Wu W, Herndon DN, Spies M, Sanford AP, Wolf SE. Effects of delayed wound excision and grafting in severely burned children. *Arch Surg*. 2002;137(9):1049-1054.
13. Munster AM, Smith-Meek M, Sharkey P. The effect of early surgical intervention on mortality and cost-effectiveness in burn care, 1978-91. *Burns*. 1994;20(1):61-64.
14. Deitch EA, Clothier J. Burns in the elderly: an early surgical approach. *J Trauma*. 1983;23(10):891-894.
15. Deitch EA. A policy of early excision and grafting in elderly burn patients shortens the hospital stay and improves survival. *Burns*. 1985;12(2):109-114.
16. Kara M, Peters WJ, Douglas LG, Morris SF. An early surgical approach to burns in the elderly. *J Trauma*. 1990;30(4):430-432.
17. Scott-Conner CE, Love R, Wheeler W. Does rapid wound closure improve survival in older patients with burns? *Am Surg*. 1990;56(1):57-60.
18. Hunt JL, Purdue GF. The elderly burn patient. *Am J Surg*. 1992;164(5):472-476.
19. Ikeda J, Sugamata A, Jimbo Y, Yukioka T, Makino K. A new surgical procedure for aged burn victims: applications of dermolipectomy for burn wounds and donor sites. *J Burn Care Rehabil*. 1990;11(1):27-31.
20. Deitch EA, Wheelahan TM, Rose MP, Clothier J, Cotter J. Hypertrophic burn scars: analysis of variables. *J Trauma*. 1983;23(10):895-898.
21. Heimbach DM. Early burn excision and grafting. *Surg Clin North Am*. 1987;67(1):93-107.
22. Engrav LH, Heimbach DM, Reus JL, Harnar TJ, Marvin JA. Early excision and grafting vs. nonoperative treatment of burns of indeterminant depth: a randomized prospective study. *J Trauma*. 1983;23(11):1001-1004.
23. Janzekovic Z. A new concept in the early excision and immediate grafting of burns. *J Trauma*. 1970;10(12):1103-1108.
24. Janzekovic Z. The burn wound from the surgical point of view. *J Trauma*. 1975;15(1):42-62.
25. Klein MB, Hunter S, Heimbach DM, et al. The Versajet water dissector: a new tool for tangential excision. *J Burn Care Rehabil*. 2005;26(6):483-487.
26. Park YS, Choi YH, Lee HS, et al. The impact of laser Doppler imaging on the early decision-making process for surgical intervention in adults with indeterminate burns. *Burns*. 2013;39(4):655-661.
27. Prindeze NJ, Fathi P, Mino MJ, et al. Examination of the early diagnostic applicability of active dynamic thermography for burn wound depth assessment and concept analysis. *J Burn Care Res*. 2015;36(6):626-635.
28. Prindeze NJ, Hoffman HA, Ardanuy JG, et al. Active dynamic thermography is a sensitive method for distinguishing burn wound conversion. *J Burn Care Res*. 2015;37(6):e559-e568.
29. Burke-Smith A, Collier J, Jones I. A comparison of non-invasive imaging modalities: Infrared thermography, spectrophotometric intracutaneous analysis and laser Doppler imaging for the assessment of adult burns. *Burns*. 2015;41(8):1695-1707.
30. Lin YH, Huang CC, Wang SH. Quantitative assessments of burn degree by high-frequency ultrasonic backscattering and statistical model. *Phys Med Biol*. 2011;56(3):757-773.
31. Hop MJ, Stekelenburg CM, Hiddingh J, et al. Cost-effectiveness of laser Doppler imaging in burn care in the Netherlands: a randomized controlled trial. *Plast Reconstr Surg*. 2016;137(1):166e-176e.
32. Desai MH, Herndon DN, Broemeling L, et al. Early burn wound excision significantly reduces blood loss. *Ann Surg*. 1990;211(6):753-759, discussion 759-762.
33. Hart DW, Wolf SE, Beauford RB, et al. Determinants of blood loss during primary burn excision. *Surgery*. 2001;130(2):396-402.
34. Jeschke MG, Chinkes DL, Finnerty CC, et al. Blood transfusions are associated with increased risk for development of sepsis in severely burned pediatric patients. *Crit Care Med*. 2007;35(2):579-583.
35. Alexander JW, MacMillan BG, Law E, Kittur DS. Treatment of severe burns with widely meshed skin autograft and meshed skin allograft overlay. *J Trauma*. 1981;21(6):433-438.
36. Meek CP. Successful microdermagrafting using the Meek-Wall microdermatome. *Am J Surg*. 1958;96(4):557-558.
37. Kreis RW, Mackie DP, Vloemans AW, Hermans RP, Hoekstra MJ. Widely expanded postage stamp skin grafts using a modified Meek technique in combination with an allograft overlay. *Burns*. 1993;19(2):142-145.
38. Heimbach DM, Warden GD, Luterman A, et al. Multicenter postapproval clinical trial of Integra dermal regeneration template for burn treatment. *J Burn Care Rehabil*. 2003;24(1):42-48.
39. McEwan W, Brown TL, Mills SM, Muller MJ. Suction dressings to secure a dermal substitute. *Burns*. 2004;30(3):259-261.
40. Sheridan R, Choucair R, Donelan M, et al. Acellular allodermis in burns surgery: 1-year results of a pilot trial. *J Burn Care Rehabil*. 1998;19(6):528-530.
41. Munster AM. Cultured skin for massive burns. A prospective, controlled trial. *Ann Surg*. 1996;224(3):372-375, discussion 375-377.
42. Barret JP, Wolf SE, Desai MH, Herndon DN. Cost-efficacy of cultured epidermal autografts in massive pediatric burns. *Ann Surg*. 2000;231(6):869-876.
43. Sood R, Balledux J, Koumanis DJ, et al. Coverage of large pediatric wounds with cultured epithelial autografts in congenital nevi and burns: results and technique. *J Burn Care Res*. 2009;30(4):576-586.
44. Hohlfeld J, de Buys Roessingh A, Hirt-Burri N, et al. Tissue engineered fetal skin constructs for paediatric burns. *Lancet*. 2005;366(9488):840-842.
45. Pouyani T, Papp S, Schaffer L. Tissue-engineered fetal dermal matrices. *In Vitro Cell Dev Biol Anim*. 2012;48(8):493-506.
46. Supp DM, Boyce ST. Engineered skin substitutes: practices and potentials. *Clin Dermatol*. 2005;23(4):403-412.
47. Boyce ST, Simpson PS, Rieman MT, et al. Randomized, paired-site comparison of autologous engineered skin substitutes and split-thickness skin graft for closure of extensive, full-thickness burns. *J Burn Care Res*. 2016;38(2):61-70.
48. Bondoc CC, Burke JF. Clinical experience with viable frozen human skin and a frozen skin bank. *Ann Surg*. 1971;174(3):371-382.
49. Sheridan RL, Tompkins RG. Skin substitutes in burns. *Burns*. 1999;25(2):97-103.
50. Branski LK, Herndon DN, Celis MM, et al. Amnion in the treatment of pediatric partial-thickness facial burns. *Burns*. 2008;34(3):393-399.
51. Irei M, Abston S, Bonds E, et al. The optimal time for excision of scald burns in toddlers. *J Burn Care Rehabil*. 1986;7(6):508-510.
52. Desai MH, Rutan RL, Herndon DN. Conservative treatment of scald burns is superior to early excision. *J Burn Care Rehabil*. 1991;12(5):482-484.
53. Barret JP, Dziewulski P, Ramzy PI, et al. Biobrane versus 1% silver sulfadiazine in second-degree pediatric burns. *Plast Reconstr Surg*. 2000;105(1):62-65.
54. Lal S, Barrow RE, Wolf SE, et al. Biobrane improves wound healing in burned children without increased risk of infection. *Shock*. 2000;14(3):314-318, discussion 318-319.
55. Boyce ST, Kagan RJ, Meyer NA, Yakuboff KP, Warden GD. The 1999 clinical research award. Cultured skin substitutes combined with Integra Artificial Skin to replace native skin autograft and allograft for the closure of excised full-thickness burns. *J Burn Care Rehabil*. 1999;20(6):453-461.

56. Gilpin DA, Barrow RE, Rutan RL, Broemeling L, Herndon DN. Recombinant human growth hormone accelerates wound healing in children with large cutaneous burns. *Ann Surg*. 1994;220(1):19-24.
57. Singh KP, Prasad R, Chari PS, Dash RJ. Effect of growth hormone therapy in burn patients on conservative treatment. *Burns*. 1998;24(8):733-738.
58. Ramirez RJ, Wolf SE, Barrow RE, Herndon DN. Growth hormone treatment in pediatric burns: a safe therapeutic approach. *Ann Surg*. 1998;228(4):439-448.
59. Demling RH, Orgill DP. The anticatabolic and wound healing effects of the testosterone analog oxandrolone after severe burn injury. *J Crit Care*. 2000;15(1):12-17.
60. Wolf SE, Thomas SJ, Dasu MR, et al. Improved net protein balance, lean mass, and gene expression changes with oxandrolone treatment in the severely burned. *Ann Surg*. 2003;237(6):801-810, discussion 810-811.
61. Rodeberg DA, Easter AJ, Washam MA, et al. Use of a helium-oxygen mixture in the treatment of postextubation stridor in pediatric patients with burns. *J Burn Care Rehabil*. 1995;16(5):476-480.
62. Salisbury RE, Taylor JW, Levine NS. Evaluation of digital escharotomy in burned hands. *Plast Reconstr Surg*. 1976;58(4):440-443.
63. Robson MC, Smith DJ Jr, VanderZee AJ, Roberts L. Making the burned hand functional. *Clin Plast Surg*. 1992;19(3):663-671.
64. Goodwin CW, Maguire MS, McManus WF, Pruitt BA Jr. Prospective study of burn wound excision of the hands. *J Trauma*. 1983;23(6):510-517.
65. Hanumadass M, Kagan R, Matsuda T. Early coverage of deep hand burns with groin flaps. *J Trauma*. 1987;27(2):109-114.
66. Spies M, McCauley RL, Mudge BP, Herndon DN. Management of acute calvarial burns in children. *J Trauma*. 2003;54(4):765-769.
67. Leon-Villapalos J, Jeschke MG, Herndon DN. Topical management of facial burns. *Burns*. 2008;34(7):903-911.
68. Leon-Villapalos J, Eldardiri M, Dziewulski P. The use of human deceased donor skin allograft in burn care. *Cell Tissue Bank*. 2010;11(1):99-104.
69. Hughes WB, DeClement FA, Hensell DO. Intradermal injection of epinephrine to decrease blood loss during split-thickness skin grafting. *J Burn Care Rehabil*. 1996;17(3):243-245.
70. Sheridan RL, Szyfelbein SK. Staged high-dose epinephrine clysis is safe and effective in extensive tangential burn excisions in children. *Burns*. 1999;25(8):745-748.
71. Acikel C, Peker F, Ulkur E. Skin grafting of the naso-orbital region as a single aesthetic unit. *Burns*. 2001;27(7):753-757.
72. Foster K, Greenhalgh D, Gamelli RL, et al. Efficacy and safety of a fibrin sealant for adherence of autologous skin grafts to burn wounds: results of a phase 3 clinical study. *J Burn Care Res*. 2008;29(2):293-303.
73. Horch RE, Jeschke MG, Spilker G, Herndon DN, Kopp J. Treatment of second degree facial burns with allografts–preliminary results. *Burns*. 2005;31(5):597-602.
74. Jurkiewicz MJ, Nahai F. The omentum: its use as a free vascularized graft for reconstruction of the head and neck. *Ann Surg*. 1982;195(6):756-765.
75. Barrow RE, Jeschke MG, Herndon DN. Early release of third-degree eyelid burns prevents eye injury. *Plast Reconstr Surg*. 2000;105(3):860-863.
76. Astori IP, Muller MJ, Pegg SP. Cicatricial, postburn ectropion and exposure keratitis. *Burns*. 1998;24(1):64-67.
77. Jiaqi C, Zheng W, Jianjun G. Eyelid reconstruction with acellular human dermal allograft after chemical and thermal burns. *Burns*. 2006;32(2):208-211.
78. Alghanem AA, McCauley RL, Robson MC, Rutan RL, Herndon DN. Management of pediatric perineal and genital burns: twenty-year review. *J Burn Care Rehabil*. 1990;11(4):308-311.
79. Quarmby CJ, Millar AJ, Rode H. The use of diverting colostomies in paediatric peri-anal burns. *Burns*. 1999;25(7):645-650.
80. Foley P, Jeeves A, Davey RB, Sparnon AL. Breast burns are not benign: long-term outcomes of burns to the breast in pre-pubertal girls. *Burns*. 2008;34(3):412-417.

13 Anesthesia for Burned Patients

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Introduction

Continuous improvement in burn care since World War II has resulted in a steady increase in the rate of survival after large burn injury.[1] These improvements have been attributed to aggressive fluid resuscitation, early excision and grafting of burn wounds, more effective antimicrobials, advances in nutritional support, and development of burn centers. Today most patients with more than 80% total body surface area (TBSA) burned will survive if promptly treated in a modern burn unit with adequate resources. In their study of risk factors for death following burn injuries Ryan et al. identified three variables that can be used to estimate the probability of death: age greater than 60 years, burns of more than 40% TBSA, and the presence of inhalation injury.[2] Mortality increased in proportion to the number of risk factors present: 0.3%, 3%, 33%, or approximately 90% mortality depending on whether zero, one, two, or three risk factors were present, respectively. The incidence of mortality is also influenced by significant coexisting disease or delays in resuscitation. O'Keefe et al. observed an approximately twofold higher death risk of death in women aged 30–59 years compared with men with similar burns and age.[3] Although it has been assumed that very young children are also at increased risk of death from burn injuries, Sheridan et al. found very low rates of mortality in children younger than 48 months who had suffered large burns.[4] One group that has not benefited as much from advances in burn care is the elderly. The morbidity and mortality (as expressed as lethal dose 50 for burns) associated with serious burns in elderly patients has not improved over the past three decades.[5] Some burn patients develop refractory burn shock soon after injury and cannot be resuscitated.[6]

Major burn injury results in pathophysiological changes in virtually all organ systems. Box 13.1 lists and Figs. 13.1 and 13.2 illustrate some of the challenges presented by the acutely burned patient during the perioperative period. In addition to the predictable challenges relating to airway management, monitoring, and vascular access, patient positioning requires close communication and teamwork. Burns involving posterior areas may require turning the patient to the prone position for optimal access (Fig. 13.1). Vascular catheters and the endotracheal tube must be secured with confidence and due care given to these life lines during patient turning. Several highly informative reviews of anesthetic management for burn surgery have been written during the past decade, each with its own special areas of concentration.[7–10]

Patients suffering burn injuries often require surgical treatment for years after the initial injury in order to correct functional and cosmetic sequelae. Anesthetic management for reconstructive burn surgery presents many special problems[11] but this chapter will concentrate on the care of acute burn patients. The acute phase of burn injury is defined as the period from injury until the wounds have been excised, grafted, and healed.

Modern burn care depends on coordination of a multidisciplinary team including surgeons, intensivists, nurse clinicians, nutritionists, rehabilitation therapists, pulmonary care therapists, and anesthesia providers. Rational and effective anesthetic management of acute burn patients requires an understanding of this multidisciplinary approach so that perioperative care is compatible with the overall treatment goals for the patient. The current standard of surgical treatment calls for early excision and grafting of nonviable burn wounds, which may harbor pathogens and produce inflammatory mediators with systemic effects resulting in cardiopulmonary compromise. After an extensive burn injury, the systemic effects of inflammatory mediators on metabolism and cardiopulmonary function reduce physiological reserve, and the patient's tolerance to the stress of surgery deteriorates with time. Assuming adequate resuscitation, extensive surgery is best tolerated soon after injury, when the patient is most fit. However it must be recognized that the initial resuscitation of patients with large burns results in large fluid shifts and may be associated with hemodynamic instability and respiratory insufficiency. Reynolds et al. reported that more than half of deaths after burn injuries occur due to failed resuscitation.[6]

Effective anesthetic management of patients with extensive burn injuries requires an understanding of the pathophysiological changes associated with large burns and careful preoperative evaluation to assure that resuscitation has been optimized and an appropriate anesthetic plan has been formulated.

Preoperative Evaluation

The preoperative evaluation of burn patients requires knowledge of the continuum of pathophysiological changes that occur in these patients from the initial period after injury through the time that all wounds have healed. The dramatic changes that occur in all organ systems following burn injury directly affect anesthetic management. The following discussion will describe the pathophysiological changes that occur in the acutely burned patient as they relate to the preoperative evaluation. In addition to the routine features of the preoperative evaluation, evaluation of acute burn patients requires special attention to airway

Box 13.1 Perioperative Challenges in the Acute Burn Patient

- Compromised airway
- Pulmonary insufficiency
- Altered mental status
- Associated injuries
- Limited vascular access
- Rapid blood loss
- Impaired tissue perfusion due to:
- Hypovolemia
- Decreased myocardial contractility
- Anemia
- Decreased colloid osmotic pressure
- Edema
- Dysrhythmia
- Impaired temperature regulation
- Altered drug response
- Renal insufficiency
- Immunosuppression
- Infection/sepsis

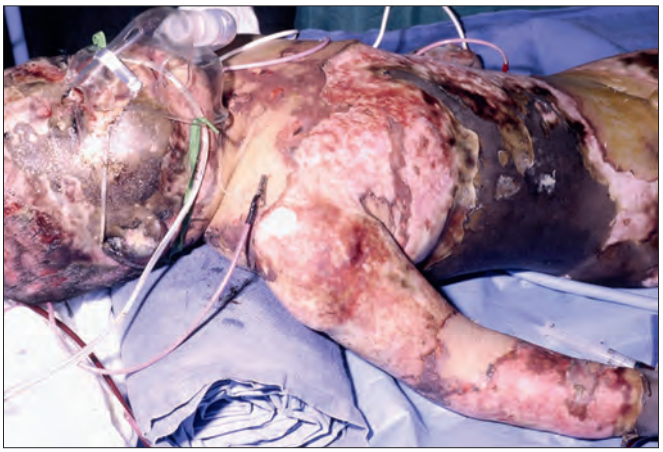


Fig. 13.1 Many of the technical challenges regarding airway management, intravenous access, application of monitors, temperature regulation, and expectation of extensive bleeding associated with anesthetic care of patients with major burn injury.

management and pulmonary support, vascular access, adequacy of resuscitation, and associated injuries. The severely burned patient presents with numerous preoperative concerns, as listed in Box 13.2. The preoperative evaluation must be performed within the context of the planned operative procedure, which will depend on the location, extent, and depth of burn wounds; time after injury; presence of infection; and existence of suitable donor sites for autografting.

INITIAL EVALUATION OF BURN INJURY

Destruction of skin by thermal injury disrupts the vital functions of the largest organ in the body. The skin provides several essential protective and homeostatic functions (Box 13.3). Treatment of patients with burn injuries must compensate for loss of these functions until the wounds are covered and healed. As a barrier to evaporation of water,

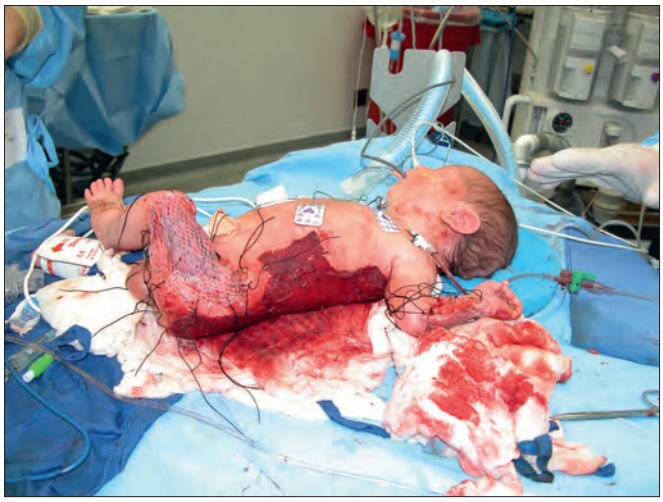


Fig. 13.2 Occasionally patients requiring burn wound excision present with special needs, as with this 3-day-old patient. Cardiovascular, hepatic, and renal physiological systems are immature, and vascular access adequate to keep up with extensive blood loss can be technically difficult.

Box 13.2 Major Preoperative Concerns in Acutely Burned Patients

Age of patient
Extent of burn injuries (total body surface area)
Burn depth and distribution (superficial or full thickness)
Mechanism of injury (flame, electrical, scald, or chemical)
Airway patency
Presence or absence of inhalation injury
Elapsed time from injury
Adequacy of resuscitation
Associated injuries
Coexisting diseases
Surgical plan

Box 13.3 Functions of Skin

1. Protection from environmental elements (e.g., radiation, mechanical irritation, or trauma)
2. Immunological: antigen presentation, antibacterial products (sebum), barrier to entry of pathological organisms
3. Fluid and electrolyte homeostasis: helps maintain protein and electrolyte concentrations by limiting evaporation
4. Thermoregulation: helps control heat loss through sweating and vasomotor regulation of superficial blood flow
5. Sensory: extensive and varied sensory organs in skin provide information about environment
6. Metabolic: vitamin D synthesis and excretion of certain substances
7. Social: appearance of skin has strong influence on image and social interactions

the skin helps maintain fluid and electrolyte balance. Heat loss through evaporation and impairment of vasomotor regulation in burned skin diminishes effective temperature regulation. The skin's barrier function also protects against infection by invading organisms. Wound exudate rich in

protein depletes plasma proteins when large body surface areas are injured.

In addition to loss of important functions of the skin, extensive burns result in an inflammatory response with systemic effects that alter function in virtually all organ systems. Preoperative evaluation of the burn patient is guided largely by a knowledge of these pathophysiological changes.

Much of the morbidity and mortality associated with burn injuries are related to the size of the injury. The extent of the burn injury is expressed as the TBSA burned. Estimates of TBSA burned are used to guide fluid and electrolyte therapy and to estimate surgical blood loss. These estimates can be made with Lund Browder charts developed from age-specific nomograms (Fig. 13.3). Simplified "Rule of Nines" charts are available in emergency departments for rapid estimates of TBSA involvement. A knowledge of the burn depth is also critical to anticipating physiological insult as well as planned surgical treatment. First-degree or superficial second -degree burns may heal without scarring or deformity and do not require surgical excision. Deeper second-degree and third-degree burns require surgical debridement and grafting with associated surgical blood loss.

Accurate estimates of blood loss are crucial in planning preoperative management of burn patients. With extensive wound excision or debridement, large amounts of blood can be lost rapidly. Adequate preparation in terms of monitors, vascular access, and availability of blood products is essential. Surgical blood loss depends on area to be excised (cm^2), time since injury, surgical plan (tangential vs. fascial excision; Fig. 13.4), and presence of infection.[12] Blood loss from skin graft donor sites will also vary depending on whether it is an initial or repeat harvest. These variables are valuable predictors of surgical blood loss, which is a critical factor in planning anesthetic management (Table 13.1).

AIRWAY AND PULMONARY FUNCTION

Special attention must be paid to the airway and pulmonary function during preoperative evaluation. Burn injuries to the face and neck can distort anatomy and reduce range of mobility in ways that make direct laryngoscopy difficult or impossible. Specific alterations include impaired mouth opening and edema of the tongue, oropharynx, and larynx, as well as decreased range of motion of the neck. The tissue injury and sloughing present after severe facial burns may make mask ventilation difficult. Inhalation injury may impair pulmonary gas exchange and lead to respiratory insufficiency or failure. The level of respiratory support must also be assessed. The level of required support may range from supplemental blow-by or mask oxygen to intubation and ventilation with high positive end-expiratory pressure (PEEP) and FIO_2. Acute lung injury can occur from inhalation of chemical irritants, systemic inflammation from burn wounds or difficulties with resuscitation, or ventilator-induced injury. Common pathologies include upper airway thermal injury, pulmonary parenchyma damage from chemical irritants or inflammation, and lower airway obstruction from mucus plugs and epithelial casts, as well as pulmonary edema due to acute lung injury or volume overload. With very high levels of PEEP or peak inspiratory pressure, it must be determined if the anesthesia ventilator is adequate or if an ICU ventilator will need to be brought to the operating room. If the patient is intubated at the time of the preoperative evaluation, it is essential to know what the indications for intubation were so that an appropriate plan for postoperative support can be made.

Table 13.1 Calculation of Expected Blood Loss

Surgical Procedure	Predicted Blood Loss
<24 h since burn injury	0.45 mL/cm^2 burn area
1–3 days since burn injury	0.65 mL/cm^2 burn area
2–16 days since burn injury	0.75 mL/cm^2 burn area
>16 days since burn injury	0.5–0.75 mL/cm^2 burn area
Infected wounds	1–1.25 mL/cm^2 burn area

There is general recognition that smoke inhalation injury increases morbidity and mortality for burn patients.[13] The presence of an inhalation injury in combination with a cutaneous burn increases the volume of fluid required for resuscitation by as much as 44%.[14] Numerous studies have also shown an increased incidence of pulmonary complications (pneumonia, respiratory failure, or acute respiratory distress syndrome [ARDS]) in patients with burns and inhalation injury when compared with burns alone.[15] Sequelae of inhalation injury include upper airway distortion and obstruction from direct thermal injury as well as impaired pulmonary gas exchange due to effects of irritant gases on lower airways and pulmonary parenchyma. These two components of the inhalation injury have separate time courses and pathophysiological consequences.

Foley described the findings of 335 autopsies performed on patients who died from extensive burns.[16] Intraoral, palatal, and laryngeal burns were not uncommon among patients with inhalation injuries. The most common sites of laryngeal injury were the epiglottis and vocal folds where their edges were exposed. In contrast, thermal necrosis below the glottis and upper trachea was not observed in any of these patients. The lower airways are nearly always protected from direct thermal injury by the efficiency of heat exchange in the oro- and nasopharynx unless the injury involves steam or an explosive blast. This has been demonstrated in an experimental model.[17] Inhalation injury to the lower airways and pulmonary parenchyma is, therefore, almost always due to the effect of toxic or irritant gases.

Clinical suspicion of inhalation injury is aroused by the presence of certain risk factors such as history of exposure to fire and smoke in an enclosed space or a period of unconsciousness at the accident scene, burns including the face and neck, singed facial or nasal hair, altered voice, dysphagia, oral and/or nasal soot deposits, or carbonaceous sputum. The earliest threat from inhalation injury, aside from asphyxia or systemic poisoning, is upper airway obstruction due to edema. Early or prophylactic intubation is recommended when this complication threatens. However exposure to smoke does not always lead to severe injury and, in the absence of overt evidence of respiratory distress or failure, it may be difficult to identify patients who will experience progressive inflammation and ultimately require intubation of the trachea. In a retrospective study, Clark

BURN DIAGRAM Shriners Burns Institute – Galveston Unit

Age: _____

Sex: _____

Date of admission: _____

Type of burn:

Flame ☐

Electrical ☐

Scald ☐

Chemical ☐

Inhalation injury ☐

Date of burn _____

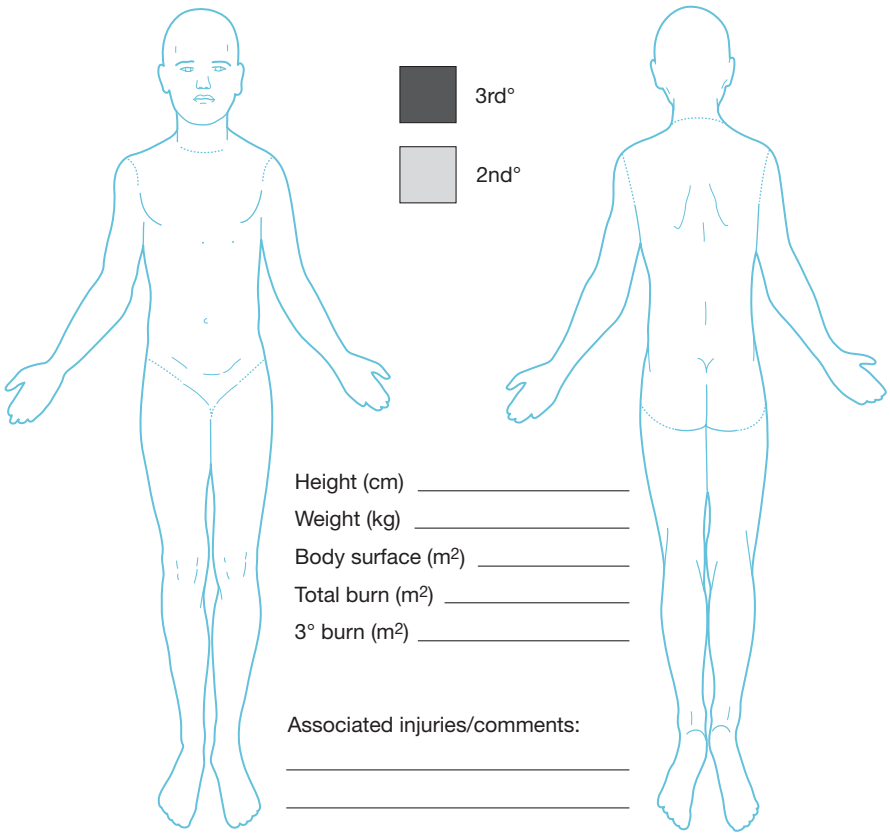
Date completed _____

Completed by _____

Date revised _____

Revised by _____

Approved by _____



Height (cm) _____

Weight (kg) _____

Body surface (m^2) _____

Total burn (m^2) _____

3° burn (m^2) _____

Associated injuries/comments:

_____

_____

Burn Estimate – Age vs. area

	Birth–1 year	1–4 years	5–9 years	10–14 years	15 years	Adult	2°	3°	TBSA%
Head	19	17	13	11	9	7			
Neck	2	2	2	2	2	2			
Anterior trunk	13	13	13	13	13	13			
Posterior trunk	13	13	13	13	13	13			
Right buttock	2.5	2.5	2.5	2.5	2.5	2.5			
Left buttock	2.5	2.5	2.5	2.5	2.5	2.5			
Genitalia	1	1	1	1	1	1			
Right upper arm	4	4	4	4	4	4			
Left upper arm	4	4	4	4	4	4			
Right lower arm	3	3	3	3	3	3			
Left lower arm	3	3	3	3	3	3			
Right hand	2.5	2.5	2.5	2.5	2.5	2.5			
Left hand	2.5	2.5	2.5	2.5	2.5	2.5			
Right thigh	5.5	6.5	8	8.5	9	9.5			
Left thigh	5.5	6.5	8	8.5	9	9.5			
Right leg	5	5	5.5	6	6.5	7			
Left leg	5	5	5.5	6	6.5	7			
Right foot	3.5	3.5	3.5	3.5	3.5	3.5			
Left foot	3.5	3.5	3.5	3.5	3.5	3.5			
						Total			

Fig. 13.3 Modified Lund and Browder for use at Shriners Hospital, Galveston. Relatively precise estimation of the percent of total body surface area affected by burns is possible with the use of the chart, which normalizes areas of different surface structures with changes that occur with age. A more rapid estimate can be made using a "Rule of Nines" chart that only distinguishes between infants and adults.

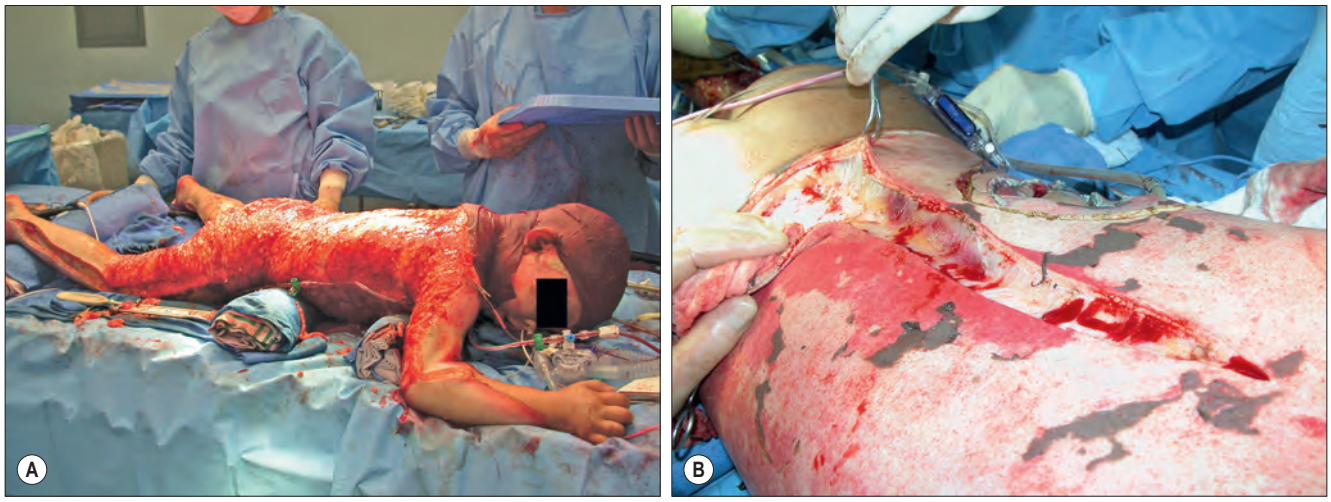


Fig. 13.4 (A) An important determinant of bleeding is surgical technique. Here the burn wound is excised tangentially with a Watson knife down to viable tissue, which is recognized by bleeding. (B) Bleeding during burn wound excision is less when the wound is excised down to the fascial layer, as in this image. Notice also the thick gelatinous layer of edematous tissue beneath the burn wound compared with the unburned tissue at the left of the image.

et al. reported that 51% of their patients exposed to smoke inhalation did not require intubation.[18] Unnecessary intubation in the presence of an inflamed laryngeal mucosa risks further damage to the larynx and subglottic area.[19,20]

Traditional clinical predictors of airway obstruction have been found to be poor predictors of airway compromise in patients with risk factors for inhalation injury.[21,22] More objective criteria for evaluation of the risk of airway obstruction are often needed. Hunt et al. found fiberoptic bronchoscopy to be a safe and accurate method for diagnosis of acute inhalation injury.[23] They described observations of severe supraglottic injuries associated with mucosal edema obliterating the piriform sinuses and causing massive enlargement of the epiglottis and arytenoid eminence. Haponic et al. made serial observations by nasopharyngoscopy in patients at risk for inhalation injury and found distortions of the upper airway described as compliant, edematous mucosa of the aryepiglottic folds, and arytenoid eminences that prolapsed to occlude the airway on inspiration.[24] Progressive upper airway edema in these patients was correlated with body surface area burned, resuscitative volume administered, and rate of infusion of resuscitative fluids. For patients who are at risk for inhalation injury but lack definitive indications for intubation, fiberoptic nasopharyngoscopy is effective in identifying impending airway compromise. Serial exams may help avoid unnecessary intubations and at the same time identify progressive inflammatory changes and allow intubation before severe airway obstruction and emergent conditions develop.[20]

Lower airway and parenchymal injuries develop more slowly than upper airway obstruction. Prior to resuscitation clinical signs and symptoms relating to respiratory function, chest x-ray, and blood gas analysis may be within normal limits despite significant injury that eventually progresses to respiratory failure requiring intubation and mechanical ventilation.[25]

Linares et al. studied the sequence of morphological changes following smoke inhalation in an experimental sheep model.[26] They observed four discrete but overlapping phases of injury described as exudative, degenerative, proliferative, and reparative. During the first 48 hours the exudative phase was characterized by polymorphonuclear (PMN) infiltration, interstitial edema, loss of type I pneumocytes, and damage to the tracheobronchial epithelium in the form of focal necrosis, hemorrhage, and submucosal edema. The degenerative phase occurred between 12 and 72 hours and was characterized by progressive epithelial damage with shedding of necrotic tissue and formation of pseudomembranes and casts. Hyaline membranes developed over alveolar surfaces. Macrophages began to accumulate to begin absorption of necrotic debris. A proliferative phase was described between days 2 and 7, during which type II pneumocytes and macrophages proliferated. After the fourth day, reparative changes were observed with regeneration of epithelium from spared epithelium from the orifices of glands.

Several reviews provide lucid descriptions of pathophysiological changes resulting from smoke inhalation.[27–29] Decreased dynamic compliance increases the work of breathing. Increased closing volume and decreased functional residual capacity lead to atelectasis and shunt resulting in hypoxia. Airways become plugged by sloughed epithelium, casts, and mucus. Impaired ciliary action exacerbates the airway obstruction by decreasing the clearance of airway debris. These changes lead to further shunt and allow colonization and pneumonia. Treatment for inhalation injury is empiric and supportive with tracheal intubation and mechanical ventilation. The application of aggressive pulmonary toilet, high-frequency percussive ventilation, and respiratory therapy protocols designed to mobilize obstructing debris are also highly beneficial. As with treating ARDS, it has been suggested that reduced tidal volumes and airway pressures may limit ventilator-induced lung injury in patients with smoke inhalation injury.[30,31] Recently, however, Sousse et al. examined the effect of reduced tidal volumes on clinical outcomes in patients with inhalation injury requiring mechanical ventilation. Historical controls

were patients previously ventilated with tidal volumes of 15 mL/kg. Outcomes of these patients were compared with current patients receiving 9 mL/kg. Patients in the group with lower tidal volumes required fewer ventilator days and had a lower incidence of atelectasis and ARDS.[32] Where the pathophysiology of ARDS relates primarily to alveolar flooding with protein rich fluid, smoke inhalation injury involves more small airway obstruction (cast and necrotic debris) resulting in increased airway resistance, decreased compliance, and V/Q mismatch. It may be that these two disease processes require different treatments.

Carbon monoxide (CO) and cyanide are two major toxic components of smoke. The burn patient with evidence of smoke inhalation injury should be evaluated for the presence of toxicity resulting from these compounds. CO binds hemoglobin 200 times more avidly than oxygen.[33] Therefore CO markedly impairs the association of oxygen with hemoglobin and decreases oxygen-carrying capacity. CO also shifts the oxy-hemoglobin dissociation curve to the left, thus decreasing the release of oxygen into tissues. These factors result in decreased oxygen delivery to tissues and, at critical levels, lead to anaerobic metabolism and metabolic acidosis. Signs and symptoms of CO poisoning include headache, mental status changes, dyspnea, nausea, weakness, and tachycardia. Patients suffering CO poisoning have a normal Pa_{O_2} and oxygen saturation by routine pulse oximetry. They are not cyanotic. Carboxyhemoglobin must be detected by co-oximetry. Carboxyhemoglobin levels above 15% are toxic and those above 50% are often lethal. The major treatment approach is administration of 100% oxygen and, in severe cases, hyperbaric treatment to increase the partial pressure of oxygen in blood.[34]

Cyanide is also a component of smoke, resulting from the burning of certain plastic products.[35] Cyanide directly impairs the oxidative apparatus in mitochondria and decreases the ability of cells to utilize oxygen in metabolism. These alterations result in conversion to anaerobic metabolism and the development of metabolic acidosis. Signs and symptoms include headache, mental status changes, nausea, lethargy, and weakness. Hydrogen cyanide levels above 100 ppm are generally fatal.[36,37]

Treatment of cyanide toxicity begins with a high inspired oxygen concentration, which may increase intracellular oxygen tension enough to cause nonenzymatic oxidation of reduced cytochromes or displace cytochrome oxidase and potentiate the effects of administered antidotes. Pharmacological intervention includes methemoglobin generators such as the nitrates (amyl nitrite inhalation 0.2 mL, or sodium nitrite, intravenous 10 mL of 3% solution for adults and 0.13–0.33 mL/kg of 3% solution for pediatrics) and dimethylaminophenol (3.25 mg/kg) to increase methemoglobin levels. Methemoglobin competes with cytochrome oxidase for cyanide. However excessive levels of methemoglobin lead to decreased oxygen-carrying capacity and may be toxic. Direct binding agents have a high affinity for cyanide. Di-cobalt edetate (20 mL of 15% solution for adults or 0.3–0.5 mL/kg of 15% solution for pediatrics) is extremely rapid in action but has significant toxicity, whereas hydroxocobalamin (adults 5–10 g or pediatrics 70 mg/kg), the precursor of vitamin B_{12}, has been shown to be safe with few systemic side effects, is actively metabolized by the liver, and avoids renal absorption. Sulfur donors such as sodium thiosulphate (adults 25 mL of 50% solution or pediatrics 1.65 mL/kg of 25% solution) accentuate the bodies' enzymatic conversion of cyanide to thiocyanate in the presence of the mitochondrial enzyme rhodanese, thus decreasing its toxicity and increasing elimination.[36,37]

EFFECT OF BURN INJURY ON CIRCULATION

Thermal injury has profound effects on the systemic circulation, and hemodynamic management is a major component of perioperative care. The skills and clinical experience of anesthesiologists match very well with the needs of patients presenting with serious burn injury, and anesthesiologists are often asked to participate in the initial resuscitation. Patients may also require surgical intervention such as escharotomy, fasciotomy, or wound excision during the first 24 hours after injury; that is, during the initial fluid resuscitation. Because of this, it is important for anesthesiologists to understand the fundamentals of burn resuscitation. It is also critical for the anesthesiologist to be able to evaluate the quality of the resuscitation and assess the hemodynamic status and physiological reserve of the patient after the initial acute resuscitation. These require familiarity with phasic changes in cardiovascular function that follow major burn injuries.

During the first few days after a large burn injury there is a biphasic change in cardiovascular function. With loss of fluid from the vascular space, hypovolemia develops quickly without aggressive replacement. This is associated with decreased cardiac output and increased systemic resistance. Over the next 2–3 days, if resuscitation is successful, this pattern is reversed. A hyperdynamic pattern develops with significantly elevated cardiac output and decreased systemic vascular resistance. Evaluation of physiological status and planning for perioperative care requires knowledge of these changes.

After massive thermal injury, a state of burn shock develops due to intravascular hypovolemia and, in some cases, myocardial depression. This state of burn shock is characterized by decreased cardiac output, increased systemic vascular resistance, and tissue hypoperfusion.[38,39] Intravascular hypovolemia results from alterations in the microcirculation in both burned and unburned tissues, leading to the extensive loss of intravascular fluid to the interstitium. Cutaneous lymph flow increases dramatically in the immediate post burn period and remains elevated for approximately 48 hours.[40] The forces responsible for this massive fluid shift involve all components of the Starling equilibrium equation,[41]

$$J_v = K_f[(P_c - P_{if}) - \sigma(\pi_c - \pi_i)],$$

where K_f is the capillary filtration coefficient, P_c is the capillary pressure, P_{if} is the interstitial hydrostatic pressure, σ s the reflection coefficient for protein, π_c is the plasma colloid osmotic pressure, and π_i the interstitial colloid osmotic pressure. The specific alterations include:

- Increase in microvascular permeability (k_f and σ) due primarily to the release of local and systemic inflammatory mediators;

- Increase in intravascular hydrostatic pressure (P_c) due to microvascular dilatation;
- Decrease in interstitial hydrostatic pressure (P_i);
- Decrease in intravascular oncotic pressure (π_c) due to leakage of protein from the intravascular space
- Relative increase in interstitial oncotic pressure due to a smaller decrease in interstitial oncotic pressure (π_i) compared to intravascular oncotic pressure (π_c).

The leakage of protein and fluid into the interstitial space often results in a washout of interstitial colloid and markedly increased lymph flow. The net effect of these changes is the development of massive edema during the first 24–48 hours after thermal injury with a concomitant loss of intravascular volume. The hypotension associated with burn injury is also due, in part, to myocardial depression. It has been 50 years since Baxter and colleagues first described burn-induced cardiac dysfunction.[42] They postulated that a circulating depressant "factor" was present in the plasma, resulting in reduced myocardial contractility. Since then, numerous groups have confirmed similar findings.[43,44] Although, this "factor" has not been specifically isolated, cytokines including tumor necrosis factor-α (TNF-α), interleukin 1-β (IL-1β), gut-derived factors from plasma and mesenteric lymphatics, and other neurohumoral mediators have been shown to reduce contractility and relaxation properties of the heart.[45-49] Both systemic activation and local tissue levels of cytokine expression are responsible for early burn-induced myocardial depression (first 2–6 hours) that begins to resolve days within days after injury.[47] There is pronounced synergy among burn injury, sepsis, and other forms of shock with regard to myocardial depression, suggesting a common pathway(s) in cardiac dysfunction.

Clinically the incidence of myocardial dysfunction following severe burn injury and its related sequelae remain somewhat controversial. Studies have often been small, underpowered, and use differing methodologies, and data have been collected at different time periods. Indirect assessments of ventricular function throughout the acute resuscitation period using right heart catheterization found that left ventricular function was hypocontractile in the context of high circulating catecholamine levels.[6,50] On the other hand, normal cardiac function has also been reported in the initial resuscitation period following burn injury. Goodwin et al., reported an increase in internal fiber shortening using M-mode echocardiography following burn injury.[51] Others reported similar findings at similar time after injury.[52] More recently diastolic dysfunction in the resuscitation period was found to be associated with increased cytokine levels and death.[53] Myocardial injury, indicated by increased plasma troponin, has also been described and associated with reduced stroke work and diastolic dysfunction.[54] Autopsy data in burns show evidence of myocardial ischemia (30–60% cases, for all age groups), suggesting non–coronary artery causes for ischemia.[55] Myocardial ischemia is likely from reduced supply (tachycardia) and increased demand (tachycardia + contractility) due to catecholamine surge and sympathetic activation. Thus cardiac dysfunction in the early (ICU) phase is likely due to myocardial stunning since fibrosis would take longer (e.g., months).[56]

If the patient survives the initial burn shock and is adequately resuscitated, a state of hyperdynamic circulation develops over the following 2–3 days that is supported by a variety of inflammatory mediators. This state of systemic inflammation has been termed the *systemic inflammatory response syndrome* (SIRS) and is characterized in burned patients by tachycardia, a marked decrease in systemic vascular resistance, and increased cardiac output. SIRS is expressed as a continuum of severity ranging from the presence of tachycardia, tachypnea, fever, and leukocytosis to refractory hypotension, and, in its most severe form, shock and multiple organ system dysfunction. In thermally injured patients, the most common cause of SIRS is the burn itself; however, sepsis (SIRS with the presence of infection or bacteremia) is also a common occurrence.

As a result of these pathophysiological mechanisms, burns involving more than 20% of the patient's TBSA will produce a state of burn shock. In patients with reduced physiologic reserve this can occur with less extensive burns (e.g., 10% TBSA burned). Initial survival from this insult requires aggressive replacement of intravascular fluid. At the same time overresuscitation can cause serious morbidity which, in extreme cases, can be lethal. Several resuscitation protocols utilizing various combinations of crystalloids, colloids, or hypertonic fluids have been developed as guides for administration of the large amounts of fluid needed by patients with acute burns (Table 13.2). Alvarado and colleagues have provided a history of the evolution of these protocols.[57] As these authors point out, little theoretical progress has been made in our understanding of burn resuscitation since current protocols were introduced in the 1970s. As a result, considerable controversy continues regarding such basic decisions as to what fluids to use or what physiological variables to use to titrate volume replacement. Whereas in the past colloid solutions were often avoided during the first 24 hours after burn injury, colloids, especially as albumin or plasma, are returning into favor.

Isotonic crystalloid is still the most commonly used fluid for resuscitation in U.S. burn centers. The most popular fluid resuscitation regimen, the Parkland Formula, uses isotonic crystalloid solutions and estimates the fluid requirements in the first 24 hours to be 4 mL/kg per TBSA burned. Another popular formula is the modified Brooke formula recommending 2 mL/kg per TBSA burned. With both of these protocols, half is given during the first 8 hours and half given over the next 16 hours. The American Burn Association "consensus formula" recommends resuscitation with 2–4 mL/kg/TBSA burned.[58]

These formulas are only estimates, and fluid requirements will vary considerably among patients with similar percentage of TBSA burned for a variety of reasons; rates and volumes must be titrated according to the patient's response. Fluid administration is generally titrated to maintain mean blood pressure above 70 and urine output at 30–50 mL/h in adults and 0.5–1.0 mL/kg per hour in pediatric patients. The use of invasive hemodynamic monitors allows targeting of determinants of oxygen delivery, which should intuitively lead to more physiologically precise resuscitation. Such efforts, however, have not improved clinical outcome and have generally resulted in more aggressive fluid administration and consequent overresuscitation.[59,60]

When evaluating the quality of resuscitation, estimates of fluid requirements based on these protocols can reveal significant departure from predicted needs. Review of the

Table 13.2 Formulas for Estimating Adult Burn Patient Resuscitation Fluid Needs

Colloid formulas	Electrolyte	Colloid	D5W
Evans	Normal saline 1.0 mL/kg/% burn	1.0 mL/kg/% burn	2000 mL/24 h
Brooke	Lactated Ringer's 1.5 mL/kg/% burn	0.5 mL/kg	2000 mL/24 h
Slater	Lactated Ringer's 2 liters/24 h	Fresh frozen plasma	75 mL/kg/24 h
Crystalloid formulas			
Parkland	Lactated Ringer's	4 mL/kg/% burn	
Modified Brooke	Lactated Ringer's	2 mL/kg/% burn	
Hypertonic saline formulas			
Hypertonic saline solution (Monafo)	Volume to maintain urine output at 30 mL/h Fluid contains 250 mEq Na/liter		
Modified hypertonic (Warden)	Lactated Ringer's +50 mEq $NaHCO_3$ (180 mEq Na/liter) for 8 hours to maintain urine output at 30–50 mL/h Lactated Ringer's to maintain urine output at 30–50 mL/h beginning 8 hours postburn		
Dextran formula (Demling)	Dextran 40 in saline—2 mL/kg/h for 8 hours Lactated Ringer's—volume to maintain urine output at 30 mL/h Fresh frozen plasma—0.5 mL/kg/h for 18 hours beginning 8 hours postburn		

patient's physiological status provides evidence of over- or underresuscitation. Crystalloid solutions generally provide adequate volume resuscitation; however the large volumes that are needed result in substantial tissue edema and hypoproteinemia. In addition, a trend toward administration of more fluid than the Parkland Formula would predict has been termed "fluid creep."[61] As mentioned earlier, overresuscitation can be associated with serious morbidity and even mortality. This has led to a search for interventions that can reduce the volume of fluid needed for resuscitation.

Although colloid was included in earlier resuscitation formulas, it was dropped during the 1970s. An overall clinical benefit was difficult to demonstrate for colloid solutions, especially when given during the first 12 hours after injury. Pruitt and colleagues reported that the addition of colloids to resuscitation fluid during the first 24 hours did not increase the intravascular volume more than crystalloid fluid alone.[62] It was also suggested that colloid use could contribute to pulmonary edema during the postresuscitation period.[51] Because of the added cost with little established benefit, colloid solutions have not been used routinely for initial volume resuscitation in burned patients in the United States until recently. In 1998, a highly publicized Cochrane meta-analysis concluded that albumin administration increases mortality in critically ill patients, including patients with severe burn injuries.[63] As relating specifically to burn-injured patients, there were serious methodological flaws with this meta-analysis sufficient for most clinicians to discount the Cochrane conclusion that albumin administration increases mortality among burn patients.[64,65] In a recent review, Saffle reported that, in nearly all studies of burn resuscitation, the use of colloid solutions has reduced the volume required as well as the complications of overresuscitation in these patients.[60] When administered specifically for the therapeutic goal of limiting the volume necessary for resuscitation, the use of colloid solutions is a rational choice for many clinicians.

In a prospective randomized study, the use of plasma for volume resuscitation was found to reduce volume infused and weight gain along with intra-abdominal pressure and the incidence of abdominal compartment syndrome (see later discussion).[66] These outcome variables have not been used for comparing crystalloid and colloid resuscitation in the past. With the trend toward larger volumes for initial resuscitation, with associated morbidity, it may be that the use of colloid is beneficial for larger injuries. The use of plasma during resuscitation may involve more than just volume and increased colloid osmotic pressure. Kozar and colleagues demonstrated that plasma but not crystalloid resuscitation partially reverses hemorrhage-induced endothelial damage in an experimental animal model.[67] Restoration of the endothelial glycocalyx may help recovery of the capillary function and reduce fluid extravasation.

Crystalloid solutions alone provide adequate intravascular expansion without unacceptable complications in many patients. However not all patients respond favorably to crystalloid resuscitation. Box 13.4 provides a list of a number of factors that can significantly increase the volume of fluid needed for resuscitation. For patients with these features, and in other patients for unknown reasons, very large volumes of crystalloid are needed to support blood pressure and maintain urine output. In these cases the excessive volume of fluid can result in dangerous morbidity, such as abdominal compartment syndrome (Fig. 13.5). For example, patients who receive more than 250 mL/kg during the first 24 hours are at risk for abdominal compartment syndrome.[68] It is important to recognize when resuscitation is difficult so that measures can be taken to limit morbidity.

Box 13.4 Factors That May Increase Fluid Needs for Resuscitation of Patients with Acute Burn Injuries

- Inhalation injury
- Delay in resuscitation
- Crush injury
- Electrical injury
- Large full-thickness burns
- Methamphetamine lab accidents
- Associated injuries

Box 13.5 Criteria for Adequate Fluid Resuscitation

- Normalization of blood pressure
- Urine output (1–2 mL/kg/h)
- Blood lactate (<2 mmol/L)
- Base deficit (<–5)
- Gastric intramucosal pH (>7.32)
- Central venous pressure
- Cardiac index (CI) (4.5 L/min/m^2)
- Oxygen delivery index (DO_2L) (600 mL/min/m^2)

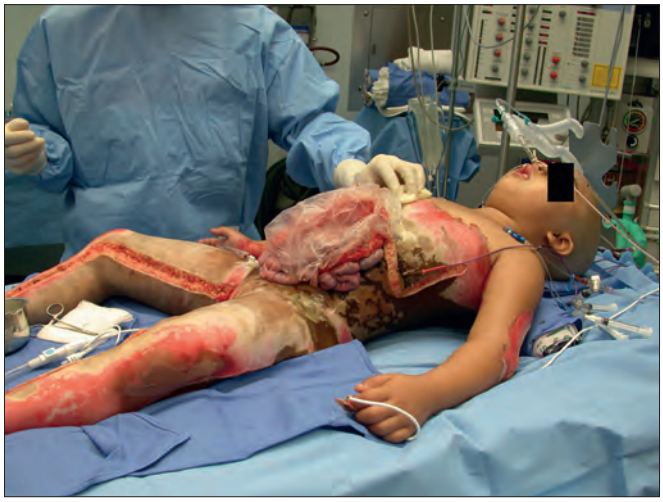


Fig. 13.5 Large volumes of crystalloid solution required for resuscitation of patients with acute burns can result in compromise of circulation in various compartments. Escharotomies or fasciotomies may be required for extremities. Laparotomy may be required for abdominal compartment syndrome when other measures do not adequately decompress the abdomen.

Extensive recent experience with burn injuries resulting from military conflicts has produced protocols that include administration of albumin for managing patients who do not have an adequate response to appropriate volumes of crystalloid fluid.[69] Likewise many civilian burn centers have adopted "colloid rescue" for patients with inadequate response to resuscitation. Lawrence and colleagues[70] evaluated responses of burn patients as an hourly ratio (I/O) of volume of fluid infused (mL/kg/%TBSA burned/h) to urine output (mL/kg/h). Patients who responded favorably to fluid administration maintained a ratio of less than 0.4, but poor responders had progressively increasing ratios to a maximum of 1.97. When patients were identified as poor responders, 5% albumin was added to their resuscitation fluid regimen. After addition of albumin each of the patients responded with a prompt decrease in the I/O ratio for the remainder of the resuscitation. In this study albumin rescue was initiated more than 12 hours after injury. The authors noted that these patients still received large volumes of fluid and that this volume might have been reduced if colloid had been given earlier. In the future it may be feasible to recognize poor responders early during resuscitation to allow earlier intervention. This study also emphasizes the heterogeneity of the burned patient population with regard to response to treatment. This heterogeneity may also explain in part why it has been difficult to show benefit from colloid administration. It would be difficult to show benefit from an intervention if it is given to a group of patients comprising both responders and nonresponders.

The use of hypertonic saline, either alone or in conjunction with colloids, has also been advocated by some in the initial resuscitation of burned patients. Among the potential benefits are reduced volume requirements to attain similar levels of intravascular resuscitation and tissue perfusion compared to isotonic fluids.[71] Theoretically, the reduced volume requirements would decrease the incidence of pulmonary and peripheral edema, thus reducing the incidence of pulmonary complications and the need for escharotomy. Hypertonic saline dextran solutions have been shown to expand intravascular volume by mobilizing fluids from intracellular and interstitial fluid compartments. Although hypertonic saline dextran solutions will transiently decrease fluid requirements, there is potential for a rebound in fluid resuscitation needs.[72] Therefore most burn centers continue to employ isotonic crystalloid fluids rather than hypertonic solutions for initial resuscitation of patients in burn shock.

Unfortunately there is no single physiological variable that is always reliable as an end point to guide resuscitation in acute burn patients. Several variables are used to assess the adequacy of volume resuscitation in burned patients (Box 13.5). The overall goal is early volume resuscitation and establishment of tissue perfusion. Traditionally urine output (0.5–1 mL/kg per h) and normalization of blood pressure (mean arterial blood pressure of greater than 70 mm Hg) have been used as endpoints. However, some studies indicate that these parameters may be poor predictors of adequate tissue perfusion. Jeng and colleagues showed that attaining urine outputs of greater than 30 mL/h and mean blood pressures of greater than 70 mm Hg correlated poorly with other global indicators of tissue perfusion such as base deficit and blood lactate levels.[73] In order to maintain perfusion of vital organs such as heart and brain, blood flow is often redistributed away from splanchnic organs. Persistent hypoperfusion of these organs ultimately results in tissue injury and may be a contributing factor to multisystem organ dysfunction. Several studies have shown that normalization of blood pressure, heart rate, and urine output alone does not by itself

correlate with improved outcome.[74,75] Therefore during the preoperative assessment of the burn patient, the anesthesiologist should not base the cardiovascular assessment on one variable but use a more global approach to evaluating the patient's physiological status and reserve.

When vital signs and urine output are within normal limits, measurements of metabolic function may provide more subtle evidence of impaired perfusion. In burn patients, tissue perfusion is not uniform. Perfusion of the splanchnic beds may be sacrificed in order to maintain the perfusion of heart, brain, and kidneys. Blood lactate and base deficit provide indirect metabolic global indices of tissue perfusion. Lactic acid is a byproduct of anaerobic metabolism and is an indicator of either inadequate oxygen delivery or impaired oxygen utilization. In the absence of conditions such as cyanide poisoning or sepsis that alter oxygen utilization at the cellular level, lactate level may be a useful marker of oxygen availability.[76] Wo and colleagues found serum lactate to be the most predictive index of adequate tissue perfusion, and a lactate level of less than 2 mmol/L in the first 24–72 hours after burn injury correlated with increased survival.[75] Base deficit is another indirect indicator of global tissue perfusion. The base deficit is calculated from the arterial blood gas using the Astrup and Siggard-Anderson nomograms. Although it is a calculated and not directly measured variable, base deficit provides a readily obtained and widely available indicator of tissue acidemia and shock. Base deficit has been shown to correlate closely with blood lactate and provides a useful indicator of inadequate oxygen delivery. A retrospective study by Kaups et al. showed that base deficit was an accurate predictor of fluid requirements, burn size, and mortality rate.[77]

Overresuscitation can also be a serious complication of fluid administration to acute burn patients. Blindness due to ischemic optic neuropathy has been reported as a complication of burn resuscitation.[78] Greenhalgh and Warden first described the association of increased abdominal pressures and compartment syndrome with burn resuscitation.[79] Several studies since then have described the common occurrence of increased intra-abdominal pressure with large-volume burn resuscitation. Intra-abdominal hypertension is termed abdominal compartment syndrome when it is associated with impaired respiration, circulation, and urine output. Mechanical ventilation is impaired by pressure on the diaphragm, circulation is impaired by restricted venous return due to caval compression, and urine output is impaired by compression of renal vessels. When this pattern presents, the patient should be examined for elevated intra-abdominal pressure. This can be accomplished by measuring bladder pressure: 50 mL of saline is instilled into the bladder through the Foley catheter and the height of the saline column above the symphysis pubis is measured (1.36 cm of H_2O = 1 mm Hg).[80] Conservative treatment of elevated intra-abdominal pressure includes attempts to limit the volume of intravenous fluid needed for resuscitation. The inclusion of plasma with resuscitation fluids has been found to reduce the volume required and was associated with significantly lower intra-abdominal pressures.[66] When intra-abdominal hypertension occurs it can be relieved to a degree by optimizing sedation and analgesia. Diuresis with furosemide and muscle relaxants to reduce muscle tone have been used to reduce intra-abdominal pressure. More invasive measures include escharotomies,[81] percutaneous peritoneal dialysis catheter drainage,[82] and laparotomy.[79]

Serious burns can also be caused by contact with caustic or corrosive chemicals. An increasingly common specific example is burns related to the illicit production of methamphetamine.[83–85] There has been a dramatic increase in burn injuries from explosions and fires related to methamphetamine production in illegal labs. Victims of these accidents present unique challenges for a variety of reasons. Substances used in methamphetamine production include chemicals that are corrosive and toxic (e.g., anhydrous ammonia, hydrochloric acid, red phosphorous, and ephedrine). Other ingredients are flammable (acetone, alcohol, and gasoline), and explosions can coat the victims with all these chemicals. As a result, in addition to the victim's toxic exposure, contacting incompletely decontaminated victims of these accidents has injured first responders and hospital workers.[86,87]

In addition to exposures just described, these patients are usually intoxicated with methamphetamine, as demonstrated by positive urine screen, and may have inhaled toxic fumes such as phosphine gas. Santos et al. found the incidence of inhalation injury twice as great in victims of methamphetamine-related burns as in age- and burn-matched controls.[85] Among their patients requiring intubation for inhalation injury, methamphetamine users also required roughly twice as many ventilator days. Clinical studies have consistently observed increased fluid requirements for resuscitation of methamphetamine patients.[85,86] For example, Santos et al. found that resuscitation volumes were 1.8 times greater for methamphetamine users with burns than for controls.[85] In addition, methamphetamine users with burns experienced more behavioral problems. These patients are more often agitated and require restraints. Santos et al. reported that all their methamphetamine patients required greater than normal doses of sedatives and displayed what they referred to as "withdrawal-type syndrome."[85] This behavior may be due to withdrawal of methamphetamine from chronic users.

EFFECT OF BURN INJURY ON RENAL FUNCTION

Acute kidney injury (AKI) is a very common and devastating complication of severe burn injuries. The incidence is often estimated at 30% or more and can increase the mortality in these patients to more than 80%.[88] The risk of AKI with burns increases with all the features intuitively associated with poor outcome. Despite improvements in critical care, AKI continues to complicate burn care and increase mortality. There have been some indications of an improvement, however. Jeschke and colleagues have shown a decrease in mortality in pediatric burn patients with ARF to 56% since 1984.[89] Also, Chung and colleagues found that early application of continuous venovenous hemofiltration in patients with evidence of AKI, especially in the presence of inhalation injury, improved survival compared with conventional care that included hemodialysis after more stringent criteria were met.[90]

The pathogenesis of AKI in burn patients is complex and can involve a number of interconnected mechanisms. A

difference between AKI that occurs early after injury has been distinguished from injury developing later.[91] Early AKI is associated with reduced renal blood flow resulting from acute burn shock, whereas AKI that occurs later is associated with sepsis and exposure to nephrotoxic drugs. Early AKI carries a worse prognosis than the late form.[88] Continuous evaluation of the patient's response to fluid resuscitation is necessary for the early recognition and correction of under- or overresuscitation to prevent early AKI.

Another mechanism of early AKI is caused by myoglobinemia resulting from rhabdomyolysis due to compartment syndrome or electrical injury.[92,93] Treatment of this form of AKI is difficult. Brown and colleagues found that rates of renal failure, dialysis, or mortality were not altered by treatment of rhabdomyolysis with bicarbonate and mannitol.[94] Early diagnosis and treatment of compartment syndrome or muscle damage due to electrical injury is, therefore, critical to preventing its development.

The presence of renal failure complicates intraoperative management. It seriously reduces the margin of error for fluid replacement of blood loss. A central venous catheter (CVC) to monitor filling pressure may be more useful in these patients. Electrolyte balance, especially potassium, should be watched closely and extra caution with dosage and rate of administration of nephrotoxic drugs such as antibiotics is needed.

METABOLIC CHANGES ASSOCIATED WITH BURN INJURY

Increased metabolic rate is the hallmark of the metabolic alterations that take place after thermal injury. The magnitude of the hypermetabolism is influenced by the size of the burn wound, how the burn patient is treated, and the ambient temperature of the patient.[95,96] Within the range of 30–70% TBSA burn injury, the hypermetabolism tends to be proportional to the size of the burn wound. With burns beyond this range, the hypermetabolism appears to plateau and only increases in smaller increments.[97] Septic complication is an important factor that can increase the metabolic response, as does the physiologic stress of pain. It has been observed that modern-day treatment of burn injuries with early excision and closed-wound treatment ameliorates this hypermetabolism.[98] Burn patients increase their metabolic rate in an effort to generate heat according to a new threshold set point for the body temperature that is influenced by the size of the burn (see the section "Thermoregulation in Burn Patients"). The recognition of this fact has led to an increased awareness of the importance of the ambient temperature in modulating the hypermetabolism of the burn patient. By indirect calorimetry, patients with major burn injuries treated according to current standards have resting energy expenditures that are 110–150% above values recorded in nonburned subjects.[99]

As a result of this hypermetabolic response, the acutely burned patient has an increased O_2 consumption along with an increased CO_2 production that demands a higher respiratory effort. The anesthetic care of the acute burned patient has to accommodate these changes, and frequently this has to be done in patients with compromised pulmonary function due to burn injury.

The hypermetabolic pattern also increases caloric needs. Numerous studies have shown that optimized nutritional care not only can ameliorate the burn-associated state of catabolism and immune suppression, but also can improve wound healing.[96] Oral or enteral feeding is recognized as the optimal feeding route of the burned patient. Frequently the acute burn patient is fed continuously over extended time periods. If standard guidelines for perioperative fasting are implemented, recurrent operative procedures can significantly impinge on the nutritional needs of the patient and ultimately cause a caloric deficit. Each surgical procedure requiring general anesthesia theoretically necessitates a 10-hour interruption of enteral nutritional support (fasting for 8 hours preoperatively and 2 hours postoperatively). To avoid this interruption of nutritional support, continuation of feeding via a post-pyloric feeding tube has been used. One study indicates that this practice provides a favorable gut oxygen balance.[100] Varon et al. reviewed records of 17 patients fed intraoperatively through post-pyloric feeding tubes and 16 patients fasted for surgery. These patients had an average of seven surgical procedures each.[101] There were no clinical adverse effects with intraoperative feeding, and these patients met nutritional goals sooner than patients fasted for surgery. Larger studies are necessary to establish the safety of intraoperative feeding but many practitioners consider this safe in the presence of a cuffed tracheal tube.

Severe insulin resistance with hyperglycemia and concurrent hyperinsulinemia is a key feature of the metabolic alterations of burn injury.[95] Critical care of burn patients often involves parenteral nutritional support and may also include insulin infusions. It is important to recognize these interventions during the preoperative evaluation of the burn patient in the ICU. Oxygen consumption and glucose balance are altered when general anesthesia, muscle relaxation, and mechanical ventilation are employed. Increased sympathetic tone due to the stress of surgical trauma can also alter glucose production and insulin resistance. These changes often result in significant changes in blood glucose levels that require treatment.

THERMOREGULATION IN BURN PATIENTS

Maintenance of proper body temperature is an important factor in the care of severely burned patients. The thermoregulatory system is controlled by three major components. These include the afferent system that senses changes in core body temperature and transmits this information to the brain, the central regulatory mechanisms located primarily in the hypothalamus that process afferent input and initiate responses, and the efferent limb that mediates specific biological and behavioral responses to changes in core body temperature (Fig. 13.6). Temperature is sensed by Aδ and C fibers present in peripheral tissues such as skin and muscle, as well as in core tissues such as brain, deep abdominal tissues, and thoracic viscera. The vast majority of afferent input arises from the core tissues. Because the skin is in direct contact with the environment, it senses immediate changes in environmental temperature. However the overall afferent input of the skin and other peripheral tissues is estimated to be only 5–20% of total afferent thermoregulatory input.[102] Therefore loss of skin following a burn injury is not likely to markedly alter overall afferent input. Wallace

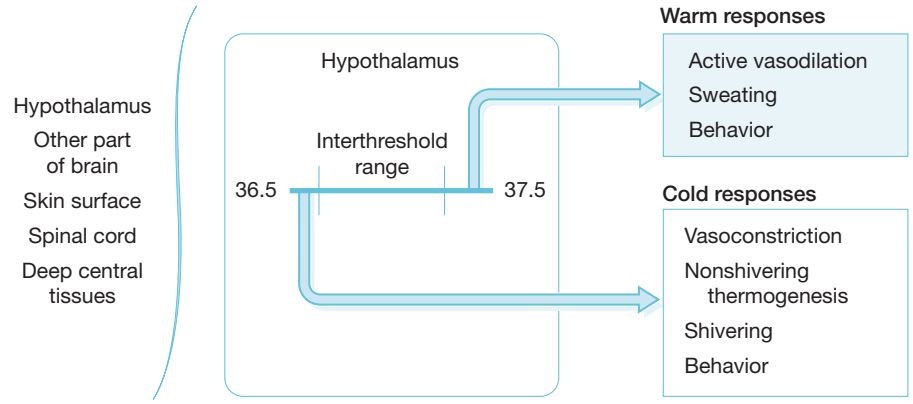


Fig. 13.6 Thermoregulatory control mechanisms. Afferent inputs from a variety of sites, most notably skin, central tissues, and brain, are processed in the central nervous system. Based on input, a variety of efferent thermoregulatory responses are initiated. (From Sessler DI. Temperature monitoring. In: Miller R, ed. *Anesthesia*, 3rd edn. New York: Churchill Livingstone; 1990.)

and colleagues have shown that burn patients perceive changes in ambient temperature as effectively as normal controls.[103] This is likely due to the retained ability of burn patients to sense changes in core temperature and transmit this information to the central nervous system. Central control of temperature is a complicated system that is not well understood. The hypothalamus plays an important role in temperature regulation, but the complete mechanism of temperature control is likely to be multifaceted and is an area of intense research. Regardless of the ultimate control mechanisms, temperature control can be divided into three main functions: threshold, gain, and maximum response intensity.

Threshold encompasses a set point at which responses to temperature change are initiated. In normal individuals the threshold range is generally near 36.5–37.5°C. In burn patients, the threshold set point is higher, and the increase is proportional to the size of the burn. The work of Caldwell and colleagues predicts that the temperature set point will increase by 0.03°C/%TBSA burn.[104] This increase in temperature threshold appears to be due to the hypermetabolic state and the presence of pyrogenic inflammatory mediators such as TNF, IL-1, and IL-6 that are present after thermal injury. The elevated temperature set point can be decreased by administration of indometacin, which suggests that prostaglandins act as final common mediators of this response.[105,106]

Gain describes the intensity of response to alterations in temperature. In most cases the gain of thermoregulatory responses is very high, with response intensity increasing from 10% to 90% with only a few tenths of a degree change in core temperature. This response is maintained in most burn patients, resulting in a further increase in metabolic rate.[103] Burn patients respond with a brisk increase in heat generation and metabolic rate in response to changes in core body temperature.[103] However work by Shiozaki and colleagues has shown that burn patients who are slow to respond to postoperative hypothermia are at increased risk of mortality.[107] The decreased responsiveness may be due, in part, to tissue catabolism, poor nutrition, or sepsis. In addition, the response to relative hypothermia is characterized by increased catecholamine release, tissue catabolism, and hypermetabolism. These responses further stress burn patients and decrease their ability to respond to their primary injury.[108]

The most important efferent responses to hypothermia are behavioral responses such as gaining shelter, covering up, and seeking a more desirable ambient temperature. In the acute postburn setting, most of these behaviors are impeded by positioning, sedation, and inability to seek a more favorable environment. Therefore caregivers must be attentive to the patient's temperature and perception of cold so that measures can be undertaken to optimize the patient's temperature. Cutaneous vasoconstriction is another important mechanism for preserving heat and core body temperature. In unburned persons, a temperature gradient of 2–4°C exists between skin and core tissues. This gradient is maintained by cutaneous vasoconstriction. Without cutaneous vasoconstriction, heat is redistributed from the core compartment to the periphery. This heat is ultimately lost to the environment. Peripheral vasoconstriction minimizes temperature redistribution and acts to maintain core body temperature. This mechanism of heat preservation is lost with the loss of large areas of skin, particularly if cutaneous tissues are excised down to the fascial level. The loss of skin facilitates the loss of core body heat into the environment and places the burn patient at risk for core hypothermia. Another mechanism of heat loss in burn patients is evaporation. Burn patients can lose as much as 4000 mL/m^2 burned per day of fluids through evaporative losses.[109] Mechanisms of nonshivering heat production and shivering remain intact in burn patients. However, shivering increases metabolic requirements and is likely deleterious.

The induction of anesthesia results in relative ablation of thermoregulatory mechanisms and puts the patient at further risk for developing hypothermia. Patients under general anesthesia exhibit a markedly decreased threshold for responding to hypothermia (Fig. 13.7). This is particularly important in burn patients, given their high temperature set point and the deleterious effects of further stress responses and hypermetabolism. Most anesthetics decrease nonbehavioral responses to hypothermia such as vasoconstriction, nonshivering thermogenesis, and shivering. Of course, behavioral responses are ablated during general anesthesia. Therefore, it is the responsibility of the

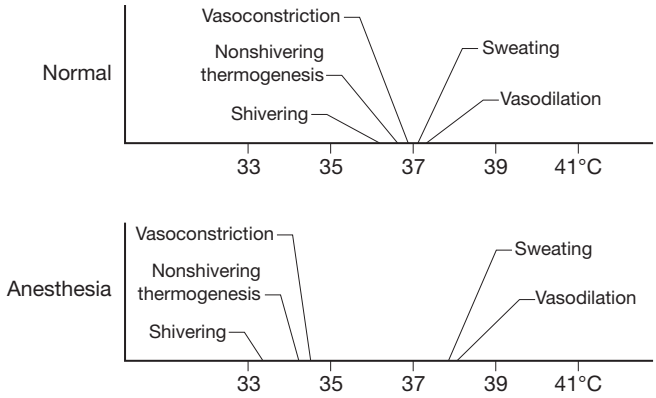


Fig. 13.7 Effects of anesthesia on thermoregulatory mechanisms. (From Sessler DI. Temperature monitoring. In: Miller R, ed. *Anesthesia*, 3rd edn. New York: Churchill Livingstone; 1990.)

intraoperative caregivers to monitor and maintain patient temperature.

Actions such as maintaining higher ambient air temperature, covering extremities and head, applying warm blankets, utilizing radiant heaters and forced air warming devices, warming fluids and blood, and warming gases are usually effective in maintaining core temperature if applied aggressively. Ideally hypothermia should be corrected prior to transport to the operating room.[110] Hypothermia revealed in the preoperative evaluation may be due to inadequate resuscitation or metabolic instability. Either situation may predispose burn patients to intolerance of anesthetic drugs or the stress of surgery.

Pharmacological Considerations

Burn injury and its treatment result in physiological changes that may profoundly alter the response to drugs. These changes alter both pharmacokinetic and pharmacodynamic determinants of drug response. Altered drug response in burned patients may require deviation from usual dosages to avoid toxicity or decreased efficacy.[111] The complex nature of the pathophysiological changes and interpatient variation in the nature and extent of burn injuries, as well as the dynamic nature of these changes during healing and recovery make it difficult to formulate precise dosage guidelines for burn patients. However an understanding of the systemic response to large burn injuries can help predict when an altered drug response can be expected and how to compensate.

The two distinct phases of cardiovascular response to thermal injury can affect pharmacokinetic parameters in different ways. During the acute or resuscitation phase the rapid loss of fluid from the vascular space due to edema formation results in decreases of cardiac output and tissue perfusion. Volume resuscitation during this phase dilutes plasma proteins and expands the extracellular fluid space especially, but not exclusively, around the burn injury itself. Decreased renal and hepatic blood flow during the resuscitation phase reduces drug elimination by these organs. Also, decreased cardiac output will accelerate the rate of alveolar accumulation of inhalation agents, which may result in an exaggerated hypotensive response during induction of general anesthesia.

After approximately 48 hours, the hypermetabolic and hyperdynamic circulatory phase is established with increased cardiac output, oxygen consumption and core temperature. During this phase, increased blood flow to the kidneys and liver may increase clearance of some drugs to the point where increased doses are required.[112]

Many drugs are highly protein bound. Drug effects and elimination are often related to the unbound fraction of the drug that is available for receptor interaction, glomerular filtration, or enzymatic metabolism. The two major drug-binding proteins have a disparate response to burn injury. Albumin binds mostly acidic and neutral drugs (diazepam or thiopental) and is decreased in burn patients. Basic drugs (pKa >8, propranolol, lidocaine, or imipramine) bind to α-acid glycoprotein (AAG). AAG is considered an acute-phase protein and its concentration may double after burns. Since these drug-binding proteins respond in opposite ways to thermal injury it can be expected that changes in drug binding and function will depend on which of these proteins has the highest affinity for the drug in question. Martyn et al. observed decreased plasma albumin concentration and increased plasma AAG concentration in burn patients.[113] These observations were associated with an increased unbound fraction for diazepam (bound by albumin) and a decreased unbound fraction for imipramine (bound by AAG).

Volume of distribution (V_d) is changed by alterations to either extracellular fluid volume or protein binding. Large changes in both of these variables occur with thermal injuries. Drugs with high protein binding and/or a V_d in the range of the extracellular fluid volume may be associated with clinically significant alterations of V_d in burned patients. V_d is the most important determinant of drug response following a rapid loading dose. However adjustments in dose to compensate for altered V_d are indicated only when V_d for the drug is small (<30 L) because with larger V_d only a small fraction of the drug is present in the plasma.[111]

Clearance is the most important factor determining the maintenance dose of drugs and can influence the response to drugs given by infusion or repeated bolus during anesthesia. Drug clearance is influenced by four factors: metabolism, protein binding, renal excretion, and novel excretion pathways. The characteristic hepatic extraction of a particular drug influences changes in its clearance that occur after thermal injury. Drugs vary greatly in their extraction by the liver. Hepatic clearance of drugs highly extracted by the liver depends primarily on hepatic blood flow and is insensitive to alterations in protein binding. Clearance of these drugs may increase during the hyperdynamic phase when hepatic blood flow is increased. In contrast, clearance of drugs that have a low hepatic extraction coefficient is not affected by changes in hepatic blood flow but is sensitive to alterations in plasma protein levels.[111] For these drugs it is the unbound fraction of the drug that is metabolized. As noted, changes in unbound fraction depend on whether the drug is bound by albumin or AAG. Changes in protein levels produce clinically significant pharmacokinetic changes only for drugs that are highly bound (>80%).[114]

During resuscitation, renal blood flow may be reduced and renal excretion of drugs may be impaired. Later, during the hypermetabolic phase, renal blood flow is increased as a result of the elevated cardiac output. During this period excretion of certain drugs can be increased to the point that the dose may need to be increased. Loirat et al. reported increased glomerular filtration rates and reduced half-life of tobramycin in burn patients.[115] However, this was age-dependent and patients over 30 years of age did not have increased glomerular filtration or reduced half-life.

Burn patients may also experience altered drug clearance due to novel excretion pathways. Glew et al. found that 20% of a daily gentamicin dose was eliminated in the exudates lost to wound dressings.[116] In addition, rapid blood loss during surgery may speed the elimination of drugs when blood loss and transfusion amount, essentially, to an exchange transfusion.

Hepatic clearance of drugs with low extraction coefficients is also sensitive to alterations of hepatic capacity (enzyme activity). There is evidence of impairment of hepatic enzyme activity in burn patients.[111] Phase I reactions (oxidation, reduction, or hydroxylation by the cytochrome P-450 system) are impaired in burn patients, whereas phase II reactions (conjugation) seem to be relatively preserved.[112] However, these generalizations do not always produce predictable alterations in pharmacokinetic parameters. For example, contradictory observations of morphine clearance in burn patients have been reported. Morphine metabolism is by glucuronidation. This is a phase II reaction that is normally retained in thermally injured patients. Morphine clearance in burn patients has been reported unchanged or decreased.[117,118] With so many variables involved, such as hepatic blood flow, V_d, plasma proteins, multiple drug exposure, and variation in burn injury, this inconsistency is not surprising. The key to effective drug therapy in burn patients is to monitor drug effects and carefully titrate the dose to the desired effect.

In terms of anesthetic management, the most profound and clinically significant effect of burn injuries on drug response relates to muscle relaxants. Burn injuries of more than 25% TBSA influence responses to both succinylcholine and the nondepolarizing muscle relaxants. In burned patients, sensitization to the muscle-relaxant effects of succinylcholine can produce exaggerated hyperkalemic responses severe enough to induce cardiac arrest.[119–121] In contrast, burned patients are resistant to the effects of nondepolarizing muscle relaxants.[122–124] These changes are explained by up-regulation of skeletal muscle acetylcholine receptors.[125–127]

Martyn and Richtsfeld have recently reviewed the mechanisms of exaggerated hyperkalemic responses to succinylcholine.[127] There are several disease states, including burns, denervation, and immobilization, that are associated with potentially lethal hyperkalemic responses to succinylcholine. The molecular mechanism appears to be both quantitative and qualitative changes in skeletal muscle postsynaptic nicotinic acetylcholine receptors. Animal and human studies consistently demonstrate an association of increased numbers of skeletal muscle acetylcholine receptors with resistance to nondepolarizing muscle relaxants and increased sensitivity to succinylcholine. In addition, the distribution of the new receptors is altered. Nicotinic receptors are normally restricted to the neuromuscular synaptic cleft, but, in these disease states, new receptors are distributed across the surface of the skeletal muscle membrane. The new receptors are also a distinctly different isoform (α7AChR) that has been referred to as an immature, extrajunctional, or fetal receptor. The immature receptors are more easily depolarized by succinylcholine, and their ion channel stays open longer. The immature receptors are also strongly and persistently depolarized by the metabolite of acetylcholine and succinylcholine, choline. It has been suggested that the hyperkalemic response to succinylcholine after burn or denervation injury results when potassium is released from receptor-associated ion channels across the entire muscle cell membrane rather than just the junctional receptors. Depolarization persists because the channels stay open longer and the breakdown product of succinylcholine, choline, is also a strong agonist for the immature receptors.

Cardiac arrest in burned patients after succinylcholine administration was first reported in 1958.[119] It was not until 1967, however, that an exaggerated hyperkalemic effect was identified as the cause of this phenomenon.[120,121] However, considerable individual variability exists, and only a few patients in these series developed dangerously high potassium levels. The size of the increase was greatest about 3–4 weeks after injury. The earliest exaggerated hyperkalemic response described occurred 9 days after injury, and normal responses were observed in the remaining patients in this series for up to 14–20 days.[128] The shortest post-burn interval of an association of succinylcholine with cardiac arrest was 21 days when a 4-year-old patient experienced a fatal cardiac arrest during a fourth anesthetic induction and intubation with succinylcholine. Controversy has surrounded recommendations regarding the safe use of succinylcholine after burn injury. Various authors recommend avoidance of succinylcholine at intervals ranging from 24 hours to 21 days after burn injury.[129,130] A series of letters from experts in this area to the editor of *Anesthesiology* illustrates the controversy.[131,132] It was pointed out by Martyn that, at the time when the mechanism of the cardiac arrest after succinylcholine was elucidated, surgical treatment of burns was delayed for approximately 2 weeks until the eschar spontaneously separated.[132] As a result, there are few clinical data regarding potassium changes during this early period. On the basis of indirect evidence from experimental data, Martyn recommended avoidance of succinylcholine starting 48 hours after injury.[132] This seems rational and prudent. Brown and Bell described the super-sensitivity of burned pediatric patients to the relaxant effect of succinylcholine.[133] They observed more than 90% depression of muscle activity with 0.2 mg/kg succinylcholine without dangerous hyperkalemia. Despite these observations Brown and Bell state that it is generally advisable not to use succinylcholine in patients with large burns. The question remains: in the presence of life-threatening laryngospasm in a burn patient, is it acceptable to give a small dose of succinylcholine (e.g., 0.1 mg/kg) to relieve laryngospasm without full paralysis and accept a theoretical risk of treatable hyperkalemia in order to treat a real and immediate risk of asphyxia? Administration of a large dose of a nondepolarizing relaxant requires more time for onset than succinylcholine and

produces total paralysis. There is not enough clinical evidence to answer this question conclusively, and, at present, it remains a matter of clinical judgment.

In some cases another clinical choice is now available since the U.S. Food and Drug Administration (FDA) approval of sugammadex in December 2015. Sugammadex is a reversal agent with a novel and unique mechanism of action. It is a cyclodextrin that irreversibly chelates aminosteroid muscle relaxants by forming a 1 : 1 tight complex (encapsulation) with the relaxant molecule, which reduces the concentration of the free drug in plasma below the minimum necessary for muscle relaxation. A Cochrane review found sugammadex to be an effective reversal agent without evidence of increased frequency of adverse effects when compared to neostigmine.[134] In fact, sugammadex has been found to provide more rapid recovery of more than 90% twitch strength than either spontaneous recovery with succinylcholine or reversal with neostigmine.[134] Sugammadex has a lower affinity for pancuronium, and higher doses are required for this agent than for rocuronium or vecuronium. Although the frequency of adverse effects due to sugammadex has been very low, there have been some serious complications associated with its administration, including anaphylaxis and severe bradycardia requiring chest compressions. Another more common issue relates to the potential for sugammadex to inactivate hormonal contraceptives. Female patients treated with contraceptives should be advised to use an alternative form of contraception for a period after receiving sugammadex.

As of this writing (January 2017), sugammadex has not yet received FDA approval for pediatric patients, and most reported pediatric data are in the form of case reports and small studies. The clinical experience with sugammadex in children has been reviewed by Tobias.[135] Sugammadex has been found to be an effective rescue agent in situations where pediatric patients cannot be intubated or ventilated. It has also proved useful in pediatric patients with neuromuscular diseases such as Duchenne muscular dystrophy and myotonic dystrophy.[135] In some situations rocuronium might be an additional choice to relieve laryngospasm in an acute burn patient when there is a risk of intubation or ventilation impossibility if sugammadex is available since it can reverse relaxation with rocuronium faster that spontaneous recovery from succinylcholine. Still, the onset of action for rocuronium is slower than for succinylcholine.

Responses to nondepolarizing relaxants are also altered by burn injury. Three- to fivefold greater doses are required to achieve adequate relaxation.[122] Resistance is apparent by 7 days after injury and peaks by approximately 40 days. Sensitivity returns to normal after approximately 70 days. Two reports described slight but measurable resistance to nondepolarizing relaxants persisting for more than a year after complete healing of the wounds. The mechanism of the altered response appears to involve pharmacodynamic rather than pharmacokinetic changes. Up-regulated immature receptors are less sensitive to nondepolarizing relaxants. Burns of greater than 25% TBSA require higher total dose and greater plasma concentrations of nondepolarizing blockers to achieve a given level of twitch depression.[124]

Proliferation of acetylcholine receptors across the muscle membrane has been used to explain both resistance to nondepolarizing muscle relaxants and the exaggerated hyperkalemic response to succinylcholine.[127] The observation of resistance of a patient to metocurine for up to 463 days after the burn has been used to suggest that hyperkalemic responses to succinylcholine also could persist for more than a year.[123] However, no pathologic hyperkalemic responses to succinylcholine in burned patients have been reported more than 66 days after burns.[129]

In contrast to other nondepolarizing neuromuscular blockers, mivacurium dosage requirements in pediatric patients appear to be unchanged by the burn injury. The time to onset of drug action, the degree of paralysis achieved by a specific dose, and the rate of infusion required to maintain a given level of relaxation were all the same in burn patients as values reported for nonburned control patients.[136] Plasma cholinesterase activity is reduced in burn patients.[137] In a study by Martyn, the observation of an inverse relationship between plasma cholinesterase activity and recovery time of 25–75% twitch tension suggests that reduction of metabolic degradation of mivacurium may compensate for other factors that induce resistance to relaxants.[136] This observation suggests that mivacurium can be administered to burn patients in normal doses that would avoid cardiovascular perturbations associated with required larger doses of other relaxants in burn patients. It also illustrates the complex nature of altered drug responses in burned patients.

Airway Management

If injuries do not preclude conventional airway management (i.e., mask fit, jaw lift, and mouth opening), standard induction and intubation procedures are appropriate. Hu et al. reported that gastric emptying was not delayed in patients with severe burns so that a rapid-sequence induction is not necessary.[138] However, attention should be given to gastric residuals during enteric feeding. Development of sepsis can slow gastric emptying, which can result in retained fluids in the stomach and risk of aspiration.

When burns include the face and neck, swelling and distortion may make direct laryngoscopy difficult or impossible. In addition, loss of mandibular mobility may impair airway manipulation and make mask ventilation difficult. Fiberoptic intubation while maintaining spontaneous ventilation is a safe and reliable technique under these conditions. Fiberoptic intubation can be performed in awake adults but pediatric patients are unable to cooperate and must be sedated. Since most anesthetics cause the collapse of pharyngeal tissues and airway obstruction, they are unsuitable for fiberoptic intubation in patients whose airway would be difficult to manage with a mask.[139] Ketamine, however, is unique among anesthetic drugs because it maintains spontaneous ventilation and airway patency.[140]

Ketamine anesthesia has been found safe and effective for airway management in infants with difficult airways caused by congenital airway anomalies. Reports of successful nasotracheal intubation in infants with congenital airway malformations have been made both by manipulations guided by fiberoptic nasopharyngoscopy and the conventional technique of fiberoptic intubation with the endotracheal tube mounted on the fiberscope.[141,142] In the latter case an ultra-thin bronchoscope (2.7 mm) was required

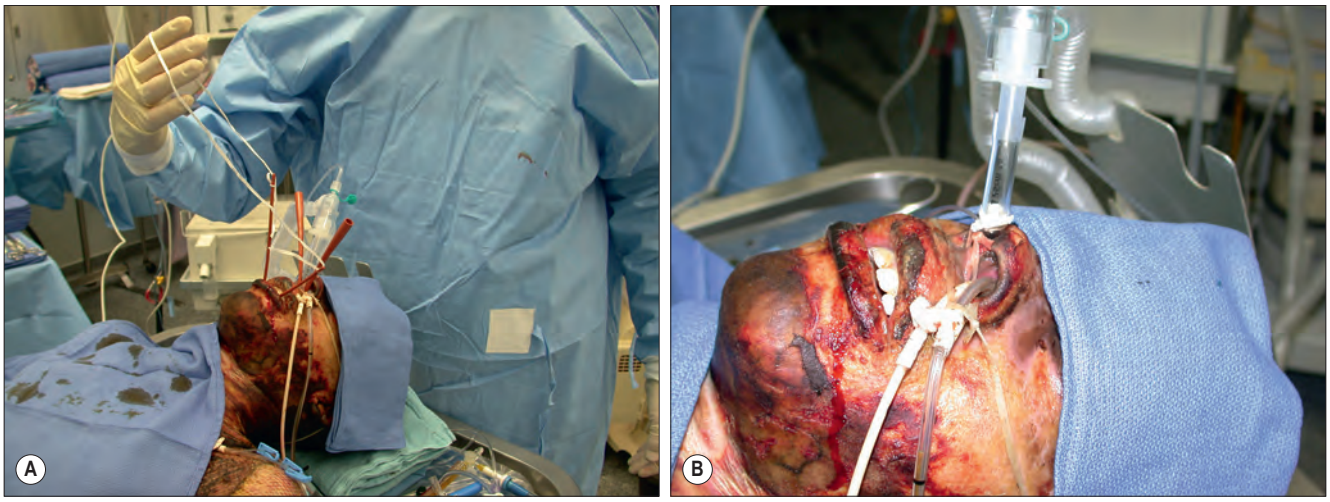


Fig. 13.8 A nasotracheal tube can be secured with confidence with a loop of umbilical tape around the bony nasal septum. (A) Red rubber catheters have been passed through each naris and retrieved from the oropharynx using McGill forceps. A length of umbilical tape is then tied to each of the catheters. When the catheters are pulled from the nose, the umbilical tape can be tied in a loop around the nasal septum. (B) Endotracheal tube, nasogastric tube, and duodenal feeding tube are all secured in place after being tied to the septal bridal. When fastened in this manner the endotracheal tube is very secure, and tape or ties do not irritate burn wounds of the face and neck.

because a larger fiberscope would not fit through the appropriate-sized endotracheal tube. To facilitate intubation under ketamine anesthesia, topical anesthesia of the larynx with lidocaine prior to instrumentation of the larynx is advised. Since the ultra-thin bronchoscope lacks a working channel for administration of topical lidocaine, fiberoptic intubation with the 2.7-mm bronchoscope was preceded by nasopharyngoscopy with a 3.5-mm fiberscope for administration of topical lidocaine. At SBH Galveston we have also found this technique, utilizing two fiberscopes, effective in infants with burn injuries. Wrigley et al. evaluated the use of a 2.2-mm intubating fiberscope during halothane anesthesia in ASA 1 or 2 children aged 6 months to 7 years.[143] In this series of 40 patients, a number of complications were experienced including laryngospasm and failure to achieve intubation with the fiberscope. This experience is in contrast to numerous reports of safe and effective airway management with ketamine.

Securing an endotracheal tube in a patient with facial burns presents a variety of problems, and numerous techniques have been described.[144] Tape will not adhere to burned skin and ties crossing over burned areas will irritate the wound or dislodge grafts. In addition, if the head is burned, especially if the patient has also required a large fluid resuscitation, then during the first few days after injury, the head is swelling due to edema formation or shrinking as edema resolves. Under these conditions tape surrounding the head will become loose or too tight within hours. A useful technique to avoid these problems involves the use of a nasal septal tie with one-eighth-inch umbilical tape (Fig. 13.8). The umbilical tape is placed around the nasal septum using 8 or 10 French red rubber catheters that are passed through each naris and retrieved from the pharynx by direct laryngoscopy and McGill forceps. A length of umbilical tape is tied to each of the catheters, and, when the catheters are pulled back through the nose, each end of the umbilical tape is pulled out of its respective naris, producing a loop around the nasal septum. Before securing with a knot, care should be taken to assure that the uvula is not captured in the loop. A knot in the nasal septal tie should be snug enough to prevent excessive movement of the endotracheal tube but loose enough to prevent ischemic necrosis of the underlying tissues. Nasal endotracheal tubes are often avoided in ICUs due to concern for sinusitis. However, nasogastric or nasal feeding tubes carry similar risk. Over the past 25 years our hospital has had two patients with suspected sinusitis. Sinus cultures from these patients were negative for bacterial growth (unpublished observations). The nasal endotracheal tube is much more secure than an oral tube, better tolerated by the patient, and the patient cannot occlude the nasal tube by biting it.

A red rubber catheter may also be used to secure an oral endotracheal tube (Fig. 13.9). A red rubber catheter is placed in a nostril and brought out the mouth by direct laryngoscopy and MacGill forceps. A loop is formed which the endotracheal tube is secured to with umbilical tape. This is very secure and avoids ties around the neck, which can irritate wounds and grafts, and the problem of changing head circumference due to formation and resolution of edema.

Airway management using a laryngeal mask airway has also been used successfully during burn surgery for children. McCall et al. reported their experience with 141 general anesthetics administered to 88 pediatric burn patients.[145] Nineteen (14.5%) of the procedures were complicated by respiratory events such as unseating, desaturation, and partial laryngospasm that required intervention. Two of these events required intraoperative intubation without sequelae, while all other events resolved with therapy. Interestingly the presence of preoperative respiratory problems or face/neck burns did not predict intraoperative respiratory problems. These authors suggest that, in patients with upper airway mucosal injury, laryngeal mask airway management may help avoid further

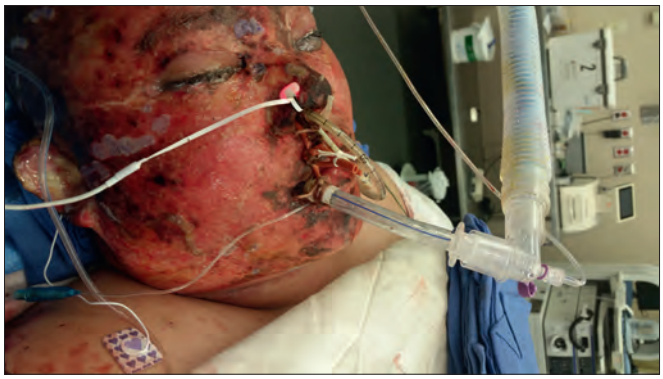


Fig. 13.9 An oral endotracheal tube can be secured to a loop created by a red rubber catheter (or similar device) passed through the nose and brought out the mouth. When the endotracheal tube is fastened to this loop there are no ties surrounding the head and neck which can irritate burn wounds and disrupt grafts. Note also the nasal pulse oximeter probe, which has undergone significant improvements recently. Other sites for pulse oximetry, such as ears and fingers, are frequently unavailable in patients with large burns.

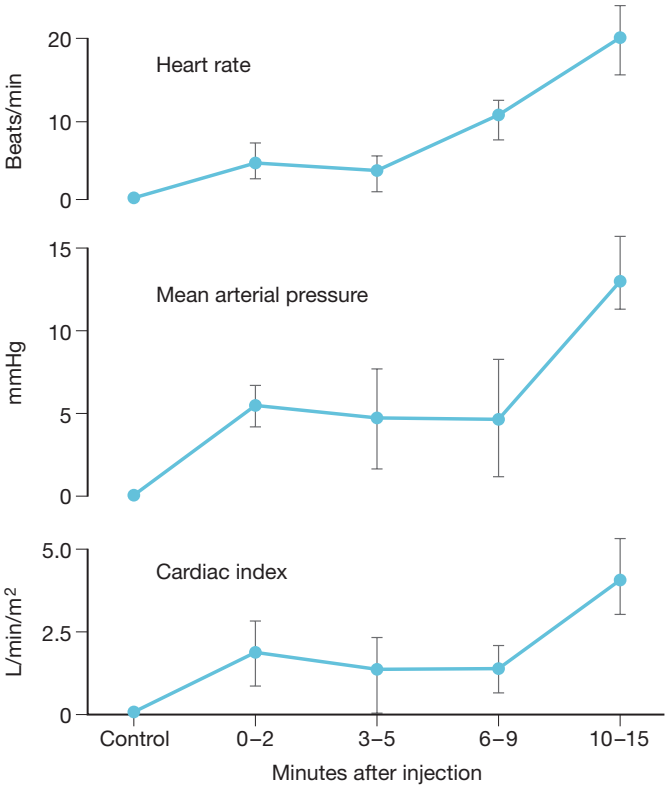


Fig. 13.10 Heart rate, mean arterial pressure, and cardiac index changes during a 15-min period of ketamine administration to critically ill patients. (From Nolan JP. Intravenous agents. In Grande CM, et al., eds. *Textbook of trauma anesthesia and critical care.* St. Louis: Mosby Yearbook; 1993.)

laryngeal injury that might occur with intubation of the trachea.

Hagberg et al. published a case report describing the successful use of an esophageal tracheal Combitube in a patient undergoing elective surgery for burn scars involving the mouth.[146] The patient had a class IV oral airway by Samsoon and Young's modification of the Mallampati airway classification and limited mouth opening. A translaryngeal endotracheal tube was undesirable because tracheostomy had resulted in subglottic stenosis that could have been exacerbated by an endotracheal tube. After induction with fentanyl and propofol, the Combitube was placed and the patient was relaxed with rocuronium and mechanically ventilated during the 60 min procedure.

Monitors

As with any critically ill patient suffering from multiorgan system involvement, the choice of monitors in a burned patient will depend on the extent of the patient's injuries, physiological state, and planned surgery. In addition to the preoperative pathophysiology associated with thermal injuries, perioperative monitoring must be adequate to assess rapid changes in blood pressure and tissue perfusion associated with the massive blood loss that can accompany excision of burn wounds. The minimum standards of the American Society of Anesthesiologists require monitoring of circulation, ventilation, and oxygenation. Standard monitors include electrocardiography (EKG), measurement of systemic blood pressure, pulse oximetry, capnography, and inspired oxygen concentration. The ability to measure body temperature should be readily available and is highly recommended for the burn patient.

Standard EKG gel electrodes usually will not adhere to burn patients because the skin is injured or covered with antibiotic ointment. For acute burn surgery, surgical staples and alligator clips are useful. Respiratory rate can be quantitated using bioimpedance from the EKG signal or from the capnogram. Pulse oximetry in burn patients can be difficult when transmission pulse oximetry sites are either burned or within the operative field. Reflectance pulse oximeter probes are now available, and nasal clip probes are much improved (Fig. 13.10 with oral red rubber).

If direct arterial pressure monitoring is not necessary, a blood pressure cuff can provide accurate measurements even if placed over bulky dressings applied to an extremity.[147] Systolic blood pressures obtained from the pressure at which the pulse oximetry signal returns during cuff deflation have also been found to be accurate.[148]

When vasoactive infusion is needed or blood loss is expected to be rapid and extensive, the blood pressure may change more rapidly than the interval between cycles of noninvasive blood pressure measurement. In this case an arterial catheter can provide direct and continuous measurement of blood pressure. This monitor can provide much more information regarding the patient's circulatory status than just systolic and diastolic blood pressure. The arterial pressure wave form is influenced by preload, contractility, and vascular tone. Perioperative variation in the rate of rise of arterial pressure, the area under the pressure wave, position of the dicrotic notch, and beat-to-beat alterations in systolic pressure related to respiration all reflect clinically significant hemodynamic changes.[149] With experience, trends in these variables can help guide volume and vasoactive therapy. Display of the beat-to-beat arterial pressure allows measurement of systolic pressure variation (SPV)

and other measures sensitive to variation in stroke volume. These dynamic measures of the interaction between preload and stroke volume have been used to predict the response to fluid volume administration. SPV is the difference between maximum and minimum systolic blood pressure during a single cycle of positive pressure mechanical ventilation. Several studies have correlated SPV with cardiac output response to volume infusion. Tavernier et al. reported that in septic patients on mechanical ventilation, SPV is a better predictor of left ventricular ejection volume response to volume loading than either pulmonary artery occlusion pressure or echocardiographic measurement of left ventricular end diastolic area.[150] When hemorrhage is brisk, the decision to administer volume is not difficult. In other cases during burn wound manipulation, hypotension and other evidence of poor perfusion can occur in the apparent absence of significant blood loss. Inappropriate fluid administration can cause hemodilution, increased cardiac filling pressure, and fluid overload. Measurement of central venous pressure (CVP) can indicate if there is room in the intravascular space for volume administration, and dynamic measures of fluid responsiveness can identify patients who will respond to fluid loading with an increase in cardiac output and tissue perfusion. The use of these dynamic measures of fluid responsiveness, as well as their limitations, have been reviewed recently.[151] However no single physiological variable can be relied on to correct all deficiencies in perfusion during burn wound debridement. Wound manipulation can release inflammatory mediators and bacterial products that alter myocardial compliance and contractility as well as vascular tone. During challenging cases with brisk bleeding volume replacement alone may not correct hemodynamic deficiencies. It is necessary to monitor blood gases, electrolyte changes, and urine output, as well as arterial and central venous pressures. Inadequate tissue perfusion may manifest as metabolic acidosis despite apparently adequate arterial and central venous blood pressures.

Arterial blood sampling for blood gas analysis can also provide valuable information regarding pulmonary function and ventilatory support, acid–base balance, and electrolyte abnormalities. Blood samples from a central vein are not truly mixed venous, but trends in central venous oxygen tension can help identify inadequate tissue perfusion. A CVC sutured into place also provides very secure intravenous access and is an ideal route for administration of vasoactive infusions. A pulmonary artery catheter is usually not required for burn surgery. In some cases, however, the ability to more closely monitor ventricular function and oxygen supply/demand relationships may be helpful in the presence of pre-existing disease or when large doses of inotropes or high PEEP is required.

Urine output is the most useful perioperative monitor of renal function. Urine output of 0.5–1.0 mL/kg per hour is often recommended as an end point for fluid management in acute burn patients. Adequate urine output is one measure of both renal and global perfusion. When intraoperative transfusion is planned, examination of the urine may be the only reliable indicator of a transfusion reaction since signs and symptoms other than hematuria are masked by general anesthesia or hemodynamic changes associated with burn surgery. Myoglobinuria may also occur after burn injury, and, in this case, a Foley catheter is necessary to monitor response to therapy. Diuretic therapy for myoglobinuria or any other indication will negate the usefulness of urine output as an index of global perfusion.

Vascular Access

Care of patients with major burn injury requires secure vascular access for resuscitation, blood sampling, hemodynamic monitoring, and intravenous medication. In patients with large burns a CVC can serve several functions. Extensive burns may preclude cannulation of peripheral veins. A CVC sutured in place can provide secure access longer than a peripheral catheter can be maintained. Multiport catheters can provide a monitor of CVP while infusing blood or other fluids and can allow simultaneous infusion of incompatible drugs.

Vascular cannulation of acutely burned patients can be one of the more technically challenging procedures facing the burn care team. Anesthesiologists are often involved in the management of vascular access for burn patients. In the pediatric age group the task can be even more difficult. Sites for percutaneous insertion of vascular catheters may be involved in the burn and nonburned sites are often distorted by burn wound, edema, or trauma. Early after burn injuries burn shock is associated with hypovolemia and vasoconstriction, which add to the difficulty. Later in the hospital course debridement and scarring further distort anatomy.

Because the systemic manifestations of wound infection and SIRS mimic those of catheter-related bloodstream infections, vascular catheters are changed to new sites more often than in nonburned patients. In addition, CVCs appropriate for ICU care are not always appropriate for rapid infusion of fluid and blood products during surgery, often necessitating placement of new catheters in the operating room. With hospitalization for major burns lasting weeks and months, patients may need multiple cannulations over a prolonged time period. With multiple technically difficult vascular cannulations over a prolonged period, risks of infectious and mechanical complications are significant. In addition to immediate mechanical complications of line insertion, repeated cannulation of vessels can result in thrombosis, which can be a source of embolic events, and the vessel can be obliterated, causing venous stasis and limiting future access. These considerations make it necessary to minimize the number of cannulations as much as possible, especially for patients expected to have a long hospital course. Infectious complications are as much a consideration as mechanical complications in burn patients. Open, possibly infected wounds near or at the insertion site as well as bacteremia that may occur during wound care increase the risk of line infection. Although it is commonly assumed that arterial catheters are less susceptible to infection, studies show that the rates are similar for arterial and central venous catheters.[152] However, since the risk of mechanical complications for femoral arterial cannulation is greater (see later discussion), the risk–benefit relationship of changing sites or exchanging over a wire is less favorable for arterial catheters than venous. There is no consensus, and a great deal of variation exists between burn centers regarding policies and procedures to minimize these risks.

Early complications of the placement of venous catheters include trauma, hematoma, bleeding, air embolus, pleural effusion, pneumothorax, or pericardial tamponade. Late complications include venous thrombosis, infection, and infiltration. Complications of arterial catheters include damage to adjacent structures, ischemia to distal tissues, and infection.

Ultrasound-guided placement of vascular catheters is now widely recommended.[153,154] This technique has been found to be faster and associated with fewer complications than cannulation with anatomical landmarks. Few studies, however, compare ultrasound-guided cannulation outcomes with other techniques in burn patients. The combination of massive edema, hypovolemia, vasoconstriction, and acoustic shadows from scars all degrade the ultrasound image. Practitioners should not rely solely on one technique but should be able to utilize multiple techniques including ultrasound, anatomical landmarks, a palpable pulse, and pencil Doppler signal to place vascular catheters.

When possible, if a percutaneous insertion site is involved in the burn wound, it is best to have surgical debridement accomplished before insertion. This facilitates both ease of placement and infection control. Catheter selection must take into account multiple clinical needs: blood sampling, hemodynamic monitoring, rapid infusion of large volumes of fluid and blood products, and infusion of medications that may be incompatible with each other. A lumen large enough to allow rapid infusion of volumes appropriate to the patient's size is necessary. When blood loss is expected to be extensive, it is helpful to monitor CVP. Although CVP correlates poorly with hemodynamic function in populations of patients, when hypotension or anemia occur, knowledge of whether the CVP is high or low can help decide if an inotrope is appropriate or if there is room in the vascular space to increase the hematocrit quickly. In addition, ICU management may require a different catheter. Some compromise or a change of catheters prior to transport to the ICU may be needed.

In recent years peripherally inserted central catheters (PICCs) have been used in burn patients. The advantages of these devices over conventional CVCs are the ease of insertion, reduced risk of some complications of CVCs, and reduced cost. At the time of this writing the largest study of complications associated with PICCs is by Austin and colleagues who described their clinical experience with 53 patients and reviewed the literature.[155] While the use of a PICC avoids some risk of a CVC, such as pneumothorax or hemothorax, the PICC carries its own unique risks. The incidence of catheter-related infections may be similar for PICCs and CVCs. Despite the use of antithrombotic prophylaxis upper extremity deep vein thrombosis (UEDVT) that can lead to fatal embolic events has been associated with PICC placement. Burn patients are often hypercoagulable and, as a result, are at risk for occlusive and embolic events. Austin et al. found symptomatic UEDVT in 5.5% of patients with PICC lines in place.[155] UEDVT associated with PICC lines appears to increase with duration longer than 7 days and with increasing diameter of the catheter. Austin and colleagues describe the PICC as an accepted standard of care for burn patients but not without risk. The decision of whether to use a PICC or a conventional CVC must balance the risks and benefits of these devices for each patient.

Table 13.3 Changes That Occur During Storage of Whole Blood in Citrate-Phosphate-Dextrose

	Days of Storage at 4°C			
	1	7	14	21
pH	7.1	7.0	7.0	6.9
P_{CO_2} (mm Hg)	48	80	110	140
Potassium (mEq/L)	3.9	12	17	21
2,3-Diphosphoglycerate (μmol/mL)	4.8	1.2	1	1
Viable platelets (%)	10	0	0	0
Factors V and VII (%)	70	50	40	20

Maintaining arterial catheters in burn patients presents an additional challenge. Radial artery catheters are problematic because the hands are often burned, and it is difficult to maintain them over prolonged periods in burn patients. As a result most burn centers rely on femoral artery catheters when arterial cannulation is indicated. Since the femoral artery is an end artery, mechanical injury can lead to the devastating complication of the loss of lower extremity tissue. For this reason it is essential to have a clear indication for arterial cannulation (Table 13.3). In many cases clinical decisions can be made with analysis of venous blood samples rather than arterial blood.

Studies in nonburned patients have compared rates of infection of different insertion sites. In nonburned patients it is recommended that cannulas not be changed over a wire to avoid infection.[156] It is also recommended that catheters not be changed in response to fever alone, and, when universal precautions are followed, catheters can be left in place for prolonged periods. However in burn patients requiring prolonged hospitalization it is often necessary to utilize all available sites as catheters are rotated to fresh sites. Also, the increased risk of line infection in patients with burns and the confounding signs and symptoms of systemic inflammation from the burn wounds that mimic catheter-related bloodstream infection make it difficult to follow guidelines established for nonburned patients. Lozano and colleagues found 9.36 catheter-related infections per 1000 catheter days when vascular catheter sites were changed only with signs of infection as per guidelines from the U.S. Centers for Disease Control and Prevention (CDC) but only 3.23 per 1000 catheter days when the sites were routinely changed every 5 days. As a result, in most burn centers, vascular insertion sites are changed more frequently than in ICUs caring for nonburn patients. Many centers will also change catheters over a wire and culture the catheter tip after a certain period of time. If the tip is colonized a new site can be cannulated. It is difficult to form universal protocols for vascular access in burn patients since they comprise such a heterogeneous group. Decisions regarding site of cannulation and when to change sites are influenced by multiple factors including which sites are available, previous complications, surgical scheduling, ICU management (e.g., need for total parenteral nutrition), and evidence of infection (wound- or catheter-related). Incidence of catheter infection increases when the insertion site

is in or near burn wounds.[157] With limited sites available it is tempting to leave catheters in unburned sites longer than in sites through burn wounds. Decisions are best guided by the general goals of minimizing infection and mechanical complications but should be individualized for each patient's immediate needs.

Although arterial catheters are generally considered less likely to be associated with infection, these catheters are infected with a frequency similar to CVCs.[152] There are fewer sites for arterial cannulation, however, and the risk of serious mechanical complications of femoral artery injury are potentially greater than with venous catheters. As a result, femoral arterial catheters are often left in place longer than venous cannulas.

Delayed complications include infection and thrombosis, which have been studied by many authors with often conflicting results. Many older studies recommend frequent catheter changes to decrease the incidence of infection, but several later studies show no increase in infection out to as many as 7–10 days. Three large randomized trials demonstrated no difference in the incidence of catheter-related infections among groups who had lines placed at a new site every 7 days and groups who had their lines changed over a guidewire every 7 days.[158–160] The incidence of mechanical complications is lower with guidewire exchange rather than changing to a new site.[161]

Vascular catheters that incorporate an antibiotic have been found effective in reducing the incidence of catheter-related bloodstream infections in burn patients. A prospective, randomized trial examined the efficacy of two types of CVCs that incorporate antibiotics: one catheter releases silver ions continuously, and the other is impregnated with two antibiotics with different mechanisms of action, rifampicin and minocycline. Both catheters were associated with low rates of catheter-related bloodstream infections.[162] If effective, these catheters can provide two significant clinical advantages. Reduced colonization of CVCs will reduce the risk of blood-borne infections, and reduced need for changes in vascular access sites for infection control will reduce the incidence of mechanical complications of catheter insertion. However, as with other clinical decisions with burn patients, the data from studies in burn patients make it difficult to form guidelines. Studies consistently show decreased rates of bloodstream infection, but the rates of infection between burn centers are greater than the effect of using antibiotic-impregnated catheters.[163,164] Moreover, since catheters are changed much more frequently in burn patients, often every 72 hours, and even earlier with signs of infection, the cost benefit in burn patients is not established.

When planning vascular access for perioperative anesthetic management it is important to be aware of and take into account the patient's hospital course. Choice of access site should avoid vessels previously involved in complications such as thrombosis or vascular injury. Note must be taken of when existing catheters were placed and what the local convention is with regard to timing of regular changes of access sites for infection control. The patient's hospital course must also be considered when choosing a catheter. The catheter should be large enough to transfuse appropriately for the case, but catheters much larger will increase risk without benefit.

Patient Transport

The safe transport of a critically ill burn patient to and from the operating room can be a formidable task. A methodical approach will help to ensure patient safety and the seamless maintenance of respiratory, hemodynamic, and general support. Hemodynamic status should be optimized prior to patient transport; pharmacological support may be required. The American Society of Anesthesiologists standards mandate evaluation, treatment, monitoring, and equipment appropriate to the patient's medical condition for any transport. Depending on the patient's condition, simple observation may be appropriate. Patients requiring supplemental oxygen should be monitored by pulse oximetry. Hemodynamic monitoring is guided by the patient's hemodynamic status. Sufficient battery power must be available for uninterrupted monitor and infusion pump function during transport.

Airway supplies should be readily available, including a full oxygen cylinder, a self-inflating Ambu bag with mask, and intubation equipment. The patient's airway and ventilation, as well as overall condition, must be continually observed by the anesthesia care team. Drugs for resuscitation should accompany the patient on any transport. As discussed earlier, hypothermia is poorly tolerated by patients with an acute burn injury. It is imperative that patients be kept warm during transport in order to avoid increasing oxygen consumption and taxing limited metabolic reserve

Selection of Anesthetic Agents

Many anesthetic agents have been used effectively for the induction and maintenance of anesthesia in burn patients. Intravenous agents can be used for both induction and maintenance, and the specific agent used will depend primarily on the patient's hemodynamic and pulmonary status as well as on the potential difficulty of securing the patient's airway. Ketamine has many advantages for use in the burn patient for induction and maintenance of anesthesia. As an induction agent, ketamine can be administered at a dose of 0.5–2.0 mg/kg. Except in patients who are catecholamine depleted, ketamine generally preserves hemodynamic stability (Fig. 13.10). In addition, ketamine preserves hypoxic and hypercapnic ventilatory responses and reduces airway resistance.[165] Compared to other IV anesthetics, airway reflexes remain more intact after ketamine administration. Patients who do not require ventilatory support can be allowed to breathe spontaneously, which provides an additional margin of safety should inadvertent extubation occur. In fact, some clinicians have reported the use of ketamine anesthesia without instrumentation of the airway.[166,167] Patients were allowed to breathe spontaneously, and the airway complication rate was comparable to that of intubated patients. The use of intramuscular ketamine can be beneficial in securing the airway of pediatric burn patients or uncooperative adults who do not have vascular access. Because ketamine preserves spontaneous ventilation and induces dissociative anesthesia, it provides good conditions for securing the airway by fiberoptic bronchoscopy. When using this

technique, the addition of potent volatile agents should be avoided until the airway is secured because these anesthetics depress respiratory drive and relax pharyngeal muscles, thus increasing the risk of apnea, upper airway obstruction, or laryngospasm. Ketamine can also be utilized, either alone or in combination with other anesthetics, for maintenance of anesthesia either by infusion or intermittent bolus. Ketamine has potent analgesic properties and is used extensively in the operating room as well as for painful dressing changes and procedures such as line insertion. A drying agent such as glycopyrrolate (2–5 μg/kg) may be given in combination with ketamine to reduce ketamine-induced secretions. Delirium during emergence from ketamine sedation is more common in adults. This is often treated with midazolam, but dexmedetomidine may be more effective and also attenuates hypertensive and tachycardic effects of ketamine.[168] Dexmedetomidine also reduces the dose of ketamine required.[169]

Propofol is the most common intravenous induction agent used in burn patients. Dose requirements for propofol will vary over time after the initial burn injury. Initially, with hypovolemia and reduced cardiac output, a lower dose may be required but as the hyperdynamic circulatory pattern develops the V_d and clearance rate for propofol are increased enough to increase dose requirements.[170]

Volatile anesthetics may be used for both induction and maintenance of anesthesia in burn patients. In pediatric patients, mask induction with sevoflurane is commonly used if the patient does not have injuries that may make airway manipulation difficult. In the acute setting, an anesthetic technique involving nasotracheal intubation after mask induction with halothane, nitrous oxide, and oxygen has been described.[171] The proponents particularly emphasize avoiding the potential problems associated with the ketamine-based technique. However volatile agents produce dose-dependent cardiac depression and vasodilation. In addition, hypoxic ventilatory drive is ablated by volatile anesthetics at low concentrations, and a dose-dependent depression of hypercapnic drive also occurs. However, as maintenance agents, volatile anesthetics have predictable wash-in and wash-out kinetics and provide a useful adjunct to other agents when titrated to hemodynamic and ventilatory parameters. Of the volatile agents, nitrous oxide has the least impact on cardiovascular and respiratory function and can serve as a useful component of a balanced anesthetic if the patient's oxygen requirements permit.

Opioids are important agents for providing analgesia for burn patients throughout the acute phase of injury and for providing postoperative analgesia in patients undergoing reconstructive procedures. The spectrum of opioids currently available provides a wide range of potencies, durations of action, and effects on the cardiopulmonary system. Burn patients experience intense pain even in the absence of movement or procedures, and opioids are the mainstay for providing analgesia in the acute phase of burn management. Selection of dosage must take into account the fact that acute burn patients usually become tolerant to opioids due to continuous and prolonged administration. Therefore opioids should be titrated to effect in the acute burn patient. Most opioids have little effect on cardiovascular function, but they are potent respiratory depressants. Therefore the ventilatory status of patients receiving opioids, particularly those with challenging airways, should be monitored closely.

Regional anesthesia can be used effectively in patients with small burns or those having reconstructive procedures. In pediatric or adult patients having procedures confined to the lower extremities, lumbar epidural or caudal anesthesia can provide a useful adjunct for control of postoperative pain. In cooperative adult patients with injuries confined to lower extremities, epidural or intrathecal anesthesia may be used if no contraindications exist. For upper extremity procedures, brachial plexus block may be considered as the primary anesthetic or as an adjunct for postoperative pain control.

Scalp donor sites are particularly painful. Sensory nerves to the scalp are superficial and easily blocked with injections of local anesthetic, and this technique has been used for awake craniotomy.[172] Scalp blocks have been used with success at our institution for donor sites in acute patients (unpublished observation) and for scalp procedures in reconstructive patients.[173]

Fluid Management

Fluid management and blood transfusion for burn wound excision can be quite challenging. Fluid administration should be guided not only by intraoperative events but previous hospital course and ICU treatment goals. If excision is performed during the first 24 hours, perioperative fluid management may involve acute resuscitation, and fluid needs will exceed replacement of shed blood. Even after this period insensible fluid requirements are increased by large open surfaces from excised wounds, hypermetabolic state, and hyperthermia. However, early in the patients' hospital course, patients are edematous from the large amounts of crystalloid solutions administered during resuscitation. At this time additional crystalloid administered during the perioperative period may be poorly tolerated and may result in complications of compartment syndrome in extremities or the abdomen. After the initial period of resuscitation ICU therapy may include vigorous attempts to reduce edema including the use of diuretics. If the ICU staff have been administering diuretics to the patients all week in order to reduce interstitial edema, it is not helpful when the patient receives several liters of fluid in the operating room. Perioperative fluid management must also take into account hypotonic clysis fluids that the surgeons may inject subcutaneously to facilitate donor skin harvest with the dermatome. In small children the volume of this fluid can be in excess of 50 mL/kg. State of hydration and electrolyte balance must be monitored carefully in order to maintain proper fluid balance. Although it is important to avoid overhydration, aggressive diuresis in the burn ICU may result in a patient who presents to the operating room intravascularly hypovolemic despite extensive peripheral edema.

Replacement of surgical blood loss during burn wound excision and grafting represents another challenge. Unlike most general surgical procedures, during burn surgery it is impossible to accurately estimate the amount of shed blood during the procedure. Shed blood is not collected in suction canisters where it can be measured. During burn surgery shed blood is concealed beneath the patient, in drapes, in

sponges, or may be washed down a drain on the operating table. As discussed earlier regarding the initial resuscitation, there is no one physiological end point to titrate volume replacement. Arterial pressure may be maintained by vasoconstriction despite significant hypovolemia, CVP is not a reliable index of preload, changes in urine output and hematocrit lag behind rapid reductions in blood volume, and metabolic acidosis may indicate deficient perfusion but does not identify the specific problem. All of these variables are useful, however, when evaluated together. Although systolic blood pressure may be within the normal range, alterations in the arterial wave form and changes with the respiratory cycle may indicate hypovolemia. Even though CVP correlates poorly with hemodynamic function, this variable is useful in determining if volume administration will be tolerated by the patient. If the perfusion appears inadequate and CVP is low or normal it is safe to give volume. If CVP is elevated, volume administration may cause pulmonary edema.

The concept of *transfusion trigger* with regard to burn care is discussed in the next section. It must be remembered, however, that during rapid blood loss the hematocrit may change more slowly than the blood loss, and often blood must be administered in anticipation of the hematocrit falling below a specific trigger.

BLOOD TRANSFUSION

The need for blood transfusion is usually not a major concern during the immediate resuscitation phase in acutely burned patients unless other coexisting trauma exists. In fact, when the resuscitation is inadequate, the hematocrit will be elevated. Nevertheless a fall in plasma hemoglobin concentration can occur during the acute resuscitative phase due to hemodilution and blood loss from escharotomies and other invasive procedures.[174] However major blood loss is common during excision and grafting of burn wounds. Desai and colleagues reported that the amount of blood loss during burn wound excision is determined by the age of the burn, the body surface area involved, and whether infection is present (see Table 13.1).[12] In general, more blood loss was observed as the time from initial injury increased and if wounds were infected. Transfusion requirements ranging from 0.45 to 1.25 mL of packed red blood cells (PRBCs) per cm^2 burn area were reported. In another study, Criswell and Gamelli reported an average transfusion rate of 0.89 mL PRBC/cm^2 burn area in a cohort of adult burn patients.[175] A study by O'Mara and colleagues showed an average transfusion rate of 0.65 mL PRBC/cm^2 in a heterogeneous group of burn patients.[176]

Controversy exists regarding transfusion triggers and targets. Some authors advocate allowing hematocrit to drop to 15–20% prior to transfusion in otherwise healthy patients undergoing limited excision and transfusing at a hematocrit of 25% in patients with pre-existing cardiovascular disease.[177] The same group proposed maintaining hematocrit near 25% in patients with more extensive burns and near 30% if the patients have pre-existing cardiovascular disease. A small study by Sittig and Deitch showed fewer transfused units and no increase in adverse hemodynamic or metabolic effects in patients transfused at a hemoglobin of 6–6.5 g/dL compared to patients maintained at a hemoglobin near 10 g/dL.[178] However, in general, few outcome data exist regarding the optimum transfusion trigger for blood transfusion during burn wound excision. Assessment of blood transfusion needs is best determined by evaluating the clinical status of the patient; specifically, assessment of ongoing blood losses, preoperative hemoglobin levels, vital signs, and urine output. Metabolic evidence of inadequate oxygen delivery such as acidemia and decreasing mixed venous oxygen tension provide important information regarding the oxygen balance in the patient. Patients with coexisting cardiac and pulmonary disease generally require higher oxygen-carrying capacity. Oxygen requirements will be determined by the type and severity of coexisting conditions. Overall American Society of Anesthesiologists guidelines indicate that blood transfusion is rarely required at a hemoglobin of 10 g/dL or above and is almost always indicated at a hemoglobin of less than 6 g/dL.[179]

During excision of large burn wounds, patients may require one or more blood volumes of transfused blood to replace intraoperative blood losses. Massive blood transfusion can be associated with a variety of complications, and the use of blood products is associated with significant financial costs.[175] Several means of decreasing surgical blood loss during burn wound excision may be employed, such as the use of tourniquets on limbs and compression dressings at sites of burn wound excision or skin graft harvesting.[180] Tourniquets have been shown to be an effective strategy for decreasing blood loss during burn wound excision.[176] The drawbacks of tourniquet use are that their effectiveness is limited to surgery on the extremities and they may interfere with the surgical field. Pharmacological interventions that may decrease blood loss include the use of epinephrine-soaked dressings or topical epinephrine spray to induce local vasoconstriction. Alternatively subcutaneous tissues may be infiltrated with epinephrine-containing fluids. The use of epinephrine may be associated with tachycardia and hypertension if significant amounts are absorbed into the systemic circulation. However some studies have reported that the use of topical or subcutaneous epinephrine in burn patients is not associated with an increased incidence of side effects or complications.[181]

The effectiveness of this approach is, however, unclear. A recent study showed that the use of topical epinephrine spray or subcutaneous epinephrine infiltration did not result in decreased blood loss during burn wound excision.[182] However the data were quite variable, and the patients also received topical thrombin. A larger study examining the effects of subcutaneous epinephrine and topical thrombin might clarify this issue. In a more recent study, Mzezewa and colleagues reported that treatment with systemic terlipressin, a vasopressin analog, decreased blood loss and transfusion requirements in a cohort of pediatric and adult burn patients.[183] The authors did not report significant complications associated with this approach.

BLOOD COMPONENTS

Several blood components are available for replacement of losses incurred during burn wound excision. These components include whole blood, PRBCs, fresh frozen plasma (FFP), platelets, and cryoprecipitates.

Box 13.6 Indications for Arterial Cannulation

1. Expected blood pressure changes more rapid than the interval between noninvasive measurements
2. Patient's fragility and reduced physiological reserve (e.g., ischemic or valvular heart disease)
3. Requirement for vasoactive infusions (other than dobutamine)
4. Need for measurement of Pa_{O_2} for management of respiratory support
5. Extremities unavailable for blood pressure cuff

Table 13.4 Comparison of Whole Blood and Packed Red Blood Cells

Value	Whole Blood	Packed Red Blood Cells
Volume (mL)	517	300
Erythrocyte mass (mL)	200	200
Hematocrit (%)	40	70
Albumin (g)	12.5	4
Globulin (g)	6.25	2
Total protein (g)	48.8	36
Plasma sodium (mEq)	45	15
Plasma potassium (mEq)	15	4
Plasma acid (citric/lactic) (mEq)	80	25
Donor/recipient ratio	1 unit per patient	1 unit every 4–6 patients

Whole Blood

Whole blood consists of unfractionated blood and contains all of the components of blood including red blood cells (RBCs), plasma, platelets, and white blood cells. However whole blood stored for more than 24 hours does not contain functional white blood cells or platelets (Box 13.6). One unit of whole blood contains approximately 200 mL of red blood cells and 250 mL of plasma. Whole blood is available in some hospitals for large-volume blood transfusions (trauma, liver transplantation, burns) and treatment of hypovolemic shock. However, because of the scarcity of blood products in most communities, whole blood is not readily available. Fractionation of whole blood into its individual components is a much more efficient and cost-effective means of maximizing blood usage. When available, however, whole blood provides an excellent means of volume expansion and to provide oxygen-carrying capacity in patients requiring large-volume blood transfusion.

Packed Red Blood Cells

PRBCs are the most common means of replacing RBC loss during surgical procedures. Most of the plasma and platelets are removed during processing so that PRBCs provide few plasma components, clotting factors, or platelets. A unit of PRBCs contains approximately 200 mL of red cells and 50 mL of residual plasma. A comparison of PRBC composition with whole blood is shown in Table 13.4. PRBCs provide oxygen-carrying capacity and, when reconstituted with crystalloid or plasma, volume resuscitation.

Fresh Frozen Plasma

In the setting of burn injury, FFP is most commonly used to replace clotting factors during massive blood transfusion. FFP will replace clotting factors as well as protein S and protein C by a factor of 2–3% per unit. The initial recommended volume is 10–15 mL/kg. The use of FFP varies among different burn centers. Plasma is frozen within 6 hours of collection, and each unit provides approximately 250 mL of plasma containing normal levels of all coagulation factors. In the setting of massive blood transfusion, FFP administration is indicated if active bleeding exists and laboratory evidence of coagulation factor depletion is shown. A volume of 2–6 units is generally used depending on the severity of the coagulopathy. Some practitioners argue that the use of FFP rather than crystalloid to reconstitute PRBCs results in less interstitial edema during the postoperative period and may enhance skin graft survival.

In the past, guidelines recommended the use of FFP to replace shed blood only for documented coagulopathy due to reduced coagulation factors. Recent experiences with both civilian and military trauma have led to more liberal use of FFP, and, as a result, early and aggressive use of FFP to treat massive hemorrhage has been associated with decreased mortality.[184,185] As a result, massive transfusion protocols including early use of blood products other than PRBCs to support coagulation (e.g., FFP, platelets, and cryoglobulin) are now activated for trauma patients requiring massive transfusion.[186,187] Blood loss during extensive burn wound excision often meets criteria for the diagnosis of massive transfusion. The physiological status of trauma patients presenting with hypovolemic shock, acidemia, hypothermia, and coagulopathy, however, is different from the post-resuscitation burn patient. Except in certain emergencies burn patients should have their wounds debrided when resuscitation is effective or in the post-resuscitation period. Under these circumstances the patient is warm, has adequate preload and oxygen-carrying capacity, adequate or increased cardiac output, and no coagulation dysfunction. As a result, all features of the massive transfusion protocol are not necessary initially. At our institution (Shriners Hospital for Children, Galveston) shed blood is initially replaced with colloid (2.5% albumin), and the HCt is allowed to diminish to a target value appropriate for the patient before PRBCs are administered. As a result of dilution, shed blood contains a smaller mass of RBCs. When shed blood reaches 50% of estimated total blood volume, it is then replaced with PRBCs mixed with FFP. Transfusion of reconstituted whole blood in burned children has been shown to be safe and efficacious.[188] Only if microvascular bleeding occurs along with thrombocytopenia and/or hypofibrinogenemia are other blood products administered.

Platelets

Platelets are stored at room temperature to maximize viability. The incidence of bacterial contamination increases exponentially after 4 days. However refrigerated platelets remain viable for only 24–48 hours. Platelets are obtained from either units of whole blood or by apheresis from a

single donor. ABO-compatible platelets, particularly if from a single donor, should be used when possible because post-transfusion viability is improved. One unit of whole blood platelets contains approximately 5×10^{10} platelets in 50 mL of plasma. Most commonly, 6 units of platelets are combined into a single bag and transfused. A unit of single-donor platelets contains about 30×10^{10} platelets suspended in 200–400 mL of plasma. Therefore, 1 unit of single-donor platelets is equal to about 6 units of whole blood platelets. One unit of whole blood platelets will increase the platelet count by 5000–10,000/μL.

Cryoprecipitate

Cryoprecipitate is prepared by thawing FFP at 4°C and collecting the precipitate. Cryoprecipitate is rich in factors VIII and XIII, fibrinogen, and von Willebrand's factor. In the setting of massive blood transfusion, it is used primarily to treat hypofibrinogenemia. Generally cryoprecipitate is administered when plasma fibrinogen levels fall below 100 mg/dL. One unit of cryoprecipitate will increase plasma fibrinogen levels by 5–7 mg/dL.

COMPLICATIONS OF MASSIVE BLOOD TRANSFUSION

Coagulopathy

Coagulopathy associated with massive blood transfusion is due to thrombocytopenia or depletion of coagulation factors. PRBCs are essentially devoid of platelets, and whole blood stored for more than 24 hours does not possess significant numbers of viable platelets.[189] Whole blood contains essentially normal levels of coagulation factors with the exception of the volatile factors V and VIII. Because most plasma is removed from PRBCs, they provide a poor source of coagulation factors. Massive blood loss and transfusion results in dilutional losses of platelets and factors V and VIII, particularly when PRBCs alone are utilized.

Thrombocytopenia is the most common cause of nonsurgical bleeding after massive blood transfusion.[190] In general, 15–20 units, or 2–4 blood volumes of blood or PRBCs, must be transfused before bleeding due to thrombocytopenia will develop (Fig. 13.11). Observed platelet counts usually remain higher than calculated values due to the release of platelets from sites of sequestration. Bleeding due to thrombocytopenia usually develops when the platelet count drops below 50,000–100,000 platelets/μL. Replacement of platelets usually requires transfusion of 6 units of whole blood platelets or 1 unit of single-donor platelets as described earlier in this chapter.

Development of coagulopathy due to depletion of coagulation factors is also possible during massive blood transfusion. Significant prolongation of the prothrombin (PT) and partial thromboplastin time (PTT) can result after transfusion of 10–12 units of PRBCs in adults. It has been recommended that FFP be given to correct dilutional coagulopathy if the PT and PTT exceed 1.5 times normal levels.[191] It is also important to know the fibrinogen level in massively transfused patients since hypofibrinogenemia can also result in prolongation of the PT and PTT. Fibrinogen may be replaced using cryoprecipitate.

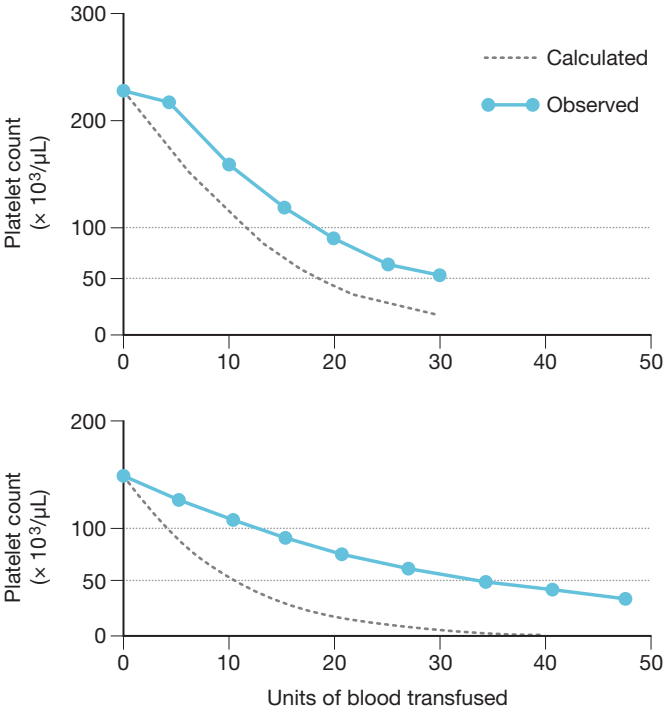


Fig. 13.11 Calculated versus observed mean platelet counts in two studies of platelet count after massive blood transfusion. (From Reed RL, et al. Prophylactic platelet administration during massive transfusion. *Ann Surg.* 1986;203:46.)

Citrate Toxicity

Citrate is universally used as an anticoagulant in the storage of blood because of its ability to bind calcium that is required for activation of the coagulation cascade. Citrate is metabolized by the liver and excreted by the kidneys. Patients with normal liver and kidney function are able to respond to a large citrate load much better than patients with hepatic or renal insufficiency. During massive blood transfusion, citrate can accumulate in the circulation, resulting in a fall in ionized calcium.[192] Hypocalcemia can result in hypotension, reduced cardiac function, and cardiac arrhythmias. Severe hypocalcemia can also result in clotting abnormalities. However, the level of calcium required for adequate coagulation is much lower than that necessary to maintain cardiovascular stability. Therefore hypotension and decreased cardiac contractility occur long before coagulation abnormalities are seen. During massive blood transfusion it is generally prudent to monitor ionized calcium, especially if hemodynamic instability is present in the hypocalcemic patient.

Potassium Abnormalities

During the storage of whole blood or packed red cells, potassium leaks from erythrocytes into the extracellular fluid and can accumulate to concentrations of 40–80 mEq/L. Once the RBCs are returned to the in vivo environment, the potassium quickly reenters RBCs. However, during rapid blood transfusion, transient hyperkalemia may result, particularly in patients with renal insufficiency.[193] The transient hyperkalemia, particularly in the presence of hypocalcemia, can lead to cardiac dysfunction and arrhythmias. In

patients with renal insufficiency, potassium load can be minimized by the use of either freshly obtained blood or washed packed RBCs. Hypokalemia can also result from massive blood transfusion due to reentry of potassium into RBCs and other cells during stress, alkalosis, or massive catecholamine release associated with large-volume blood loss. Therefore potassium levels should be monitored routinely during large-volume blood transfusions.

Acid–Base Abnormalities

During the storage of whole blood, an acidic environment develops due to the accumulation of lactate and citrate with a pH in the range of 6.5–6.7. Rapid transfusion of this acidic fluid can contribute to the metabolic acidosis observed during massive blood transfusion. However metabolic acidosis in this setting is more commonly due to relative tissue hypoxia and anaerobic metabolism resulting from an imbalance of oxygen consumption and delivery. The anaerobic metabolism that occurs during states of hypovolemia and poor tissue perfusion results in lactic acidosis.[186] Generally, administration of sodium bicarbonate is not indicated. The re-establishment of tissue perfusion and homeostasis is a much more important factor in re-establishing acid–base balance. In contrast, many patients receiving massive blood transfusion will develop a metabolic alkalosis during the post-transfusion phase. This is due to the conversion of citrate to sodium bicarbonate by the liver and is an additional reason to avoid sodium bicarbonate administration during massive blood transfusion except in cases of severe metabolic acidosis (base deficit >12).

Altered Oxygen Transport

During the storage of blood, red blood cell 2,3-diphosphoglycerate (DPG) levels decline. This results in a shift in the oxyhemoglobin dissociation curve to the left. Under these conditions, oxygen has a higher affinity for hemoglobin, and oxygen release at the tissue level is theoretically diminished. In clinical practice, this alteration in oxygen affinity has not been shown to be functionally significant.

Hypothermia

Rapid infusion of large volumes of cold (4°C) blood can result in significant hypothermia.[194] When added to the already impaired thermoregulatory mechanisms in burn patients this can result in clinically significant hypothermia. Potential complications of hypothermia include altered citrate metabolism, coagulopathy, and cardiac dysfunction. During large-volume blood transfusion in burn patients, fluids should be actively warmed with systems designed to effectively warm large volumes of rapidly transfused blood. In addition, the room temperature should be elevated and the patient's extremities and head covered to minimize heat loss. Body temperature should be maintained at or above 37°C in burn patients.

Pulmonary Complications

Pulmonary edema is a potential complication of massive blood transfusion. This may result from volume overload and/or pulmonary capillary leak due to inflammation and microaggregates present in transfused blood. Some studies have indicated that the incidence of pulmonary edema is more related to the patient's underlying injury than to blood transfusion per se. However volume status should be monitored closely during large-volume blood transfusion so that volume overload may be avoided.

Table 13.5 Blood Groups and Cross-Match

Blood Group	Antigen on Erythrocyte	Plasma Antibodies	Incidence (%)	
			Whites	African-Americans
A	A	Anti-B	0.40	27
B	B	Anti-A	11	20
AB	AB	None	4	4
O	None	Anti-A	45	49
Anti-B				
Rh	Rh	42	17	

Transfusion-associated acute lung injury (TRALI) is a relatively rare complication characterized by acute hypoxemia and noncardiogenic pulmonary edema occurring within 6 hours of blood transfusion.[195] Although relatively uncommon, TRALI is among the most common causes of transfusion-related mortality.[196] The pathogenesis is not well understood but is thought to be related to transfusion-associated inflammatory responses. Although the incidence is higher in critically ill patients, specific risk factors are difficult to identify and treatment is supportive. In cases of transfusion-related lung injury, it is important to rule out other causes of ARDS and the presence of transfusion-associated volume overload (TACO).

Transfusion Reactions

Hemolytic transfusion reactions are a relatively rare but devastating complication of blood transfusion. The incidence of transfusion reactions is approximately 1 : 5000 units transfused, and fatal transfusion reactions occur at a rate of 1 : 100,000 units transfused. Most severe reactions result from ABO incompatibility. The most common cause of transfusing ABO-incompatible blood is clerical error. Therefore most hospitals have developed policies that require multiple checks of the blood prior to transfusion. A list of blood types and associated circulating antibodies is shown in Table 13.5. Massive hemolytic transfusion reactions result from destruction of transfused erythrocytes by circulating antibodies and complement. Many of the common signs and symptoms of transfusion reactions, such as chills, chest pain, and nausea, cannot be detected in a patient under general anesthesia. The most commonly recognized signs of transfusion reaction in the anesthetized patient are fever, hypotension, hemoglobinuria, and coagulopathy. The cornerstones of treatment are to stop the transfusion, protect the kidneys with aggressive hydration and alkalization of urine, and treat existing coagulopathy.[197]

Delayed hemolytic transfusion reactions can occur in patients who have received prior blood transfusions and result from a secondary immune response with production of antibodies to blood antigens. This reaction can occur from 2 to 21 days after transfusion and should be suspected in patients with unexplained decreases in hematocrit during the postoperative period. Renal injury is less common than in acute hemolytic reactions, but adequate hydration and

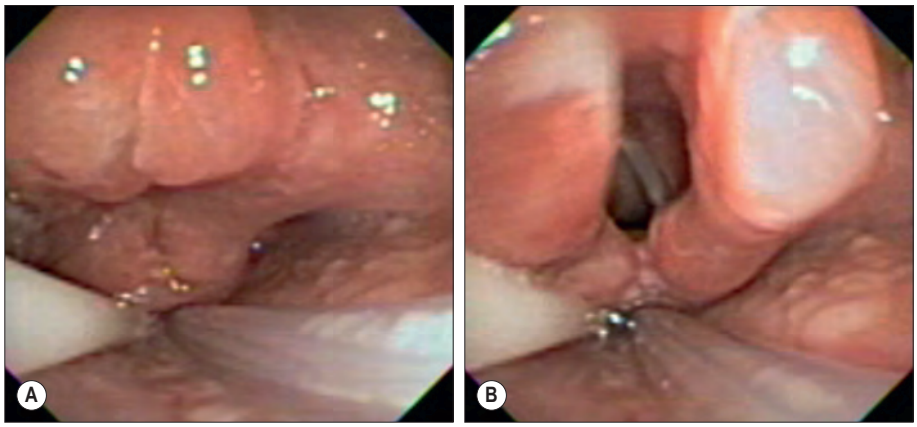


Fig. 13.12 Dynamic obstruction of the upper airway in a pediatric patient with thermal injury of the larynx. Edematous tissues collapse and obstruct during inhalation (A) but expand and allow exhalation (B).

alkalization of urine are usually indicated. Febrile reactions are common following blood transfusion and are generally due to contaminating leukocytes and leukocyte antigens present in transfused blood. Pure febrile reactions usually do not require termination of the transfusion, but the patient should be monitored closely to assure that a more severe transfusion reaction is not developing.

Infection

Infection is a major problem in burn patients due to disruption of the cutaneous barrier and immunosuppression. Blood transfusion adds to the infection risk. Graves and colleagues showed a significant correlation between the number of blood transfusions and infectious complications in burn patients.[198] The most common source of major infection from blood products is hepatitis. Hepatitis C is the most common offender, followed by hepatitis B. The incidence of hepatitis C is approximately 3 in 10,000 units transfused. The development of rigorous screening mechanisms has markedly decreased the incidence of HIV infection to 1 in 200,000–500,000 units transfused. Cytomegalovirus (CMV) has been identified in blood products and could cause clinically significant problems in immunocompromised burn patients. However the incidence of clinically important CMV infection is low in burn patients.

Postoperative Care

Decisions regarding postoperative airway management and support of ventilation depend on several factors. Extubation is desirable as soon as it is indicated, but, in burn patients, for a number of reasons it often may be even more important not to extubate when it is not indicated. If the patient came to the operating room intubated, the indication for intubation must be determined. If the initial indication has resolved, the decision to extubate depends on perioperative events. Some patients with neck and facial burns are intubated to protect the airway from obstruction by edema. The airway must be examined to be sure edematous pharyngeal tissues will not cause obstruction of the airway when the endotracheal tube is removed. Air leaking around a deflated endotracheal tube cuff during positive pressure ventilation is an encouraging sign that the airway may remain patent after extubation. The upper airway can also be examined by direct laryngoscopy or with an endoscope. In marginal cases the endotracheal tube can be removed while an exchanger is left in the trachea. Another technique is to extubate under direct vision with a bronchoscope with an endotracheal tube already loaded on the bronchoscope. Especially in small pediatric patients a common reason for post-extubation stridor and failed extubation is edematous and redundant mucosa over the arytenoid eminences that obstruct the glottic inlet during inspiration (Fig. 13.12A, video). This condition can be exacerbated by an endotracheal tube that is too large, excessive patient motion due to inadequate sedation and analgesia, reflux of acidic gastric contents, and mechanical irritation due to compression of the posterior laryngeal structures between the endotracheal tube and gastric tubes. These irritants can also cause laryngomalacia in pediatric patients (Fig. 13.12B). If laryngeal obstruction persists despite attention to all these details a short course of steroids is often effective as long as concerns regarding burn wound infection do not preclude the use of steroids (unpublished observations.) Heliox has also been used successfully in this situation.[199]

The decision to extubate must also take into consideration the metabolic state and the burn-related decrease in strength of the patient. Increased generation of CO_2 must be matched by increased minute ventilation and respiratory effort. Work of breathing is often also increased by poor pulmonary compliance and diaphragmatic elevation due to hepatomegaly.[200] At the same time skeletal muscle wasting and decreased strength are also products of the catabolic state.[98] If the patient's physiological reserve was marginal preoperatively, it may be best to continue mechanical ventilation until extubation criteria can be assessed objectively in the ICU.

After transfer of monitors and ventilatory support in the ICU, a full report of the intraoperative anesthetic course is given, along with information about the patient's current condition and therapy. A chest radiograph may be needed for vascular catheters placed in the OR to check the position of an endotracheal tube if the patient will be ventilated postoperatively. Laboratory studies, including arterial blood gas, blood chemistries, renal function tests, hematocrit,

platelet count, and coagulation studies, are sent soon after patient arrival to the ICU. These studies are particularly important if massive transfusion was required in the operating room.

One of the most important issues in the immediate postoperative period for burn patients is adequate analgesia and sedation, particularly for the intubated and mechanically ventilated patient. Debridement of burned tissue and the harvesting of skin grafts are painful procedures that merit ample analgesic doses in order to ensure patient comfort. It is not uncommon for burn patients to be quite tolerant to narcotic analgesics, especially after they have had several operative procedures, and, in this case, larger doses than normal are required.

Ongoing blood loss is unfortunately a common problem after the excision and grafting of a large burn wound, even when strict attention is placed on intraoperative hemostasis by surgical personnel. The burn wounds are necessarily excised down to bleeding tissue before skin grafts are applied. Massive intraoperative transfusion adds to the problem with dilutional thrombocytopenia and coagulopathy. Diligent postoperative care is needed to continually assess ongoing blood loss and to transfuse additional blood products as they are indicated by clinical course and laboratory studies. Postoperative bleeding can be concealed by bulky burn dressings. Such bleeding may manifest as hypovolemia and hypotension even in the brief period of transport from the operating room to the ICU. Monitoring of CVP and urine output also help in guiding postoperative blood and fluid therapy.

Adequate ventilation is essential in the postoperative period in order to minimize hypoxemia and hypercarbia. Blood gases and oxygen saturation can be used as guides to ventilator management. Patients with inhalation injury benefit not only from rational ventilator management but also from a program of inhaled bronchodilators and mucolytics combined with judicious airway suctioning. Extubated patients require supplemental oxygen for at least the first few hours postoperatively in order to maintain adequate oxygen saturation. Airway support may also be necessary initially in these patients until they are more alert and responsive.

Finally, burn patients must be recovered in a warm environment. Postoperative hypothermia can result in vasoconstriction, hypoperfusion, and metabolic acidosis and exaggeration of the hyperdynamic and catabolic metabolic response to their injury. Radiant heaters, blood and fluid warmers, warm blankets, heated humidifiers for gas delivery, and high room temperature are all useful in the postoperative period to provide warmth to the recovering patient.

Conclusion

Anesthetic management of the burn patient presents numerous challenges. Anatomical distortions make airway management and vascular access difficult. Pathophysiological changes in cardiovascular function range from initial hypovolemia and impaired perfusion to a hyperdynamic and hypermetabolic state that develops after the resuscitative stage. These and other changes profoundly alter response to anesthetic drugs. Effective anesthetic management will depend on knowledge of the continuum of pathophysiological changes, technical skills, proper planning, and availability of proper resources. A team approach is necessary, keeping in mind that perioperative management should be compatible with ICU management and goals. This requires close communication with other members of the burn care team, which is one of the most important principles of effective anesthetic management of these challenging patients.

Complete references available online at
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References

1. Saffle JR. Predicting outcomes of burns. *N Engl J Med*. 1998;338(6):387-388.
2. Ryan CM, Schoenfeld DA, Thorpe WP, et al. Objective estimates of the probability of death from burn injuries. *N Engl J Med*. 1998;338(6):362-366.
3. O'Keefe GE, Hunt JL, Purdue GF. An evaluation of risk factors for mortality after burn trauma and the identification of gender-dependent differences in outcomes. *J Am Coll Surg*. 2001;192(2):153-160.
4. Sheridan RL, Remensnyder JP, Schnitzer JJ, et al. Current expectations for survival in pediatric burns. *Arch Pediatr Adolesc Med*. 2000;154(3):245-249.
5. Jeschke MG, Patsouris D, Stanojcic M, et al. Pathophysiologic response to burns in the elderly. *EBioMedicine*. 2015;2(10):1536-1548.
6. Reynolds EM, Ryan DP, Sheridan RL, Doody DP. Left ventricular failure complicating severe pediatric burn injuries. *J Pediatr Surg*. 1995;30(2):264-269; discussion 269-270.
7. Fuzaylov G, Fidkowski CW. Anesthetic considerations for major burn injury in pediatric patients. *Paediatr Anaesth*. 2009;19(3):202-211.
8. Kaiser HE, Kim CM, Sharar SR, Olivar HP. Advances in perioperative and critical care of the burn patient: anesthesia management of major thermal burn injuries in adults. *Adv Anesthesia*. 2013;31:137-161.
9. Anderson TA, Fuzaylov G. Perioperative anesthesia management of the burn patient. *Surg Clin North Am*. 2014;94(4):851-861.
10. Bittner EA, Shank E, Woodson L, Martyn JA. Acute and perioperative care of the burn-injured patient. *Anesthesiology*. 2015;122(2):448-464.
11. Woodson LC, Sherwood ER, Cortiella J, Peterson L. Anesthesia for reconstructive burn surgery. In: McCauley RL, ed. *Functional and Aesthetic Reconstruction of Burned Patients*. Boca Raton, FL: Taylor and Francis; 2005:85-103.
12. Desai MH, Herndon DN, Broemeling L, et al. Early burn wound excision significantly reduces blood loss. *Ann Surg*. 1990;211(6):753-759; discussion 759-762.
13. Thompson PB, Herndon DN, Traber DL, Abston S. Effect on mortality of inhalation injury. *J Trauma*. 1986;26(2):163-165.
14. Navar PD, Saffle JR, Warden GD. Effect of inhalation injury on fluid resuscitation requirements after thermal injury. *Am J Surg*. 1985;150(6):716-720.
15. Hollingsed TC, Saffle JR, Barton RG, Craft WB, Morris SE. Etiology and consequences of respiratory failure in thermally injured patients. *Am J Surg*. 1993;166(6):592-596; discussion 596-597.
16. Foley FD. The burn autopsy. Fatal complications of burns. *Am J Clin Pathol*. 1969;52(1):1-13.
17. Moritz AR, Henriques FC, McLean R. The effects of inhaled heat on the air passages and lungs: an experimental investigation. *Am J Pathol*. 1945;21(2):311-331.
18. Clark WR, Bonaventura M, Myers W. Smoke inhalation and airway management at a regional burn unit: 1974–1983. Part I: Diagnosis and consequences of smoke inhalation. *J Burn Care Rehabil*. 1989;10(1):52-62.
19. Colice GL, Munster AM, Haponik EF. Tracheal stenosis complicating cutaneous burns: an underestimated problem. *Am Rev Respir Dis*. 1986;134(6):1315-1318.
20. Muehlberger T, Kunar D, Munster A, Couch M. Efficacy of fiberoptic laryngoscopy in the diagnosis of inhalation injuries. *Arch Otolaryngol Head Neck Surg*. 1998;124(9):1003-1007.
21. Madnani DD, Steele NP, de Vries E. Factors that predict the need for intubation in patients with smoke inhalation injury. *Ear Nose Throat J*. 2006;85(4):278-280.
22. Ching JA, Shah JL, Doran CJ, et al. The evaluation of physical exam findings in patients assessed for suspected burn inhalation injury. *J Burn Care Res*. 2015;36(1):197-202.
23. Hunt JL, Agee RN, Pruitt BA Jr. Fiberoptic bronchoscopy in acute inhalation injury. *J Trauma*. 1975;15(8):641-649.
24. Haponik EF, Meyers DA, Munster AM, et al. Acute upper airway injury in burn patients. Serial changes of flow-volume curves and nasopharyngoscopy. *Am Rev Respir Dis*. 1987;135(2):360-366.
25. Lee MJ, O'Connell DJ. The plain chest radiograph after acute smoke inhalation. *Clin Radiol*. 1988;39(1):33-37.
26. Linares HA, Herndon DN, Traber DL. Sequence of morphologic events in experimental smoke inhalation. *J Burn Care Rehabil*. 1989;10(1):27-37.
27. Demling RH, Chen C. Pulmonary function in the burn patient. *Semin Nephrol*. 1993;13(4):371-381.
28. Demling RH. Smoke inhalation lung injury: an update. *Eplasty*. 2008;8:e27.
29. Rehberg S, Maybauer MO, Enkhbaatar P, et al. Pathophysiology, management and treatment of smoke inhalation injury. *Expert Rev Respir Med*. 2009;3(3):283-297.
30. Cioffi WG Jr, Rue LW III, Graves TA, et al. Prophylactic use of high-frequency percussive ventilation in patients with inhalation injury. *Ann Surg*. 1991;213(6):575-580; discussion 580-582.
31. Sheridan RL, Kacmarek RM, McEttrick MM, et al. Permissive hypercapnia as a ventilatory strategy in burned children: effect on barotrauma, pneumonia, and mortality. *J Trauma*. 1995;39(5):854-859.
32. Sousse LE, Herndon DN, Andersen CR, et al. High tidal volume decreases adult respiratory distress syndrome, atelectasis, and ventilator days compared with low tidal volume in pediatric burned patients with inhalation injury. *J Am Coll Surg*. 2015;220(4):570-578.
33. Ernst A, Zibrak JD. Carbon monoxide poisoning. *N Engl J Med*. 1998;339(22):1603-1608.
34. Tibbles PM, Perrotta PL. Treatment of carbon monoxide poisoning: a critical review of human outcome studies comparing normobaric oxygen with hyperbaric oxygen. *Ann Emerg Med*. 1994;24(2):269-276.
35. Clark CJ. Measurement of toxic combustion products in fire survivors. *J R Soc Med*. 1982;75(suppl 1):40-44.
36. Cummings TF. The treatment of cyanide poisoning. *Occup Med (Lond)*. 2004;54(2):82-85.
37. Brunton LL, ed. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. New York: McGraw Hill Medical; 2011.
38. Horton JW, Baxter CR, White DJ. Differences in cardiac responses to resuscitation from burn shock. *Surg Gynecol Obstet*. 1989;168(3):201-213.
39. Deitch EA. The management of burns. *N Engl J Med*. 1990;323(18):1249-1253.
40. Zetterstrom H, Arturson G. Plasma oncotic pressure and plasma protein concentration in patients following thermal injury. *Acta Anaesthesiol Scand*. 1980;24(4):288-294.
41. Kinsky MP, Guha SC, Button BM, Kramer GC. The role of interstitial Starling forces in the pathogenesis of burn edema. *J Burn Care Rehabil*. 1998;19(1 Pt 1):1-9.
42. Baxter CR, Cook WA, Shires GT. Serum myocardial depressant factor of burn shock. *Surg Forum*. 1966;17:1-2.
43. Ferrara JJ, Franklin EW, Kukuy EL, et al. Lymph isolated from a regional scald injury produces a negative inotropic effect in dogs. *J Burn Care Rehabil*. 1998;19(4):296-304.
44. Horton JW. Left ventricular contractile dysfunction as a complication of thermal injury. *Shock*. 2004;22(6):495-507.
45. Eichenholz PW, Eichacker PQ, Hoffman WD, et al. Tumor necrosis factor challenges in canines: patterns of cardiovascular dysfunction. *Am J Physiol*. 1992;263(3 Pt 2):H668-H675.
46. Heard SO, Perkins MW, Fink MP. Tumor necrosis factor-alpha causes myocardial depression in guinea pigs. *Crit Care Med*. 1992;20(4):523-527.
47. Horton JW, Garcia NM, White DJ, Keffer J. Postburn cardiac contractile function and biochemical markers of postburn cardiac injury. *J Am Coll Surg*. 1995;181(4):289-298.
48. Maass DL, White J, Horton JW. Nitric oxide donors alter cardiomyocyte cytokine secretion and cardiac function. *Crit Care Med*. 2005;33(12):2794-2803.
49. Westphal M, Noshima S, Isago T, et al. Selective thromboxane A2 synthase inhibition by OKY-046 prevents cardiopulmonary dysfunction after ovine smoke inhalation injury. *Anesthesiology*. 2005;102(5):954-961.
50. Minifee PK, Barrow RE, Abston S, Desai M, Herndon DN. Improved myocardial oxygen utilization following propranolol infusion in adolescents with postburn hypermetabolism. *J Pediatr Surg*. 1989;24(8):806-810; discussion 810-811.
51. Goodwin CW, Dorethy J, Lam V, Pruitt BA Jr. Randomized trial of efficacy of crystalloid and colloid resuscitation on hemodynamic response and lung water following thermal injury. *Ann Surg*. 1983;197(5):520-531.
52. Papp A, Uusaro A, Parviainen I, Hartikainen J, Ruokonen E. Myocardial function and haemodynamics in extensive burn trauma: evaluation by clinical signs, invasive monitoring, echocardiography and cytokine concentrations. A prospective clinical study. *Acta Anaesthesiol Scand*. 2003;47(10):1257-1263.

53. Lin CY, Wu CK, Yeong EK, et al. Prognostic significance of left ventricular diastolic function in burn patients. *Shock*. 2012;37(5):457-462.
54. Bak Z, Sjoberg F, Eriksson O, Steinvall I, Janerot-Sjoberg B. Cardiac dysfunction after burns. *Burns*. 2008;34(5):603-609.
55. Pereira CT, Barrow RE, Sterns AM, et al. Age-dependent differences in survival after severe burns: a unicentric review of 1,674 patients and 179 autopsies over 15 years. *J Am Coll Surg*. 2006;202(3):536-548.
56. Camici PG, Prasad SK, Rimoldi OE. Stunning, hibernation, and assessment of myocardial viability. *Circulation*. 2008;117(1):103-114.
57. Alvarado R, Chung KK, Cancio LC, Wolf SE. Burn resuscitation. *Burns*. 2009;35(1):4-14.
58. Schwartz SI. Supportive therapy in burn care. Consensus summary on fluid resuscitation. *J Trauma*. 1979;19(11 suppl):876-877.
59. Holm C, Mayr M, Tegeler J, et al. A clinical randomized study on the effects of invasive monitoring on burn shock resuscitation. *Burns*. 2004;30(8):798-807.
60. Saffle JR. Fluid creep and over-resuscitation. *Crit Care Clin*. 2016;32(4):587-598.
61. Pruitt BA Jr. Protection from excessive resuscitation: pushing the pendulum back. *J Trauma*. 2000;49(3):567-568.
62. Pruitt BA Jr, Mason AD Jr, Moncrief JA. Hemodynamic changes in the early postburn patient: the influence of fluid administration and of a vasodilator (hydralazine). *J Trauma*. 1971;11(1):36-46.
63. Cochrane Injuries Group. Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. *Brit Med J*. 1998;317(7153):235-240.
64. Frame JD, Moiemem N. Human albumin administration in critically ill patients. Statisticians not trained in burns care should not evaluate data. *BMJ*. 1998;317(7162):884-885.
65. Cole RP. The UK albumin debate. *Burns*. 1999;25(7):565-568.
66. O'Mara MS, Slater H, Goldfarb IW, Caushaj PF. A prospective, randomized evaluation of intra-abdominal pressures with crystalloid and colloid resuscitation in burn patients. *J Trauma*. 2005;58(5):1011-1018.
67. Kozar RA, Peng Z, Zhang R, et al. Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock. *Anesth Analg*. 2011;112(6):1289-1295.
68. Ivy ME, Atweh NA, Palmer J, et al. Intra-abdominal hypertension and abdominal compartment syndrome in burn patients. *J Trauma*. 2000;49(3):387-391.
69. Chung KK, Blackbourne LH, Wolf SE, et al. Evolution of burn resuscitation in operation Iraqi freedom. *J Burn Care Res*. 2006;27(5):606-611.
70. Lawrence A, Faraklas I, Watkins H, et al. Colloid administration normalizes resuscitation ratio and ameliorates "fluid creep. *J Burn Care Res*. 2010;31(1):40-47.
71. Guha SC, Kinsky MP, Button B, et al. Burn resuscitation: crystalloid versus colloid versus hypertonic saline hyperoncotic colloid in sheep. *Crit Care Med*. 1996;24(11):1849-1857.
72. Elgjo GI, Poli de Figueiredo LF, Schenarts PJ, et al. Hypertonic saline dextran produces early (8–12 hrs) fluid sparing in burn resuscitation: a 24-hr prospective, double-blind study in sheep. *Crit Care Med*. 2000;28(1):163-171.
73. Jeng JC, Lee K, Jablonski K, Jordan MH. Serum lactate and base deficit suggest inadequate resuscitation of patients with burn injuries: application of a point-of-care laboratory instrument. *J Burn Care Rehabil*. 1997;18(5):402-405.
74. Dries DJ, Waxman K. Adequate resuscitation of burn patients may not be measured by urine output and vital signs. *Crit Care Med*. 1991;19(3):327-329.
75. Wo CC, Shoemaker WC, Appel PL, et al. Unreliability of blood pressure and heart rate to evaluate cardiac output in emergency resuscitation and critical illness. *Crit Care Med*. 1993;21(2):218-223.
76. Porter JM, Ivatury RR. In search of the optimal end points of resuscitation in trauma patients: a review. *J Trauma*. 1998;44(5):908-914.
77. Kaups KL, Davis JW, Dominic WJ. Base deficit as an indicator or resuscitation needs in patients with burn injuries. *J Burn Care Rehabil*. 1998;19(4):346-348.
78. Pirson J, Zizi M, Jacob E, Deleuze JP. Acute ischemic optic neuropathy associated with an abdominal compartment syndrome in a burn patient. *Burns*. 2004;30(5):491-494.
79. Greenhalgh DG, Warden GD. The importance of intra-abdominal pressure measurements in burned children. *J Trauma*. 1994;36(5):685-690.
80. Ivatury RR, Sugerman HJ, Peitzman AB. Abdominal compartment syndrome: recognition and management. *Adv Surg*. 2001;35:251-269.
81. Oda J, Ueyama M, Yamashita K, et al. Effects of escharotomy as abdominal decompression on cardiopulmonary function and visceral perfusion in abdominal compartment syndrome with burn patients. *J Trauma*. 2005;59(2):369-374.
82. Corcos AC, Sherman HF. Percutaneous treatment of secondary abdominal compartment syndrome. *J Trauma*. 2001;51(6):1062-1064.
83. Warner P, Connolly JP, Gibran NS, Heimbach DM, Engrav LH. The methamphetamine burn patient. *J Burn Care Rehabil*. 2003;24(5):275-278.
84. Danks RR, Wibbenmeyer LA, Faucher LD, et al. Methamphetamine-associated burn injuries: a retrospective analysis. *J Burn Care Rehabil*. 2004;25(5):425-429.
85. Santos AP, Wilson AK, Hornung CA, et al. Methamphetamine laboratory explosions: a new and emerging burn injury. *J Burn Care Rehabil*. 2005;26(3):228-232.
86. Mitka M. Meth lab fires put heat on burn centers. *JAMA*. 2005;294(16):2009-2010.
87. Wright J, Edwards J, Walker S. Exposures associated with clandestine methamphetamine drug laboratories in Australia. *Rev Environ Health*. 2016;31(3):329-352.
88. Witkowski W, Kawecki M, Surowiecka-Pastewka A, et al. Early and late acute kidney injury in severely burned patients. *Med Sci Monit*. 2016;22:3755-3763.
89. Jeschke MG, Barrow RE, Wolf SE, Herndon DN. Mortality in burned children with acute renal failure. *Arch Surg*. 1998;133(7):752-756.
90. Chung KK, Lundy JB, Matson JR, et al. Continuous venovenous hemofiltration in severely burned patients with acute kidney injury: a cohort study. *Crit Care*. 2009;13(3):R62.
91. Holm C, Horbrand F, von Donnersmarck GH, Muhlbauer W. Acute renal failure in severely burned patients. *Burns*. 1999;25(2):171-178.
92. Stewart IJ, Cotant CL, Tilley MA, et al. Association of rhabdomyolysis with renal outcomes and mortality in burn patients. *J Burn Care Res*. 2013;34(3):318-325.
93. Coban YK. Rhabdomyolysis, compartment syndrome and thermal injury. *World J Crit Care Med*. 2014;3(1):1-7.
94. Brown CV, Rhee P, Chan L, et al. Preventing renal failure in patients with rhabdomyolysis: do bicarbonate and mannitol make a difference? *J Trauma*. 2004;56(6):1191-1196.
95. Wolfe RR. Herman Award Lecture, 1996: relation of metabolic studies to clinical nutrition – the example of burn injury. *Am J Clin Nutr*. 1996;64(5):800-808.
96. Herndon DN, Tompkins RG. Support of the metabolic response to burn injury. *Lancet*. 2004;363(9424):1895-1902.
97. Wilmore DW, Long JM, Mason AD Jr, Skreen RW, Pruitt BA Jr. Catecholamines: mediator of the hypermetabolic response to thermal injury. *Ann Surg*. 1974;180(4):653-669.
98. Hart DW, Wolf SE, Chinkes DL, et al. Effects of early excision and aggressive enteral feeding on hypermetabolism, catabolism, and sepsis after severe burn. *J Trauma*. 2003;54(4):755-761; discussion 761-764.
99. Liusuwan RA, Palmieri TL, Kinoshita L, Greenhalgh DG. Comparison of measured resting energy expenditure versus predictive equations in pediatric burn patients. *J Burn Care Rehabil*. 2005;26(6):464-470.
100. Andel D, Kamolz LP, Donner A, et al. Impact of intraoperative duodenal feeding on the oxygen balance of the splanchnic region in severely burned patients. *Burns*. 2005;31(3):302-305.
101. Varon DE, Freitas G, Goel N, et al. Intraoperative feeding improves calorie and protein delivery in acute burn patients. *J Burn Care Res*. 2017.
102. Sessler DI. Perioperative heat balance. *Anesthesiology*. 2000;92(2):578-596.
103. Wallace BH, Caldwell FT Jr, Cone JB. The interrelationships between wound management, thermal stress, energy metabolism, and temperature profiles of patients with burns. *J Burn Care Rehabil*. 1994;15(6):499-508.
104. Caldwell FT Jr, Wallace BH, Cone JB. The effect of wound management on the interaction of burn size, heat production, and rectal temperature. *J Burn Care Rehabil*. 1994;15(2):121-129.
105. Caldwell FT Jr, Graves DB, Wallace BH. Pathogenesis of fever in a rat burn model: the role of cytokines and lipopolysaccharide. *J Burn Care Rehabil*. 1997;18(6):525-530.

106. Caldwell FT Jr, Graves DB, Wallace BH. Chronic indomethacin administration blocks increased body temperature after burn injury in rats. *J Burn Care Rehabil*. 1998;19(6):501-511.
107. Shiozaki T, Kishikawa M, Hiraide A, et al. Recovery from postoperative hypothermia predicts survival in extensively burned patients. *Am J Surg*. 1993;165(3):326-330; discussion 331.
108. Pereira CT, Murphy KD, Herndon DN. Altering metabolism. *J Burn Care Rehabil*. 2005;26(3):194-199.
109. Zawacki BE, Spitzer KW, Mason AD Jr, Johns LA. Does increased evaporative water loss cause hypermetabolism in burned patients? *Ann Surg*. 1970;171(2):236-240.
110. Vanni SM, Braz JR, Modolo NS, Amorim RB, Rodrigues GR Jr. Preoperative combined with intraoperative skin-surface warming avoids hypothermia caused by general anesthesia and surgery. *J Clin Anesth*. 2003;15(2):119-125.
111. Jaehde U, Sorgel F. Clinical pharmacokinetics in patients with burns. *Clin Pharmacokinet*. 1995;29(1):15-28.
112. Bonate PL. Pathophysiology and pharmacokinetics following burn injury. *Clin Pharmacokinet*. 1990;18(2):118-130.
113. Martyn JA, Abernethy DR, Greenblatt DJ. Plasma protein binding of drugs after severe burn injury. *Clin Pharmacol Ther*. 1984;35(4):535-539.
114. Blaschke TF. Protein binding and kinetics of drugs in liver diseases. *Clin Pharmacokinet*. 1977;2(1):32-44.
115. Loirat P, Rohan J, Baillet A, et al. Increased glomerular filtration rate in patients with major burns and its effect on the pharmacokinetics of tobramycin. *N Engl J Med*. 1978;299(17):915-919.
116. Glew RH, Moellering RC Jr, Burke JF. Gentamicin dosage in children with extensive burns. *J Trauma*. 1976;16(10):819-823.
117. Furman WR, Munster AM, Cone EJ. Morphine pharmacokinetics during anesthesia and surgery in patients with burns. *J Burn Care Rehabil*. 1990;11(5):391-394.
118. Perreault S, Choiniere M, du Souich PB, Bellavance F, Beauregard G. Pharmacokinetics of morphine and its glucuronidated metabolites in burn injuries. *Ann Pharmacother*. 2001;35(12):1588-1592.
119. Moncrief JA. Complications of burns. *Ann Surg*. 1958;147(4):443-475.
120. Tolmie JD, Joyce TH, Mitchell GD. Succinylcholine danger in the burned patient. *Anesthesiology*. 1967;28(2):467-470.
121. Schaner PJ, Brown RL, Kirksey TD, et al. Succinylcholine-induced hyperkalemia in burned patients. 1. *Anesth Analg*. 1969;48(5):764-770.
122. Martyn JA, Szyfelbein SK, Ali HH, Matteo RS, Savarese JJ. Increased d-tubocurarine requirement following major thermal injury. *Anesthesiology*. 1980;52(4):352-355.
123. Martyn JA, Matteo RS, Szyfelbein SK, Kaplan RF. Unprecedented resistance to neuromuscular blocking effects of metocurine with persistence after complete recovery in a burned patient. *Anesth Analg*. 1982;61(7):614-617.
124. Martyn JA, Liu LM, Szyfelbein SK, Ambalavanar ES, Goudsouzian NG. The neuromuscular effects of pancuronium in burned children. *Anesthesiology*. 1983;59(6):561-564.
125. Kim C, Fuke N, Martyn JA. Burn injury to rat increases nicotinic acetylcholine receptors in the diaphragm. *Anesthesiology*. 1988;68(3):401-406.
126. Martyn JA, White DA, Gronert GA, Jaffe RS, Ward JM. Up-and-down regulation of skeletal muscle acetylcholine receptors. Effects on neuromuscular blockers. *Anesthesiology*. 1992;76(5):822-843.
127. Martyn JA, Richtsfeld M. Succinylcholine-induced hyperkalemia in acquired pathologic states: etiologic factors and molecular mechanisms. *Anesthesiology*. 2006;104(1):158-169.
128. Viby-Mogensen J, Hanel HK, Hansen E, Graae J. Serum cholinesterase activity in burned patients. II: anaesthesia, suxamethonium and hyperkalaemia. *Acta Anaesthesiol Scand*. 1975;19(3):169-179.
129. Yentis SM. Suxamethonium and hyperkalaemia. *Anaesth Intensive Care*. 1990;18(1):92-101.
130. MacLennan N, Heimbach DM, Cullen BF. Anesthesia for major thermal injury. *Anesthesiology*. 1998;89(3):749-770.
131. Gronert GA. Succinylcholine hyperkalemia after burns. *Anesthesiology*. 1999;91(1):320.
132. Martyn J. Succinylcholine hyperkalemia after burns. *Anesthesiology*. 1999;91:321-322.
133. Brown TC, Bell B. Electromyographic responses to small doses of suxamethonium in children after burns. *Br J Anaesth*. 1987;59(8):1017-1021.
134. Abrishami A, Ho J, Wong J, Yin L, Chung F. Sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular blockade. *Cochrane Database Syst Rev*. 2009;(4):CD007362.
135. Tobias JD. Current evidence for the use of sugammadex in children. *Paediatr Anaesth*. 2016.
136. Martyn JA, Chang Y, Goudsouzian NG, Patel SS. Pharmacodynamics of mivacurium chloride in 13- to 18-yr-old adolescents with thermal injury. *Br J Anaesth*. 2003;89(4):580-585.
137. Viby-Mogensen J, Hanel HK, Hansen E, Sorensen B, Graae J. Serum cholinesterase activity in burned patients. I: biochemical findings. *Acta Anaesthesiol Scand*. 1975;19(3):159-168.
138. Hu OY, Ho ST, Wang JJ, et al. Evaluation of gastric emptying in severe, burn-injured patients. *Crit Care Med*. 1993;21(4):527-531.
139. Mathru M, Esch O, Lang J, et al. Magnetic resonance imaging of the upper airway. Effects of propofol anesthesia and nasal continuous positive airway pressure in humans. *Anesthesiology*. 1996;84(2):273-279.
140. Wilson RD, Nichols RJ, McCoy NR. Dissociative anesthesia with CI-581 in burned children. *Anesth Analg*. 1967;46(6):719-724.
141. Alfery DD, Ward CF, Harwood IR, Mannino FL. Airway management for a neonate with congenital fusion of the jaws. *Anesthesiology*. 1979;51(4):340-342.
142. Kleeman PP, Jantzen JP, Bonfils P. The ultra-thin bronchoscope in management of the difficult paediatric airway. *Can J Anaesth*. 1987;34(6):606-608.
143. Wrigley SR, Black AE, Sidhu VS. A fibreoptic laryngoscope for paediatric anaesthesia. A study to evaluate the use of the 2.2 mm Olympus (LF-P) intubating fibrescope. *Anaesthesia*. 1995;50(8):709-712.
144. McDonald I. Anchoring endotracheal tubes on patients with facial burns. Medical Center Hospital of Vermont. *J Burn Care Rehabil*. 1987;8(3):233-234.
145. McCall JE, Fischer CG, Schomaker E, Young JM. Laryngeal mask airway use in children with acute burns: intraoperative airway management. *Paediatr Anaesth*. 1999;9(6):515-520.
146. Hagberg CA, Johnson S, Pillai D. Effective use of the esophageal tracheal Combitube following severe burn injury. *J Clin Anesth*. 2003;15(6):463-466.
147. Bainbridge LC, Simmons HM, Elliot D. The use of automatic blood pressure monitors in the burned patient. *Br J Plast Surg*. 1990;43(3):322-324.
148. Talke P, Nichols RJ Jr, Traber DL. Does measurement of systolic blood pressure with a pulse oximeter correlate with conventional methods? *J Clin Monit*. 1990;6(1):5-9.
149. Murray WB, Foster PA. The peripheral pulse wave: information overlooked. *J Clin Monit*. 1996;12(5):365-377.
150. Tavernier B, Makhotine O, Lebuffe G, Dupont J, Scherpereel P. Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. *Anesthesiology*. 1998;89(6):1313-1321.
151. Monnet X, Marik PE, Teboul JL. Prediction of fluid responsiveness: an update. *Ann Intensive Care*. 2016;6(1):111.
152. O'Horo JC, Maki DG, Krupp AE, Safdar N. Arterial catheters as a source of bloodstream infection: a systematic review and meta-analysis. *Crit Care Med*. 2014;42(6):1334-1339.
153. Aouad-Marou M, Raphael CK, Sayyid SK, Farah F, Akl EA. Ultrasound-guided arterial cannulation for paediatrics. Ultrasound-guided arterial cannulation for paediatrics. *Cochrane Database Syst Rev*. 2016.
154. Rezayat T, Stowell JR, Kendall JL, et al. Ultrasound-Guided Cannulatin: Time to bring subclavian central lines back. *West J Emerg Med*. 2016;17(2):216-221.
155. Austin R, Shahrokhi ES, Bolourani S, Jeschke MG. Peripherally inserted central venous catheter safety in burn care: a single-center retrospective cohort review. *J Burn Care Res*. 2015;36(1):111-117.
156. O'Grady NP, Alexander M, Burns LA, Healthcare Infection Control Practices Advisory, et al. Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control*. 2011;39(4 suppl 1):S1-S34.
157. Echevarria-Guanilo ME, Ciofi-Silva CL, Canini SR, Farina JA, Rossi LA. Preventing infections due to intravascular catheters in burn victims. *Expert Rev Anti Infect Ther*. 2009;7(9):1081-1086.
158. Eyer S, Brummitt C, Crossley K, Siegel R, Cerra F. Catheter-related sepsis: prospective, randomized study of three methods of long-term catheter maintenance. *Crit Care Med*. 1990;18(10):1073-1079.
159. Hagley MT, Martin B, Gast P, Traeger SM. Infectious and mechanical complications of central venous catheters placed by percutaneous

venipuncture and over guidewires. *Crit Care Med*. 1992;20(10):1426-1430.
160. Sheridan RL, Weber JM, Peterson HF, Tompkins RG. Central venous catheter sepsis with weekly catheter change in paediatric burn patients: an analysis of 221 catheters. *Burns*. 1995;21(2):127-129.
161. Cobb DK, High KP, Sawyer RG, et al. A controlled trial of scheduled replacement of central venous and pulmonary-artery catheters. *N Engl J Med*. 1992;327(15):1062-1068.
162. Fraenkel D, Rickard C, Thomas P, et al. A prospective, randomized trial of rifampicin-minocycline-coated and silver-platinum-carbon-impregnated central venous catheters. *Crit Care Med*. 2006;34(3):668-675.
163. Weber JM, Sheridan RL, Fagan S, et al. Incidence of catheter-associated bloodstream infection after introduction of minocycline and rifampin antimicrobial-coated catheters in a pediatric burn population. *J Burn Care Res*. 2012;33(4):539-543.
164. Kagan RJ, Neely AN, Rieman MT, et al. A performance improvement initiative to determine the impact of increasing the time interval between changing centrally placed intravascular catheters. *J Burn Care Res*. 2014;35(2):143-147.
165. White PF, Way WL, Trevor AJ. Ketamine: its pharmacology and therapeutic uses. *Anesthesiology*. 1982;56(2):119-136.
166. Layon AJ, Vetter TR, Hanna PG, Bingham HG. An anesthetic technique to fabricate a pressure mask for controlling scar formation from facial burns. *J Burn Care Rehabil*. 1991;12(4):349-352.
167. Maldini B. Ketamine anesthesia in children with acute burns and scalds. *Acta Anaesthesiol Scand*. 1996;40(9):1108-1111.
168. Levanen J, Makela ML, Scheinin H. Dexmedetomidine premedication attenuates ketamine-induced cardiostimulatory effects and postanesthetic delirium. *Anesthesiology*. 1995;82(5):1117-1125.
169. Ravipati P, Reddy PN, Kumar C, et al. Dexmedetomidine decreases the requirement of ketamine and propofol during burns debridement and dressings. *Indian J Anaesth*. 2014;58(2):138-142.
170. Han TH, Greenblatt DJ, Martyn JA. Propofol clearance and volume of distribution are increased in patients with major burns. *J Clin Pharmacol*. 2009;49(7):768-772.
171. Irving GA, Butt AD. Anaesthesia for burns in children: a review of procedures practised at Red Cross War Memorial Children's Hospital, Cape Town. *Burns*. 1994;20(3):241-243.
172. Costello TG, Cormack JR. Anaesthesia for awake craniotomy: a modern approach. *J Clin Neurosci*. 2004;11(1):16-19.
173. Talon MW, Sherwood LE. Regional sensory nerve blocks of the scalp decrease the incidence of post-operative nausea and vomiting in reconstructive burn children: a pilot study. *J Burn Care Res*. 2006;27(2):S149.
174. Sheridan RL, Szyfelbein SK. Trends in blood conservation in burn care. *Burns*. 2001;27(3):272-276.
175. Criswell KK, Gamelli RL. Establishing transfusion needs in burn patients. *Am J Surg*. 2005;189(3):324-326.
176. O'Mara MS, Hayetian F, Slater H, et al. Results of a protocol of transfusion threshold and surgical technique on transfusion requirements in burn patients. *Burns*. 2005;31(5):558-561.
177. Mann R, Heimbach DM, Engrav LH, Foy H. Changes in transfusion practices in burn patients. *J Trauma*. 1994;37(2):220-222.
178. Sittig KM, Deitch EA. Blood transfusions: for the thermally injured or for the doctor? *J Trauma*. 1994;36(3):369-372.
179. American Society of Anesthesiologists. Practice guidelines for blood component therapy: a report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. *Anesthesiology*. 1996;84(3):732-747.
180. Smoot ECIII. Modified use of extremity tourniquets for burn wound debridement. *J Burn Care Rehabil*. 1996;17(4):334-337.
181. Missavage AE, Bush RL, Kien ND, Reilly DA. The effect of clysed and topical epinephrine on intraoperative catecholamine levels. *J Trauma*. 1998;45(6):1074-1078.
182. Barret JP, Dziewulski P, Wolf SE, et al. Effect of topical and subcutaneous epinephrine in combination with topical thrombin in blood loss during immediate near-total burn wound excision in pediatric burned patients. *Burns*. 1999;25(6):509-513.
183. Mzezewa S, Jonsson K, Aberg M, Sjoberg T, Salemark L. A prospective double blind randomized study comparing the need for blood transfusion with terlipressin or a placebo during early excision and grafting of burns. *Burns*. 2004;30(3):236-240.
184. Teixeira PG, Inaba K, Shulman I, et al. Impact of plasma transfusion in massively transfused trauma patients. *J Trauma*. 2009;66(3):693-697.
185. Pidcoke HF, Aden JK, Mora AG, et al. Ten-year analysis of transfusion in Operation Iraqi Freedom and Operation Enduring Freedom: increased plasma and platelet use correlates with improved survival. *J Trauma Acute Care Surg*. 2012;73(6 suppl 5):S445-S452.
186. Shaz BH, Dente CJ, Harris RS, MacLeod JB, Hillyer CD. Transfusion management of trauma patients. *Anesth Analg*. 2009;108(6):1760-1768.
187. Cantle PM, Cotton BA. Prediction of massive transfusion in trauma. *Crit Care Clin*. 2017;33(1):71-84.
188. Barret JP, Desai MH, Herndon DN. Massive transfusion of reconstituted whole blood is well tolerated in pediatric burn surgery. *J Trauma*. 1999;47(3):526-528.
189. Bordes J, Joubert C, Esnault P, et al. Coagulopathy and transfusion requirements in war related penetrating traumatic brain injury. A single centre study in a French role 3 medical treatment facility in Afghanistan. *Injury*. 2016.
190. Kashuk JL, Moore EE, Sawyer M, et al. Postinjury coagulopathy management: goal directed resuscitation via POC thrombelastography. *Ann Surg*. 2010;251(4):604-614.
191. Spinella PC, Holcomb JB. Resuscitation and transfusion principles for traumatic hemorrhagic shock. *Blood Rev*. 2009;23(6):231-240.
192. Dzik WH, Kirkley SA. Citrate toxicity during massive blood transfusion. *Transfus Med Rev*. 1988;2(2):76-94.
193. Kruskall MS, Mintz PD, Bergin JJ, et al. Transfusion therapy in emergency medicine. *Ann Emerg Med*. 1988;17(4):327-335.
194. Kendigelen P, Kamalak Z, Abat D. Should warm fresh whole blood be the first choice in acute massive hemorrhage in emergency conditions? *Ulus Travma Acil Cerrahi Derg*. 2016;22(2):195-198.
195. Vlaar AP, Binnekade JM, Prins D, et al. Risk factors and outcome of transfusion-related acute lung injury in the critically ill: a nested case-control study. *Crit Care Med*. 2010;38(3):771-778.
196. Kim J, Na S. Transfusion-related acute lung injury; clinical perspectives. *Korean J Anesthesiol*. 2015;68(2):101-105.
197. Dasararaju R, Marques MB. Adverse effects of transfusion. *Cancer Control*. 2015;22(1):16-25.
198. Graves TA, Cioffi WG, Mason AD Jr, McManus WF, Pruitt BA Jr. Relationship of transfusion and infection in a burn population. *J Trauma*. 1989;29(7):948-952; discussion 952–954.
199. Rodeberg DA, Easter AJ, Washam MA, et al. Use of a helium-oxygen mixture in the treatment of postextubation stridor in pediatric patients with burns. *J Burn Care Rehabil*. 1995;16(5):476-480.
200. Barrow RE, Hawkins HK, Aarsland A, et al. Identification of factors contributing to hepatomegaly in severely burned children. *Shock*. 2005;24(6):523-528.

14 The Skin Bank

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History

The first skin autograft was described by Reverdin[1] in 1871, and the use of allograft skin as a clinical method for wound coverage soon followed.[2] In 1874, Thiersch published a report about a small series of patients on whom he had used partial-thickness skin grafts.[3] This led to extensive trials of harvesting extremely thin grafts, leaving some of the surface epithelium behind to aid in donor site healing. Results from the use of these small, thin grafts, known as "Thiersch grafts," "pinch grafts," "epidermis grafts," or "razor grafts" were generally so unsatisfactory for resurfacing large areas that they were typically limited to the treatment of small ulcerated wounds. The first successful use of allogeneic skin for burn wound coverage was reported by Girdner[4] in 1881. Five years later, Thiersch described the histologic anatomy of skin engraftment which popularized the clinical use of split-thickness skin grafts.[3]

Storage of human skin did not begin until the early 1900s, when Wentscher[5] reported his experience with the transplantation of human skin that had been refrigerated for 3–14 days; however it was not until the 1930s that blood and tissue banking took their place in the clinical practice of medicine. The clinical utility of allograft skin in burn wound coverage was first described in 1938, when Bettman[6] reported his success in the treatment of children with extensive full-thickness burn injuries. Webster[7] and Matthews[8] later described the successful healing of skin autografts stored for 3 weeks at 4–7°C; however it was not until 1949, following the establishment of the United States Navy tissue bank, that modern-day skin banking began.

The establishment of skin banking signaled the beginning of significant research related to the processing, preservation, and storage of human tissues. Baxter[9] explored the histologic effects of freezing on human skin and discovered that the formation of ice crystals caused the destruction of skin architecture. This was followed in 1952 by the pioneering research of Billingham and Medawar[10] who demonstrated that skin could be effectively cryopreserved using glycerol. Soon afterward, Taylor[11] was able to demonstrate that the addition of glycerol to storage solutions decreased ice crystal formation in frozen tissues. These advancements permitted Brown[12] and Jackson[13] to popularize the use of allogeneic human skin grafts as biologic dressings for extensive burns and denuded tissue. By 1966, Zaroff[14] had reported the 10-year experience using allograft skin in the treatment of thermally injured patients at the Brooke Army Medical Center. In this report, he described the mechanical and physiologic advantages of allograft skin as a biologic dressing. In 1966, Cochrane[15] reported the first successful use of frozen autologous skin grafts following controlled-rate freezing in 15% glycerol and rapid rewarming prior to implantation. This was followed by Morris's[16] report demonstrating the beneficial effects of using allogeneic skin in the treatment of infected ulcers and other contaminated wounds and Shuck et al.'s[17] report suggesting the potential use of allogeneic skin in the treatment of traumatic wounds based on their Vietnam War experience. These increased uses of allograft skin led to further research into the beneficial effects of allograft skin on wound healing, including its association with a reduced incidence of bacterial infections[18,19] and the stimulation of wound bed neovascularization.[20]

Bondoc and Burke[21] are credited with the establishment of the first functional skin bank in 1971. Their experience with allograft skin led to a report of successful burn wound excision and allografting with temporary immunosuppression in children with extensive injuries.[22] Today allograft skin remains an ideal temporary cover for extensive or excised cutaneous or soft tissue wounds, particularly when sufficient autograft skin is not available or when temporary wound coverage is desired.

Another biologic dressing with a long history in the treatment of burned patients is amniotic membrane, with the first use for the purpose taking place in 1912 by Sabella a few short years after it was originally used in skin transplantation by Davis in 1910.[23,24] During the immediate period following these reports, the use of amniotic membranes was attempted as permanent skin replacements, although the grafts were rejected. In 1952, Douglas was the first to report the use of amniotic membrane as a temporary burn wound covering. Since that time, amnion has been one of the tools available in the treatment of partial-thickness burns.[25–30] Amnion has been shown to alleviate pain, prevent infection,[23,28,31,32] reduce pruritus,[30] and accelerate wound healing.[24,26,31] Our institution has used amniotic membrane for temporary total ocular surface coverage in the treatment of toxic epidermal necrolysis, which has shown improvements in corneal clarity, conjunctival scaring, and dry eye symptoms at 3-month follow-up as compared to a historical group that received maximal medical treatment.[33] The preparation and storage of amnion has been a role in many skin banks around the world.

The Growth of Skin Banking

The widespread use of allograft skin in the management of patients with extensive burn, traumatic, and soft tissue injuries has had a major impact on the number of skin banking facilities over the past two decades or so. Consequently the majority of skin banks have been founded in close proximity to regional burn centers or within the burn center hospitals themselves. Skin banks must therefore maintain a close working relationship with regional burn

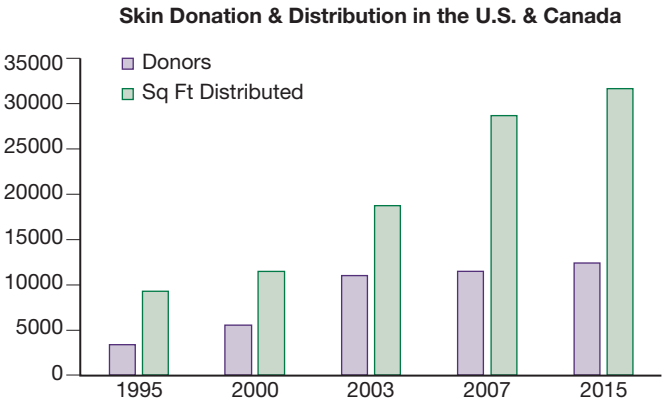

Fig. 14.1 Skin donation and distribution in the United States and Canada from 1995 through 2015.

centers not only to meet the specific needs of the burn surgeon but also to help generate community support for skin donation through combined educational outreach programs.

From 1969 to 1988, there was a steady growth in the number of skin banks; however this number declined, reaching its nadir in 2002. Since that time, however, there has been a steady increase in the number of skin banking facilities to its current total of 81 American Association of Tissue Banks (AATB)-accredited tissue banks that recover, process, store, and/or distribute skin for transplantation. In 1983, DeClement and May estimated that as much as 32,000 square feet of skin might be needed in burn and wound care centers.[34] Fig. 14.1 shows the total number of skin donors as well as total number of square feet of skin distributed by skin banks throughout the United States and Canada from 1995 through 2015.

Role of the American Association of Tissue Banks

As skin banking facilities grew in number, it became apparent that policies and procedures required standardization. This was quite difficult initially because there was insufficient data to develop a consensus regarding standards of practice. As early as 1976, the AATB had begun to address this issue by the formation of a Skin Council. This provided a forum for the discussion of skin banking practices and was complemented by the activities of the American Burn Association's Skin Banking Special Interest Group. The Standards and Procedures Committees were created in 1977 and produced the first guidelines for tissue banking in 1979. The first Standards for Tissue Banking were published in 1984, and tissue-specific technical manuals (including skin) were developed in 1987. Since that time, the Standards have been modified and refined based on consensus and, where available, supportive scientific research, with the latest edition, the 14th, released in 2016. In addition, shortly after the development and promulgation of its Standards for Tissue Banking, the AATB created an inspection and accreditation committee in 1982 and began conducting voluntary inspections in 1986. This program continues today and is important in ensuring that tissue banks adhere not only to AATB Standards but also the U.S. Food and Drug Administration (FDA) regulations governing all aspects of human tissue banking. In 1992, the AATB presented its Year 2000 Plan, outlining the institution's goals of supporting tissue and cell banks and ensuring the safety and quality of tissues, as well as advancing and strengthening the AATB.[35] The AATB has worked with many organizations, such as the FDA, the Centers for Disease Control (CDC), and the American Burn Association, to update standards and quickly respond when necessary, such as through the timely creation of instructions and methods to screen potential donors for emerging infectious diseases, including West Nile, Ebola, and Zika viruses in order to reduce risk of infection.

Box 14.1 Indications for Allograft Skin Use in Wound Management.

- Coverage of extensive wounds where autologous tissue is not available
- Coverage of widely meshed skin autografts
- Extensive partial-thickness burns
- Extensive epidermal slough
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis
  - Staphylococcal scalded skin syndrome
- Testing the wound bed's ability to accept autograft
- Template for the delayed application of keratinocytes.

Clinical Uses of Allograft Skin

COVERAGE OF EXTENSIVE FULL-THICKNESS WOUNDS

The increasing use of allograft skin in specialized burn care centers has been one of the driving forces behind the growth and development of skin banks in the United States. The general indications for its use in wound management are listed in Box 14.1. Allograft skin possesses many of the ideal properties of biologic dressings and plays a major role in the surgical management of extensive wounds when autologous tissue may not be immediately available (Box 14.2). It reduces evaporative water loss and the exudation of protein-rich fluids, prevents wound desiccation, and suppresses microbial proliferation. Wound pain is lessened, and this is associated with better patient compliance with occupational and physical therapy. By restoring the physiologic barrier at the wound surface, the allografts reduce heat loss through the wound and mitigate the hypermetabolic response to burn injury. The frequent and unpredictable demand for allograft skin in specialized burn care centers has prompted the growth and development of local and regional skin banks throughout the world.

Fresh allograft skin represents the gold standard for all biologic dressings employed for temporary wound closure based on a number of its distinctive properties compared to cryopreserved skin (Box 14.3). Its availability is critically important for the surgeon faced with the need to provide immediate coverage of large excised burn wounds. Fresh allografts become well-vascularized,

Box 14.2 Advantages of Human Allograft Skin Use.

- Reduce water, electrolyte, and protein loss
- Prevent desiccation of tissue
- Suppress bacterial proliferation
- Reduce wound pain
- Reduce energy requirements
- Promote epithelialization
- Prepare wounds for definitive closure
- Provide dermal template for epidermal grafts.

Box 14.3 Advantages of Fresh Allograft Skin.

- Rapidity and strength of adherence to the wound
- Control of microbial growth
- Rapidity of revascularization
- Reproducible clinical results

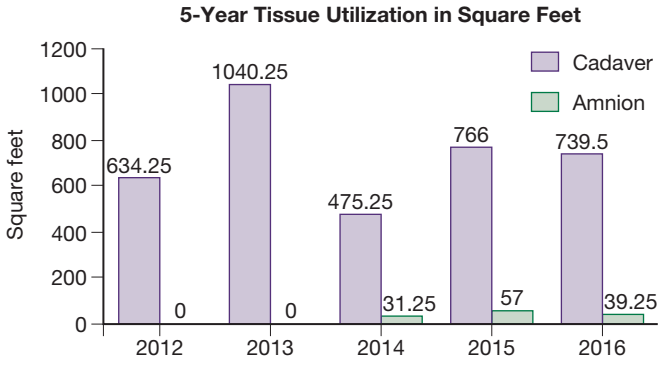

Fig. 14.2 Allograft and amnion skin usage at the Shriners Hospitals for Children – Galveston, Texas.

stimulate neovascularization in the underlying wound bed, and prepare the recipient sites for permanent coverage with autologous skin. In addition, fresh allografts tolerate modest wound contamination and adhere better to the freshly excised subcutaneous fat than do cryopreserved grafts. The allogeneic skin is usually removed once the patient's donor sites have healed sufficiently for reharvesting or once autologous cultured skin is available for permanent wound closure.

The use of fresh allografts has become extremely limited in recent years, however, due to increased FDA regulations put in place to reduce risk of disease transmission. When fresh allograft is not available, cryopreserved skin is an excellent alternative for temporary wound coverage. Although frozen cryopreserved skin generally has less measurable viability than fresh skin, it is currently difficult to maintain continuous and ample stores of fresh skin beyond 14 days. It has therefore been standard skin banking practice to cryopreserve allograft skin within 7–10 days of recovery if it is not going to be utilized within the time period that viability can be maintained. Fig. 14.2 depicts the quantitative use of allograft skin and amnion in thermally injured children treated at the Shriners Hospital for Children in Galveston, Texas, since 2012.

Alternative wound coverings such as Integra dermal regeneration template have provided alternatives to allograft skin for the treatment of excised burn wounds in patients with extensive full-thickness burn injuries. When compared with artificial dermis, fresh, refrigerated allograft has been shown to have a better rate of engraftment than the dermal regeneration template.[36] A study performed at our institution in 2007 indicated that Integra can safely be used for wound coverage in children with burns of more than 50% total body surface area (TBSA) burned with an associated attenuation of post-burn hypermetabolism with no increased risk of infection.[37]

COVERAGE OF WIDELY MESHED ZSKIN AUTOGRAFTS AND PARTIAL-THICKNESS WOUNDS

Another use of allograft skin has been its application as an overlay on top of widely expanded, meshed autologous skin grafts (Fig. 14.3). This technique was originally described utilizing meshed allograft[38] and provides immediate, as well as both temporary and permanent, wound closure. Our institution utilizes 2:1 meshed cadaver skin for the coverage of widely expanded autografts (with a ratio greater than 2:1). Because it is usually less viable than fresh skin, it functions more as a biologic dressing than as a temporary skin replacement. Its adherence to the underlying wound bed results in the relief of pain and the limitation of exudative and water losses, and it reduces the need for frequent dressing changes. As the underlying wound bed reepithelializes, the allograft slowly separates without disturbing the delicate underlying epithelium. These properties of frozen allograft are also utilized in the coverage of partial-thickness wounds. Studies by Rose[39] and Naoum[40] demonstrated more rapid healing times and shorter hospital stays for children with extensive partial-thickness burns when treated with early wound débridement and allografting compared to conventional topical antimicrobial therapy. However due to lower costs and ease of use, Shriners Hospitals for Children – Galveston primarily uses xenograft for partial thickness burns.

There has been some concern that allografts may induce an inflammatory rejection response resulting in delayed reepithelialization of underlying autografts; therefore the use of lyophilized tissue has been suggested because the lyophilization process destroys cellular components and results in a diminished immunologic response from the graft recipient.[41,42] A 2013 study of 11 patients treated with lyophilized allograft showed no evidence of immunologic reactions due to the administration of allograft.[42]

TEMPLATE FOR DELAYED APPLICATION OF KERATINOCYTES

The clinical use of cultured epidermal autografts (CEA) in the care of burn patients was first described by O'Connor et al.[43] in 1981. Since that time, there have been numerous reports supporting its use as a permanent skin replacement for patients with extensive full-thickness burn injuries. This methodology has not been without problems, however, with many authors describing variable take rates and instability of the grafts. Cuono first advocated the use of

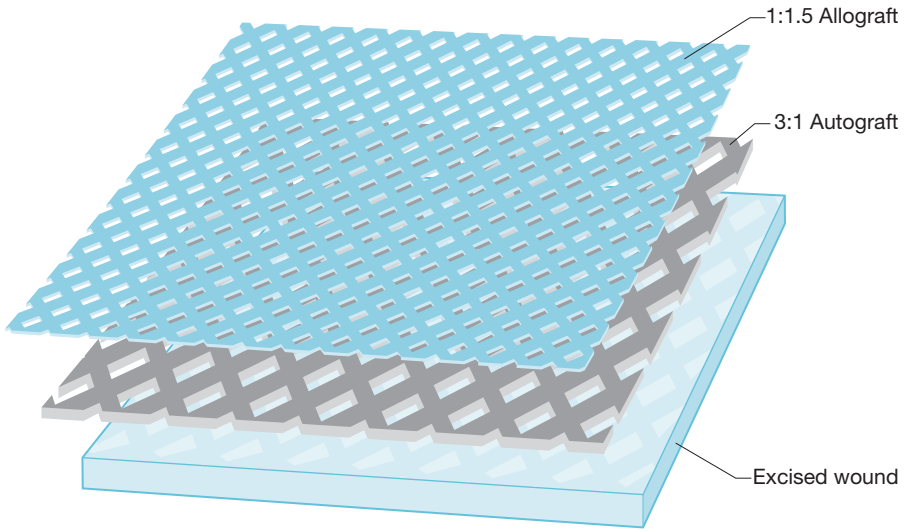

Fig. 14.3 Diagrammatic illustration of meshed allograft overlay technique (as described by Alexander et al.). The allograft is generally meshed 1.5:1 or 2:1 while the underlying autograft may be meshed 3: 1 or greater. (From Alexander JW, MacMillan BG, Law E, et al. Treatment of severe burns with widely meshed skin autograft and widely meshed skin allograft overlay. *J Trauma.* 1981; 21:433–438.)

allogeneic skin with CEA, allowing the allograft skin to vascularize before removing the antigenic epidermal layer by dermabrasion.[44] Hickerson et al. reported results on five burn patients demonstrating more than 90% CEA take on the allogeneic dermis and supple, durable grafts up to 4 years postoperatively.[45] A recent multicenter randomized trial compared patients with full-thickness burns who were treated with split-thickness skin autografts to those who were additionally treated with CEA. The application of CEA resulted in faster wound epithelialization, improved perception of scarring, and improved pigmentation and elasticity of the skin at follow-up.[46]

ACELLULAR DERMAL MATRIX

The past decade or so has also witnessed the development of an acellular allogeneic dermal matrix (AlloDerm) as a template for the simultaneous application of thin split-thickness autografts.[47] The potential advantage of the dermal template is reasoned to be the use of a thinner autologous skin graft resulting in more rapid donor site healing and reduced morbidity. A multicenter clinical trial demonstrated equivalence of this technique with a standard split-thickness meshed autograft; however autograft take rates were somewhat lower than that for controls and varied from center to center.[48] In addition, the allogeneic dermal grafts measured only 36–116 cm^2 and were only evaluated up to 180 days post-grafting. AlloDerm has also been used as a template for CEA; however there have been only a few anecdotal reports related to this potential application.

Potential Disadvantages of Allograft Use

INFECTION

Allograft skin has been reported to cause bacterial infection.[49] It is therefore imperative that skin banks perform microbial cultures prior to releasing the tissue for transplantation. In fact, the AATB Standards[50] require that skin be discarded if pathogenic bacteria or fungi are present. This is particularly important given the immunocompromised status of the potential recipient and the potential for developing wound sepsis following such contamination.

There have also been reports of viral disease transmission by skin allografts. In 1987, Clarke reported what was thought to be the transmission of HIV-1 to a burn patient from an HIV-positive donor[51]; however, the results of donor testing were not known prior to skin use. Moreover, the recipient, who had a number of risk factors for HIV, had not been tested prior to receiving the allograft. To date, there have been no other reported cases of HIV or hepatitis transmission from skin allografts.

Kealey et al. have reported the transmission of cytomegalovirus (CMV) from cadaver skin allografts.[52] Because nearly 23% of the CMV-negative patients seroconverted, they recommended the use of CMV-negative allograft skin for seronegative burn patients. Plessinger et al. reviewed 479 consecutive skin donors and found 63% of this predominantly adult donor pool to be CMV-positive.[53] They reasoned that while tissue from seronegative donors would be ideal for use in seronegative patients, such a practice would significantly limit the availability of fresh allograft skin for most thermally injured patients. In addition, while there is good evidence to support the transmission of CMV by allograft in burn patients, there is little evidence that CMV seroconversion is clinically significant or affects outcome in thermally injured patients.[54,55] Furthermore Herndon and Rose[54] reiterated that the benefits of using cadaver allograft skin for the treatment of burn patients clearly outweigh the small risks associated with CMV seroconversion. At present, most burn surgeons and skin banks recommend that the decision regarding the use of allograft skin from CMV-positive donors should be made by the burn/transplanting surgeon.

REJECTION

While demonstrating many characteristics of an ideal wound covering, allograft skin contains Langerhans cells that express class II antigens on their surface. These cells reside in the epidermis of the skin and are ultimately rejected as the result of an immunologic rejection response. This typically results in an acute inflammatory reaction and can lead to wound infection. Vascularized allogeneic skin grafts typically remain intact on the wound of a burn patient for 2–3 weeks, although there have been reports of allograft skin survival for up to 67 days due to the inherent immunosuppression of extensive burn injury.[56] Recent improvements in immunonutrition, critical care management, and a more aggressive surgical approach to definitive wound closure, however, have made the persistence of allografts less predictable.

Efforts to prevent rejection have included methods that might reduce antigen expression by controlling the activity of the Langerhans cells in the allograft skin. Treatment of the allografts with ultraviolet light irradiation and incubation of the skin in glucocorticoids has been reported to result in a modest prolongation of allograft survival compared to nontreated skin; however the utility of this methodology has not been substantiated. Other investigators have studied the effects of pharmacologic agents to induce immunosuppression in patients with major burn injuries. Initial clinical trials reported an improvement in both allograft and patient survival when children were treated with azathioprine and antithymocyte globulin[57]; however this regimen was associated with azathioprine-induced neutropenia, and the clinical outcomes were not corroborated by others. More recently, the use of cyclosporin A was demonstrated to prolong skin allograft survival in patients with extensive full-thickness burns.[58,59] In these studies, allograft rejection was generally observed within a few days of discontinuing treatment; however there were instances where engraftment persisted after the completion of therapy. Further studies of these and newer immunosuppressive agents may be warranted.

Technical Aspects of Skin Banking

DONOR SCREENING

It is vitally important that complete and accurate medical information about the potential tissue donor be obtained to ensure the safety of the tissue for transplantation. The AATB and the FDA require a comprehensive medical and social history of the donor. In this regard, the AATB developed a Donor Risk Assessment Interview (DRAI) with the cooperation and assistance of other organ and tissue recovery organizations and the FDA.

A panel of serologic screening tests for transmissible diseases is required.[50] These include:

- Antibodies to human immunodeficiency virus, types 1 and 2 (anti-HIV-1 and anti-HIV-2)
- Nucleic acid test (NAT) for HIV-1
- Hepatitis B surface antigen
- Total antibodies to hepatitis core antigen (including both IgG and IgM)
- Antibodies to hepatitis C virus (anti-HCV)
- Nucleic acid test (NAT) for HCV
- Syphilis (a non-treponemal or treponemal-specific assay may be performed)
- Nucleic acid test (NAT) for the hepatitis B virus (HBV)

Test kits should be FDA-licensed, approved, or cleared for donor screening and, ideally, should be approved for cadaveric specimens. Barnett et al. reported their 2-year experience with cadaveric skin donor discards due to positive serologic tests. In that report, they noted that 61 of 813 donors (7.5%) required tissue discard due to positive serologic tests. A positive hepatitis B core antibody test accounted for 52.3% of the serology-based discards, whereas hepatitis B surface antigen testing accounted for 18.1%, and hepatitis C, HIV-1/2, HTLV-1, and syphilis tests accounted for 14.3%, 4.9%, 4.9%, and 5.5%, respectively.[60] This finding was substantiated by Plessinger et al. in their 5-year review of 1235 donors, of whom 93 7.5%) were deferred based on positive serologic tests.[61]

Although it is also necessary for the tissue bank medical director to review the results of an autopsy (if one was performed), a 10-month follow-up study of 264 donors recovered following the 1998 changes in the AATB Standards revealed that none of the donors required deferral based on autopsy findings alone.[61] A review of 468 consecutive skin donors and 457 consecutive amnion donors recovered by our tissue bank from February of 2014 through September of 2016 indicated that 50 skin donors (10.7%) and 32 amnion donors (7.0%) required discard as a result of the autopsy, serology, DRAI, or physical exam findings. [62]

SKIN RECOVERY

Once donor screening is complete and proper authorization has been obtained, the recovery team must arrange the time and location for skin recovery in an appropriate facility (i.e., hospital morgue or operating room, medical examiner's office, or the tissue bank). It is extremely important that the time of death and body storage conditions be accurately documented because these have a significant bearing on skin viability and microbial contamination, as can the time from skin recovery to banking.[62] Current AATB Standards require that skin prep begin within 24 hours of asystole, provided the donor's body was cooled (e.g., application of sufficient amounts of wet ice or a cooling blanket, cold weather conditions) or refrigerated within 12 hours of asystole. The skin prep shall begin within 15 hours of death if the deceased donor's body has not been cooled or refrigerated. If the donor's body is cooled for a period of time then not cooled for a period of time, the time period the donor's body is not cooled cannot exceed 15 cumulative hours.[50]

In brief, the skin is recovered under aseptic conditions but first a thorough physical assessment is necessary to determine if the donor should be deferred for other medical reasons as well as to determine the quality of the skin and the technical feasibility of skin recovery by evaluating the donor's size and skin condition. Box 14.4 lists disease states that are commonly associated with deferral of a potential skin donor. Blood samples are also obtained for the required infectious disease testing. The areas from which the skin is

Box 14.4 Disease States Commonly Associated With Potential Skin Donor Deferral.

- Extensive dermatitis
- Acute burn injuries
- Cutaneous malignancy
- Poor skin quality
- Extensive tattoos
- Collagen vascular disease
- Toxic chemical exposure
- Skin infections
- Extensive skin lesions
- Extensive skin or soft tissue trauma.

taken are shaved of hair and cleansed with an antimicrobial agent approved for use in operative procedures (i.e., povidone-iodine, chlorhexidine). The tissue recovery technician wears the appropriate personal protective equipment (PPE; i.e., surgical cap, mask with face shield, shoe covers), performs a surgical scrub, and dons a sterile gown and gloves while the circulating technician completes the required documentation of the tissue recovery as well as prepares the tissue and transport containers. This is usually followed by a chlorhexidine prep surgical scrub of the tissue donor, rinsing with 70% isopropyl alcohol after the required contact time of the surgical scrub and allowing the skin surface to dry. A back table with all the required supplies for skin recovery is set up, and the donor is then surgically draped. Split-thickness skin grafts are then removed using a dermatome at a thickness of 0.012–0.018 inches. The width of the grafts generally should range from 3 to 4 inches but ideally should be determined by the preference of the transplanting surgeon(s). Skin retrieval sites are usually limited to the torso, hips, thighs, and upper calves. The amount of skin obtained may vary depending on body habitus, skin defects or lesions, and body geometry; however an average yield of 4–6 square feet per donor is not unusual for an experienced tissue recovery technician. After tissue is obtained from the posterior surfaces, the donor is turned to expose the anterior surface, reprepped, and draped prior to completing the recovery process. The skin is then placed in tissue culture medium and maintained at wet ice temperatures (above freezing to −10°C) during transport to the skin bank for processing.[63]

SKIN PROCESSING

Processing Environment

Skin should be processed under aseptic conditions in a bacteriologically and climate-controlled environment (Fig. 14.4). While current AATB Standards mandate the processing of cardiovascular tissues in a class 100 laminar flow environment, no such requirement exists for human skin banking. In fact, a study performed by Plessinger et al. failed to demonstrate any statistically significant quantitative or qualitative difference in microbial growth whether the skin was processed and packaged in a class 100 laminar flow hood or a class 10 000 clean room.[64]

Fig. 14.4 Aseptic tissue processing environment.

Microbiologic Testing

After returning to the skin bank, the tissue recovery team should obtain cultures for aerobic and anaerobic bacteria, yeast, and fungi. Tissue cultures can be obtained by swabbing, destructive testing of companion tissue, or by fluid elution.[65] Cultures from representative anatomical areas shall be obtained prior to processing. Culture methods shall be validated to ensure the suitability of the culture method selected. Inhibitory substances (e.g., skin prep solution(s), transport media, antibiotics, etc.) that may be added to unprocessed skin during recovery or for transport must not interfere with culture results (i.e., produce false-negative results). Testing should be conducted in accordance with adherence to relevant standards (e.g., CAP, ISO, ASTM, AAMI, USP), and the skin should not be used for transplantation if it contains any of the following microorganisms[50]:

- Staphylococcus aureus
- Group A, β-hemolytic Streptococci
- *Enterococcus* spp.
- Gram-negative bacilli
- *Clostridium* spp.
- Fungi (yeasts or molds).

While AATB Standards require that microbiology culture results should not be reported before 7 days of incubation before releasing the tissues for transplantation, when fresh, non-cryopreserved allograft skin is used for transplantation within days of tissue recovery, the results of the microbial cultures are frequently unavailable. Plessinger et al. reviewed the results of the microbiologic skin cultures from 219 consecutive skin donors whose tissues were released for transplantation prior to the availability of culture results. Although 14.3% of the cultures were positive for microbial growth, only 1.8% of the cultures identified organisms that required subsequent notification of the transplanting surgeon. In each of these instances, there was no adverse outcomes in any of the patients who received the skin transplants.[66] These findings were substantiated by Britton-Byrd et al.[67] in their review of tissue donors whose skin was used after only 3 days of incubation. They reported

three cases resulting in tissue recall due to positive microbiological cultures and concluded that 3-day culture results do not result in significant microbiologic contamination of allograft skin. White et al.[68] have suggested that cadaver allograft containing less than 10^3 organisms per gram of tissue can be safely used for temporary wound coverage. Despite the results of these studies, it is strongly recommended that the tissue bank communicate all available information regarding donor and tissue suitability to the transplanting surgeon so that he or she can adequately assess the potential risks and benefits for the recipient.

Maintenance of Viability

Maintenance of cell viability and structural integrity are vital for the engraftment and neovascularization of allograft skin yet there have been no studies that have quantified the degree of viability necessary to ensure allograft take. Postmortem time lapse appears to have the single greatest effect on skin viability, as May demonstrated that the functional metabolic activity of the skin rapidly declined if the donor was not refrigerated within 18 hours of death.[69,70] The ideal nutrient tissue culture medium also has not yet been identified. Eagle's MEM and RPMI-1640 continue to be generally accepted; however, Cuono demonstrated the potential benefits of University of Wisconsin (UW) solution.[71] To date, it remains unclear which cryoprotectants offer the greatest preservation of cell viability and structural integrity. Glycerol (10%–20%) and dimethylsulfoxide (10%–15%) have been reported to maintain skin viability following incubation times ranging from 30 minutes to 2 hours; however the optimal concentrations of these cryoprotectants have not been identified nor have these agents been compared for efficacy. Last, factors such as age and gender do not appear to influence skin viability.

REFRIGERATION

Refrigeration slows the metabolic rate of the viable cells, and nutrient tissue culture medium supports cellular metabolic activity. "Fresh" allograft skin is typically stored at 4°C in tissue culture medium with or without antibiotics. The skin should be free-floating in a sterile container with approximately 300 mL of medium per square foot of skin. Recent studies suggest that skin viability can be maintained for up to 2 weeks at 4°C if the nutrient medium is changed every 3 days.[72,73]

It has been common practice to cryopreserve the skin within 10 days of tissue recovery. This has been based on the work of May et al., who demonstrated that glucose metabolism declined at a rate of 10%–15% each day during refrigerated storage.[70] Recently demonstrated has been the benefit of a two-layer storage method utilizing 95% oxygen-enriched perfluorocarbon (O_2PFC) combined with changing the nutrient medium every 3 days in an effort to prolong the viability of refrigerated skin. This method results in maintenance of skin viability for up to 41–63 days, as well as maintenance of normal skin anatomy.[74]

CRYOPRESERVATION

When skin is frozen for long-term storage, it is important that the methods utilized maintain cell viability and structural integrity. AATB Standards dictate that refrigerated skin should not be stored for longer than 14 days; however if the skin is not to be used "fresh," it should be cryopreserved within 10 days of recovery if the nutrient medium is changed every 72 hours. If the medium is not utilized or changed in this manner, AATB Standards dictate that the skin must be frozen within 96 hours of recovery.[50] The skin is generally incubated in cryoprotectant solution for 30 minutes at 4°C. Skin that is to be frozen may be meshed (Fig. 14.5) or kept as a sheet, and it should be folded with fine mesh gauze or bridal veil covering the dermal surface prior to placement in a flat packet (Fig. 14.6) to ensure uniformity of the cooling process.[75] This is followed by slow-rate cooling at a rate of approximately −1°C/min. Although computer-assisted, control-rate freezing is thought to be optimal, studies have demonstrated that cooling in a heat sink box at less than −2°C/min is equally effective and does not compromise the metabolic activity of the skin.[76] The skin is frozen to a temperature of −70 to −100°C prior to placement in either a mechanical freezer

Fig. 14.5 Processed tissue after being run through a 2:1 mesher.

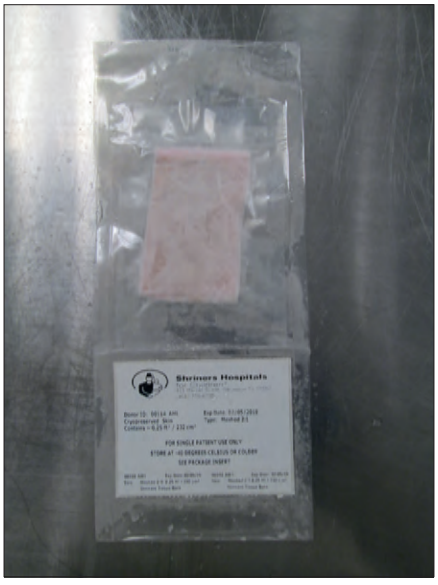

Fig. 14.6 Completed, frozen, packaged tissue.

or liquid nitrogen. Skin stored in a mechanical freezer (below −40°C) can be maintained for up to 5 years. Although this methodology has been reported to result in 85% retention of viability, there is a need for research to determine the optimal technology for skin preservation.[77]

LYOPHILIZATION

Skin can also be lyophilized by freeze-drying or incubation in glycerol.[78] This process has been reported to decrease biologic degradation and antigenicity; however this also results in epidermal cell destruction, the loss of barrier function, and resulting poor adherence to the wound bed and less effective control of microbial growth. Its clinical use has been further limited by its high cost of production compared to conventional allograft.

IRRADIATION

Human allograft skin can also be treated with γ-irradiation to significantly reduce and possibly eliminate the risk for viral disease transmission. The preservative and sterilizing effects of this treatment allow it to be stored at room temperature for up to 2 years. One such product, GammaGraft, has been successfully utilized to treat partial-thickness burn injuries and skin graft donor sites; however it is not often utilized to provide temporary coverage for excised full-thickness burn wounds. Its most common indications, however, are for the management of chronic wounds/ulcers and exposed soft tissues.[79]

Transport

Refrigerated skin should be transported in tissue culture medium at wet ice temperatures (above 0–10°C) in an insulated container. Frozen allograft skin is transported on dry ice in an insulated container to prevent the skin temperature from rising to greater than −40°C. If the frozen skin is thawed at the tissue bank, it should be transported at wet ice temperatures.

Rewarming

Rewarming of frozen cryopreserved allograft skin must be performed in such a manner as to minimize cryodamage and preserve the structural integrity and viability of the skin. Early studies demonstrated that warming rates of 50–70°C/min resulted in 80%–95% graft survival. Subsequent research[75] has revealed that warming should be performed in 2–4 minutes or less at a temperature of 10–37°C (127–470°C/min). Rewarming in a microwave oven is not recommended due to uneven heating and excessive intracellular temperatures.

FDA Regulation of Human Skin Banking

Concerns related to the potential transmission of disease from tissue donors triggered concern within Congress and the FDA, which resulted in the FDA's publication of an interim rule for the regulation of human tissues intended for transplantation in 1993.[80] The interim rule required that all donors have an accurately recorded medical and social history to assure freedom from risk factors for or clinical evidence of hepatitis B, hepatitis C, and HIV infection. Since then, the FDA has published its proposed final rules concerning establishment registration and listing, donor eligibility, and good tissue practices [81]. Numerous guidance documents are also posted on its website (http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/default.htm). Burn centers should only obtain allograft skin from tissue banks that comply with these regulations and preferably from those facilities accredited by the AATB. Obtaining tissue that complies with FDA regulations is required for burn center verification by the American Burn Association.

AMNION PROCESSING

The methods for processing amniotic membranes are remarkably similar to that of cadaveric skin, with only a few important differences. First, amniotic membranes are collected from living donors, so first-person consent is obtained from the donor prior to caesarean section. Following consent, the medical chart is reviewed for exclusionary criteria, and recent physical exam by a physician may be examined in lieu of direct physical examination. The donor completes a DRAI form, and blood is collected for serology as described in the processing of cadaveric skin, with the addition of testing for West Nile virus. During the caesarean section, the amnion is aseptically collected into a specimen container and refrigerated at 0–10°C until the tissue can be delivered to the skin bank within hours. From this point, the processing of the amnion is identical to cadaveric skin, with the exception that amnion must be frozen within 5 days of processing instead of 10 days.

The Future of Skin Banking

Skin banking must continue to evolve as engineered skin substitutes enter the clinical arena for the temporary and permanent coverage of partial- and full-thickness wounds. Allograft skin has the potential to play a major role in permanent skin reconstruction after extensive thermal injury; however this will require interactive research with the burn centers caring for these patients.

Moving forward, tissue banks have the opportunity to play a major role in continued research into regenerative medicine, stem cell therapies, and decellularized tissue that may provide novel uses for human tissue in the treatment of burns and many other conditions. Application of mesenchymal stem cells has been shown to result in faster healing of burn wounds, decreased inflammation, and improved scar quality, as well as improved corneal wound healing.[82–84] Decellularized tissue is an important area of research for tissue banking due to the improved compatibility of using these products in patients. In burn care, decellularized human allografts (AlloDerm) and porcine xenografts (Permacol) are already in use, although they are under continuing research scrutiny. In addition, research into methods to

preserve tissue will continue to be an important avenue of investigation. Tools such as glycerolization and irradiation of tissue produce nonviable tissue, which are useful as temporary wound coverage, as they result in decreased rejection and reduced risk of infectious disease transmission.[85] It will become increasingly important for skin banks to perform basic science and clinical research (in conjunction with burn and wound healing centers) to demonstrate the clinical indications and efficacy of allograft skin products in various clinical applications.

Skin banks must also identify ways of increasing cadaveric skin donation, ensuring recipient safety from potential disease transmission, and reducing costs of tissue recovery and processing while optimizing allograft viability. This will become increasingly difficult as it becomes necessary to perform additional infectious disease testing procedures to ensure recipient safety. To accomplish these goals, it has recently become necessary for many skin banking operations to consolidate, and tissue banks may even begin to expand internationally. Such an undertaking could enhance tissue supplies and availability and result in increased clinical use by surgeons.

Complete references available online at
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References

1. Reverdin JL. Sur la greffe épidermique. *CR Acad Sci*. 1871;(73).
2. Reverdin JL. De la greffe épidermique. *Arch Gen Med*. 1872;19(suppl).
3. Thiersch JC. On skin grafting. *Verhandl 2nd Deutsch Ges Chir*. 1886;15:17-20.
4. Girdner JH. Skin grafting with grafts taken from the dead subject. *Med Rec*. 1881;20:119-120.
5. Wentscher J. A further contribution about the survivability of human epidermal cells. *Dtsch Z Chir*. 1903;70:21-44.
6. Bettman AG. Homogeneous Thiersch grafting as a life saving measure. *Am J Surg*. 1938;39:156-162.
7. Webster JP. Refrigerated skin grafts. *Ann Surg*. 1944;120(4):431-448.
8. Matthews DN. Storage of skin for autogenous grafts. *Lancet*. 1945;2: 775-778.
9. Baxter H, Entin MA. Experimental and clinical studies of reduced temperatures in injury and repair in man; direct effect of cooling and freezing on various elements of the human skin. *Plast Reconstr Surg (1946)*. 1948;3(3):303-334.
10. Billingham RE, Medawar PB. The freezing, drying, and storage of mammalian skin. *J Exp Biol*. 1952;19:454-468.
11. Taylor AC. Survival of rat skin and changes in hair pigmentation following freezing. *J Exp Zool*. 1949;110(1):77-111.
12. Brown JB, Fryer MP, Randall P, Lu M. Postmortem homografts as biological dressings for extensive burns and denuded areas; immediate and preserved homografts as life-saving procedures. *Ann Surg*. 1953;138(4):618-630.
13. Jackson D. A clinical study of the use of skin homografts for burns. *Br J Plast Surg*. 1954;7(1):26-43.
14. Zaroff LI, Mills W Jr, Duckett JW Jr, Switzer WE, Moncrief JA. Multiple uses of viable cutaneous homografts in the burned patient. *Surgery*. 1966;59(3):368-372.
15. Cochrane T. The low temperature storage of skin: a preliminary report. *Br J Plast Surg*. 1968;21(2):118-125.
16. Morris PJ, Bondoc C, Burke JF. The use of frequently changed skin allografts to promote healing in the nonhealing infected ulcer. *Surgery*. 1966;60:13-19.
17. Shuck JM, Pruitt BA Jr, Moncrief JA. Homograft skin for wound coverage. A study of versatility. *Arch Surg*. 1969;98(4):472-479.
18. Eade GG. The relationship between granulation tissue, bacteria, and skin grafts in burned patients. *Plast Reconstr Surg Transplant Bull*. 1958;22(1):42-55.
19. Wood WB Jr. Phagocytosis, with particular reference to encapsulated bacteria. *Bacteriol Rev*. 1960;24(1):41-49.
20. O'Donoghue MN, Zarem HA. Stimulation of neovascularization—comparative efficacy of fresh and preserved skin grafts. *Plast Reconstr Surg*. 1971;48(5):474-478.
21. Bondoc CC, Burke JF. Clinical experience with viable frozen human skin and a frozen skin bank. *Ann Surg*. 1971;174(3):371-382.
22. Burke JF, Quinby WC, Bondoc CC, et al. Immunosuppression and temporary skin transplantation in the treatment of massive third degree burns. *Ann Surg*. 1975;182(3):183-197.
23. Robson MC, Krizek TJ. The effect of human amniotic membranes on the bacteria population of infected rat burns. *Ann Surg*. 1973;177(2):144-149.
24. Maral T, Borman H, Arslan H, et al. Effectiveness of human amnion preserved long-term in glycerol as a temporary biological dressing. *Burns*. 1999;25(7):625-635.
25. Haberal M, Oner Z, Bayraktar U, Bilgin N. The use of silver nitrate-incorporated amniotic membrane as a temporary dressing. *Burns Incl Therm Inj*. 1987;13(2):159-163.
26. Quinby WC Jr, Hoover HC, Scheflan M, et al. Clinical trials of amniotic membranes in burn wound care. *Plast Reconstr Surg*. 1982;70(6):711-717.
27. Ramakrishnan KM, Jayaraman V. Management of partial-thickness burn wounds by amniotic membrane: a cost-effective treatment in developing countries. *Burns*. 1997;23(suppl 1):S33-S36.
28. Robson MC, Krizek TJ, Koss N, Samburg JL. Amniotic membranes as a temporary wound dressing. *Surg Gynecol Obstet*. 1973;136(6):904-906.
29. Branski LK, Herndon DN, Celis MM, et al. Amnion in the treatment of pediatric partial-thickness facial burns. *Burns*. 2008;34(3): 393-399.
30. Loeffelbein DJ, Rohleder NH, Eddicks M, et al. Evaluation of human amniotic membrane as a wound dressing for split-thickness skin-graft donor sites. *Biomed Res Int*. 2014;2014:572183.
31. Ninman C, Shoemaker P. Human amniotic membranes for burns. *Am J Nurs*. 1975;75(9):1468-1469.
32. Salisbury RE, Carnes R, McCarthy LR. Comparison of the bacterial clearing effects of different biologic dressings on granulating wounds following thermal injury. *Plast Reconstr Surg*. 1980;66(4):596-598.
33. Capek KD, Trocme SD, Marsh D, et al Total ocular surface coverage with amniotic membrane transplantation in acute pediatric toxic epidermal necrolysis: a retrospective comparison with topical treatments. Poster presented at Association for Research in Vision and Ophthalmology 2016 Annual Meeting; May 1; Seattle.
34. DeClement FA, May SR. Procurement, cryopreservation and clinical application of skin. In: Glassman A, Umlas J, eds. *The Preservation of Tissues and Solid Organs for Transplantation*. Arlington, VA: American Association of Blood Banks; 1983:29-56.
35. Noonan T. *Honoring the Gift: The American Association of Tissue Banks at 40*. Chapel Hill, NC: Heritage Histories; 2016.
36. Stamper B, Plessinger RT, Rieman M, et al. A comparison of 'fresh' allograft and Integra in the management of extensive full-thickness burns. *J Burn Care Rehabil*. 1999;20.
37. Branski LK, Herndon DN, Pereira C, et al. Longitudinal assessment of Integra in primary burn management: a randomized pediatric clinical trial. *Crit Care Med*. 2007;35(11):2615-2623.
38. Alexander JW, MacMillan BG, Law E, Kittur DS. Treatment of severe burns with widely meshed skin autograft and meshed skin allograft overlay. *J Trauma*. 1981;21(6):433-438.
39. Rose JK, Desai MH, Mlakar JM, Herndon DN. Allograft is superior to topical antimicrobial therapy in the treatment of partial-thickness scald burns in children. *J Burn Care Rehabil*. 1997;18(4):338-341.
40. Naoum JJ, Roehl KR, Wolf SE, Herndon DN. The use of homograft compared to topical antimicrobial therapy in the treatment of second-degree burns of more than 40% total body surface area. *Burns*. 2004;30(6):548-551.
41. Herrmann L, Rogowitz L, Ullrich H. Basic principles of skin transplantation in burns and use of lyophilized skin transplants. *Zentralbl Chir*. 1965;90(26):1129-1134.
42. Mahdavi-Mazdeh M, Nozary Heshmati B, Tavakoli SA, et al. Human split-thickness skin allograft: skin substitute in the treatment of burn. *Int J Organ Transplant Med*. 2013;4(3):96-101.
43. O'Connor NE, Mulliken JB, Banks-Schlegel S, et al. Grafting of burns with cultured epithelium prepared from autologous epidermal cells. *Lancet*. 1981;1(8211):75-78.
44. Cuono C, Langdon R, McGuire J. Use of cultured epidermal autografts and dermal allografts as skin replacement after burn injury. *Lancet*. 1986;1(8490):1123-1124.
45. Hickerson WL, Compton C, Fletchall S, Smith LR. Cultured epidermal autografts and allodermis combination for permanent burn wound coverage. *Burns*. 1994;20(suppl 1):S52-S55, discussion S55-S56.
46. Gardien KL, Marck RE, Bloemen MC, et al. Outcome of burns treated with autologous cultured proliferating epidermal cells: a prospective randomized multicenter intrapatient comparative trial. *Cell Transplant*. 2016;25(3):437-448.
47. Livesey SA, Herndon DN, Hollyoak MA, Atkinson YH, Nag A. Transplanted acellular allograft dermal matrix. Potential as a template for the reconstruction of viable dermis. *Transplantation*. 1995;60(1):1-9.
48. Wainwright D, Madden M, Luterman A, et al. Clinical evaluation of an acellular allograft dermal matrix in full-thickness burns. *J Burn Care Rehabil*. 1996;17(2):124-136.
49. Monafo WW, Tandon SN, Bradley RE, Condict C. Bacterial contamination of skin used as a biological dressing. A potential hazard. *JAMA*. 1976;235(12):1248-1249.
50. AATB. *Standards for Tissue Banking*. 14th ed. McLean, VA: American Association of Tissue Banks; 2016.
51. Clarke JA. HIV transmission and skin grafts. *Lancet*. 1987;1(8539):983.
52. Kealey GP, Aguiar J, Lewis RW 2nd, et al. Cadaver skin allografts and transmission of human cytomegalovirus to burn patients. *J Am Coll Surg*. 1996;182(3):201-205.
53. Plessinger RT, Robb EC, Kagan RJ. Cytomegalovirus in skin donors. *Proc Am Assoc Tissue Banks*. 1996;20:56.
54. Herndon DN, Rose JK. Cadaver skin allograft and the transmission of human cytomegalovirus in burn patients: benefits clearly outweigh risks. *J Am Coll Surg*. 1996;182(3):263-264.
55. Keown PA. Cytomegalovirus infection in transplantation: a risk and management perspective. *Transplantation*. 1996;12:22-23.
56. Ninnemann JL, Fisher JC, Frank HA. Prolonged survival of human skin allografts following thermal injury. *Transplantation*. 1978;25(2):69-72.

57. Burke JF, May JW Jr, Albright N, Quinby WC, Russell PS. Temporary skin transplantation and immunosuppression for extensive burns. *N Engl J Med*. 1974;290(5):269-271.
58. Achauer BM, Hewitt CW, Black KS, et al. Long-term skin allograft survival after short-term cyclosporin treatment in a patient with massive burns. *Lancet*. 1986;1(8471):14-15.
59. Sakabu SA, Hansbrough JF, Cooper ML, Greenleaf G. Cyclosporine A for prolonging allograft survival in patients with massive burns. *J Burn Care Rehabil*. 1990;11(5):410-418.
60. Barnett JR, McCauley RL, Schutzler S, Sheridan K, Heggers JP. Cadaver donor discards secondary to serology. *J Burn Care Rehabil*. 2001;22(2):124-127.
61. Plessinger RT, Robb EC, Kagan RJ. The impact of autopsy report findings on the acceptability of the potential tissue donor. *Proc Am Assoc Tissue Banks*. 1999;48.
62. Pianigiani E, Tognetti L, Ierardi F, et al. Assessment of cryopreserved donor skin viability: the experience of the regional tissue bank of Siena. *Cell Tissue Bank*. 2016;17(2):241-253.
63. Holder IA, Robb E, Kagan R. Antimicrobial mixtures used to store harvested skin: antimicrobial activities tested at refrigerator (4 degrees C) temperatures. *J Burn Care Rehabil*. 1999;20(6):501-504.
64. Plessinger RT, Robb EC, Kagan RJ. Allograft skin cultures II: should allograft skin be processed in a class 10,000 or better environment? *Proc Am Assoc Tissue Banks*. 1997;S23.
65. AATB Guidance Document, Microbiological Process Validation & Surveillance Program. 2016.
66. Plessinger RT, Robb EC, Kagan RJ. Safe use of refrigerated allograft skin in burn patients. *Proc Am Assoc Tissue Banks*. 2005;29: A35.
67. Britton-Byrd BW, Lynch JP, Williamson S, McCauley RL. Early use of allograft skin: are 3-day microbiologic cultures safe? *J Trauma*. 2008;64(3):816-818.
68. White MJ, Whalen JD, Gould JA, Brown GL, Polk HC Jr. Procurement and transplantation of colonized cadaver skin. *Am Surg*. 1991;57(6): 402-407.
69. May SR, DeClement FA. Skin banking. Part III. Cadaveric allograft skin viability. *J Burn Care Rehabil*. 1981;2(3):128-141.
70. May SR, DeClement FA. Development of a radiometric metabolic viability testing method for human and porcine skin. *Cryobiology*. 1982;19:362-371.
71. Brown W, Cuono CB. Approaches to minimizing leakage of beneficial glycosaminoglycans in processing skin for cryopreservation. *Proc Am Assoc Tissue Banks*. 1992;S3.
72. Robb EC, Bechmann N, Plessinger RT, et al. A comparison of changed vs. unchanged media for viability testing of banked allograft skin. *Proc Am Assoc Tissue Banks*. 1997;S3.
73. Robb EC, Bechmann N, Plessinger RT, et al. Storage media and temperature maintain normal anatomy of cadaveric human skin for transplantation to full-thickness skin wounds. *J Burn Care Rehabil*. 2001;22(6):393-396.
74. Koizumi T, Robb EC, Bechmann N, et al. Prolonging human skin viability using 95% oxygen-enriched perfluorocarbon (PFC). *Proc Am Assoc Tissue Banks*. 2004;25:S80.
75. May SR, DeClement FA. Skin banking methodology: an evaluation of package format, cooling and warming rates, and storage efficiency. *Cryobiology*. 1980;17(1):33-45.
76. Cuono CB, Langdon R, Birchall N, et al. Viability and functional performance of allograft skin preserved by slow, controlled, non-programmed freezing. *Proc Am Assoc Tissue Banks*. 1988;20:55.
77. Aggarwal SJ, Baxter CR, Diller KR. Cryopreservation of skin: an assessment of current clinical applicability. *J Burn Care Rehabil*. 1985;6(6):469-476.
78. Mackie DP. The Euro Skin Bank: development and application of glycerol-preserved allografts. *J Burn Care Rehabil*. 1997;18(1 Pt 2):S7-S9.
79. Rosales MA, Bruntz M, Armstrong DG. Gamma-irradiated human skin allograft: a potential treatment modality for lower extremity ulcers. *Int Wound J*. 2004;1(3):201-206.
80. Department of Health and Human Services. Human tissue intended for transplantation—FDA. Interim rule; opportunity for public comment. *Fed Regist*. 1993;58(238):65514-66521.
81. Human Cells, Tissues, and Cellular and Tissue-Based Products, 21 C.F.R. § 1271. 2001.
82. Ghieh F, Jurjus R, Ibrahim A, et al. The use of stem cells in burn wound healing: a review. *Biomed Res Int*. 2015;2015:684084.
83. Yao L, Li ZR, Su WR, et al. Role of mesenchymal stem cells on cornea wound healing induced by acute alkali burn. *PLoS ONE*. 2012;7(2):e30842.
84. Clover AJ, Kumar AH, Isakson M, et al. Allogeneic mesenchymal stem cells, but not culture modified monocytes, improve burn wound healing. *Burns*. 2015;41(3):548-557.
85. Bohac M, Csobonyeiova M, Kupcova I, et al. Stem cell regenerative potential for plastic and reconstructive surgery. *Cell Tissue Bank*. 2016;17(4):735-744.

15 Skin Substitutes and 'the next level'

ESTHER MIDDELKOOP and ROBERT L. SHERIDAN

Introduction

STRUCTURE AND FUNCTION OF THE SKIN

Skin, the body's largest organ, is incredibly complex. Functionally, there are two layers with a highly specialized and effective bonding mechanism. Numerous appendages traverse the skin, and a rich and reactive capillary network provides nutrient flow while controlling temperature. The epidermis, consisting of the strata basale, spinosum, granulosum, and corneum, provides a vapor and bacterial barrier. The dermis provides strength, mechanical resistance, and elasticity. The thin epidermal layer is constantly refreshing itself from its basal layer, with new keratinocytes undergoing terminal differentiation over approximately 4 weeks to anuclear keratin-filled cells that make up the stratum corneum, which provides much of the barrier function of the epidermis. The basal layer of the epidermis is firmly attached to the dermis by a complex bonding mechanism containing among others collagen types IV and VII. When this bond fails, serious morbidity results, as demonstrated by the disease processes of toxic epidermal necrolysis (TEN) (Fig. 15.1)[1] and epidermolysis bullosa.[2]

CONSEQUENCES OF LOSS OF BARRIER FUNCTION

Loss of the epidermal barrier has serious adverse physiologic effects. Direct and evaporative fluid losses are immediately seen. If wounds are large, this quickly leads to dehydration and shock. Protein losses are also substantial, leading to loss of colloid oncotic pressure and secondary edema. Microorganisms have unimpeded access to the microcirculation with resulting systemic infection. Deep tissues become desiccated with secondary cell death and progression of wound depth.

Open wounds present a high risk of fluid loss, high inflammation, bacterial colonization, infection, and sepsis, which can lead to a poor prognosis in terms of prolonged healing times and scarring. Timely wound closure is therefore one of the key objectives in modern burn care.

An increasingly effective group of temporary and permanent wound coverings is available.

The objective of this chapter is to review the currently available strategies for temporary and (semi-) permanent skin substitutes in terms of origin of the material (tissue, biological, or synthetic material) and wound indication (partial-thickness vs full-thickness wounds).

Temporary Skin Substitutes and Dressings

Partial-thickness wounds remain confined to the dermal part of the skin. Usually, these wounds have a good healing potential because epidermal cells present in (remnants of) sebaceous glands, sweat glands, and hair follicles are available to close the wound.

In these wounds, the main demands to reach pain reduction and high-quality wound healing without scarring is to warrant undisturbed wound healing. A moist environment and protection against bacterial invasion are the most important qualities that need to be provided.

Wound dressings for partial-thickness wounds should:

- Provide a moist environment (migration of cells is more difficult if when there is a dry scab on the wound).[3]
- Protect the wound from excessive fluid loss and bacterial invasion.
- Require a limited number of dressing changes (pain reduction).

Modern wound dressing are able to fulfil these requirements. Generally, membranous dressings such as hydrocolloids and hydrofibers fulfill these requirements better than topical antimicrobial creams such as silver sulfadiazine (SSD) cream.[4-6] The main indication for temporary skin substitutes is partial-thickness wounds, of which donor sites are a special category, but essentially are similar wounds.

We can classify temporary skin substitute materials by their tissue origin into:

1. Biological tissues, such as allograft, xenograft, and amnion (keratinocyte sheets and cells)
2. Synthetic materials such as hydrocolloids and hydrofibers

BIOLOGICAL TISSUES

Allograft

The first type of membranous wound coverage used was human allograft skin. Human allograft is generally used as a split-thickness graft after being procured from organ donors. When used in a viable fresh or cryopreserved state, it vascularizes and remains the "gold standard" of temporary wound closures.[7-9] It can be refrigerated for up to 7 days, but it can be stored for extended periods when cryopreserved. It is also used in a nonviable state after

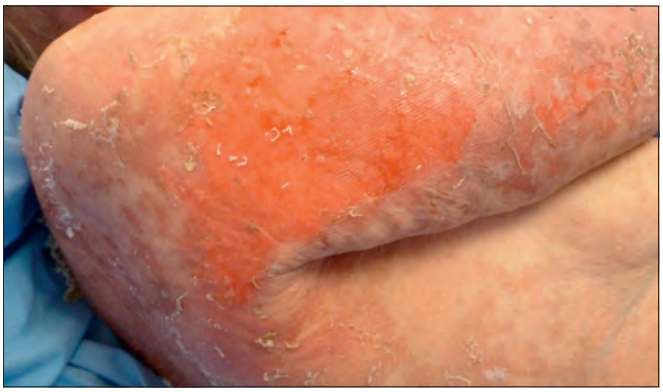

Fig. 15.1 Patient with toxic epidermal necrolysis.

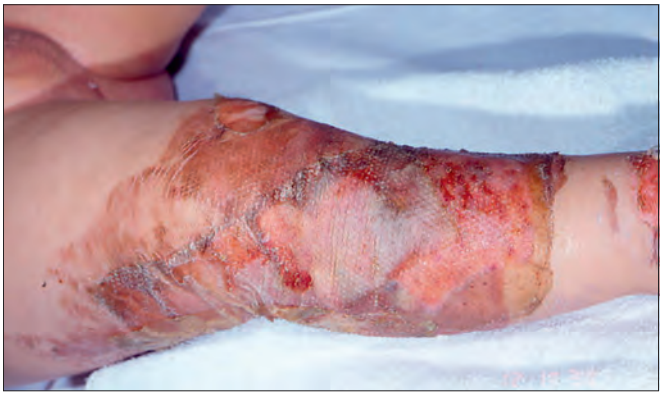

Fig. 15.2 Glycerolized allograft on a partial-thickness scald burn.

preservation in glycerol or after lyophilization. Viable split-thickness allograft provides durable biologic cover until it is rejected by the host, usually within 3 or 4 weeks. Prolongation of allograft survival, through the use of antirejection drugs, has been advocated[10] but is not generally practiced for fear that antirejection drugs will increase the risk of infection.[11]

A frequently used application of glycerolized allograft skin is as a membranous dressing on partial-thickness burns, especially scald burns in children (Fig. 15.2).[12] Modern banking techniques and regulations warrant the safety and quality of banked skin.[13] Allograft is also effectively used in combination with meshed autograft in patients with large burns, the interstices of the meshed graft being immediately closed by the overlying unexpanded allograft, possibly reducing metabolic stress and local wound inflammation.

Human Amnion

Human amniotic membrane is used in many parts of the world as a relatively cheap temporary dressing for superficial wounds.[14,15] Amniotic membrane is generally procured fresh and used after brief refrigerated storage.[16,17] It can also be used in a nonviable state after preservation with glycerol.

Beneficial effects have been described in a randomized controlled trial comparing amnion membrane with SSD by Mostaque et al on partial-thickness burns, with a better outcome using amnion membrane on time to epithelialization, length of stay (LOS), pain, and frequency of dressing changes.[18]

The principal concern with amnion is the difficulty in screening the material for viral diseases unless preservation methods can eliminate potential viral contamination. Without the ability to screen the material in this way, the risks of disease transmission must be balanced against the clinical need and the known characteristics of the donor.

Xenograft

Although various animal skins have been used for many years to provide temporary coverage of wounds,[19] only porcine xenograft is widely used today. It has been used as primary temporary cover and as a scaffold for dermal regeneration efforts.[20] Porcine xenograft is commonly distributed as a reconstituted product consisting of homogenized porcine dermis that is fashioned into sheets and meshed.[21] Split-thickness porcine skin is also used fresh, after brief refrigeration, after cryopreservation, or after glycerol preservation. It effectively provides temporary coverage of clean wounds such as superficial partial-thickness burns and donor sites[22] and has been used in patients with TEN.[1,23] Porcine xenograft has been combined with silver to suppress wound colonization.[24,25] Porcine xenograft does not vascularize, but it adheres to clean superficial wounds and can provide excellent pain control while the underlying wound heals.

SYNTHETIC MATERIALS

Nowadays, synthetic membranous dressings are increasingly capable of replacing biological membranous dressings. Next to protection against bacteria and fluid loss, pain reduction and mechanical protection, they provide a moist environment in which wound healing can proceed undisturbed. A number of semipermeable membrane dressings can provide a vapor and bacterial barrier and control pain while the underlying superficial wound or donor sites heal. These typically consist of a single semipermeable layer that provides a mechanical barrier to bacteria and has physiologic vapor transmission characteristics.[26]

The main advantages of synthetic membranes over biological ones are their constant composition, sterility, and availability. Disadvantages include their higher costs.

Nevertheless, in a number of recent studies, superiority of synthetic membranes over topical creams and ointments has been shown, especially with regard to healing time, LOS, and pain management.[4]

Some examples are mentioned here:

Biobrane (Smith & Nephew, Andover, MA) is a two-layer membrane constructed of an inner layer of nylon mesh that allows fibrovascular ingrowth and an outer layer of silastic that serves as a vapor and bacterial barrier.[27] It is widely used to provide temporary closure of superficial burns and donor sites.[28] All synthetic membranes

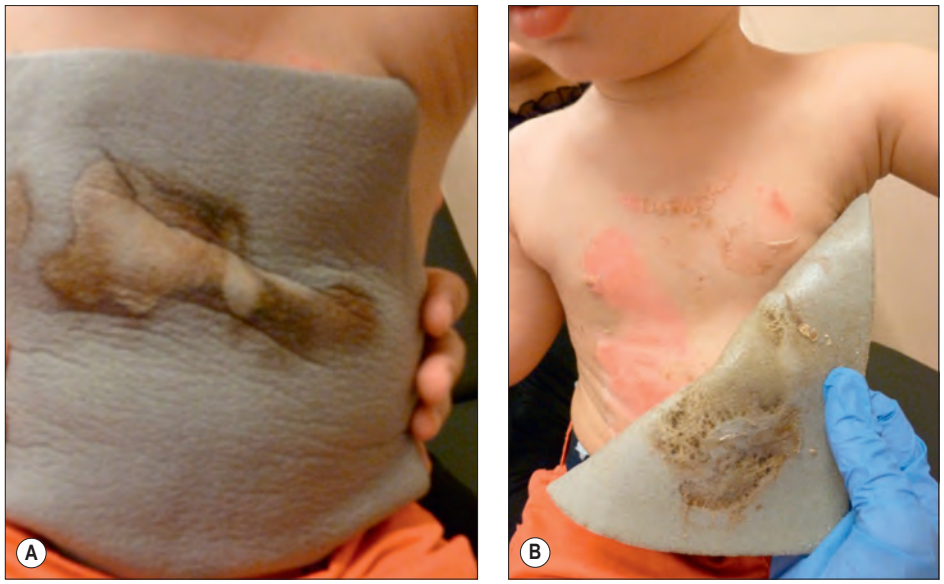

Fig. 15.3 Mepilex Ag for partial-thickness burn treatment, 7 days after burn.

are occlusive and can foster infection if placed over contaminated wounds, especially in the presence of necrotic tissue.[29] Appropriate monitoring is essential to their proper use.

Another category of silicone containing dressings is formed by the silicone-coated dressings such as Mepitel and Mepilex (Mölnlycke, Göteborg, Sweden) (Fig. 15.3) of which advantages are reported in terms of time to healing, pain reduction, and number of dressing changes.[30,31]

Hydrocolloid dressings are generally designed with a three-layer structure: a porous, gently adherent inner layer; a methyl cellulose absorbent middle layer; and a semipermeable outer layer. They foster a moist wound environment while absorbing exudate. A moist wound environment has been found to favor wound healing.[32] A variety of pastes and powders made from hydrocolloid materials are also widely available. These can be applied to superficial or deeper chronic wounds to absorb wound exudate while maintaining a moist wound environment.

Hydrofiber dressings absorb wound exudate and have been used as temporary wound membranes. When combined with ionic silver (Aquacel-Ag; ConvaTec, Flintshire, UK), additional antimicrobial activity is seen. This membrane has been used successfully in some burn programs as an adjunct in the management of partial-thickness burns and donor sites (Fig. 15.4).[33]

Alginate dressings (e.g., Kaltostat, ConvaTec; Comfeel, Coloplast, Humlebaek, Denmark) are fibrous dressings derived from seaweed. They have a high absorption capacity because of strong hydrophilic gel formation.[34] Their use in burns is mainly as dressing for donor sites. Not many comparative prospective trials are available.

Other synthetic wound dressings include Suprathel (a polylactic acid membrane; Polymedics, Denkendorff, Germany), Urgotul (polyester mesh impregnated with hydrocolloid and petroleum jelly; Urgo Medical, Chenove, France), and Allevyn (a polyurethane foam dressing) (Smith & Nephew), and new materials appear on the market very frequently.

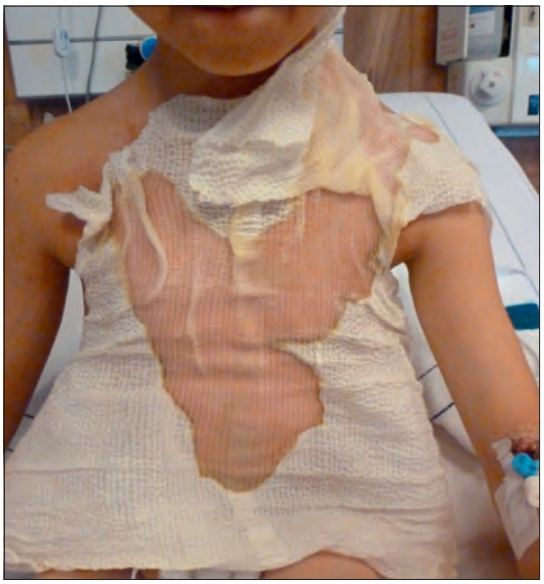

Fig. 15.4 Aquacel Burn hydrofiber dressing, 2 days after application on a partial-thickness burn.

Permanent Skin Substitutes

In contrast to partial-thickness wounds, full-thickness skin lesions lack the availability of enough viable epidermal cells that could close the wound within a reasonable time frame. Therefore, for deep wounds, surgical intervention is indicated. The main purpose of the surgery is to bring a new source of epidermal cells to the wound to speed up wound closure. This can be done in different ways, such as a

split-skin graft, cultured epithelial sheets, carriers or sprays, or skin substitutes.[35] Furthermore, full-thickness grafts or flaps are also used for treatment of full-thickness wounds of limited size.

In addition to providing epidermal coverage, replacement of dermal tissue is also important. From the early studies on treatments with cultured epithelial sheets, it is now known that even after a prolonged time, the dermal–epidermal junction is not fully regenerated, which leaves a rather vulnerable skin that is prone to mechanical damage.[36] Healing of full-thickness wounds is generally accompanied by scar formation. The use of dermal substitutes in full-thickness skin defects may contribute to a better quality of healing with reduced scarring.[37,38]

EPIDERMAL CELLS AND CONSTRUCTS

For more than 40 years, it has been possible to culture vast numbers of epithelial cells from a small skin biopsy,[39,40] and this has led to the widespread clinical use of cultured epithelial grafts to cover burn wounds. Originally, epithelial cells were procured from a full-thickness skin biopsy, the cells were cultured in medium containing fetal calf serum, insulin, transferrin, hydrocortisone, epidermal growth factor, and cholera toxin, overlying a layer of murine fibroblasts that had been treated with a nonlethal dose of radiation that prevented them from multiplying. After some weeks, epithelial sheets were removed from the dishes after treatment with Dispase.

When epithelial cultures were first used in patients with large burns, it was hoped that they would provide the definitive answer to the clinical problem of the massive wound.[41-43] With more frequent use of epithelial grafts, specific liabilities have become apparent, including suboptimal engraftment rates and long-term durability.[44,45] However, when faced with a very large wound and minimal donor sites, epithelial cell wound closure is a useful adjunct to split-thickness autograft, their liabilities and expense becoming more acceptable as wound size increases.

The elimination of risks of transmission of animal derived disease components such as viruses or prions to the patient nowadays represent serious regulatory and safety issues because from a regulatory point of view, these defined xenobiotic materials and cells should not be used for clinical treatment of a patient.

Many of the imperfections associated with epithelial cell wound closure may be attributed to the absence of a dermal element. Epithelial grafts are now commercially available, although several early biotech startup companies providing these services frequently experienced problems to reach an acceptable level of funding. The limited commercial volume of the products, high production costs, and increasing demands in terms of regulatory issues represent some of the challenges for small biotechnology companies.[35]

New developments in this line are found in eliminating the murine fibroblasts and (most of) the animal derived products in culture media, reducing culture time by transplanting subconfluent (proliferating) cells rather than confluent sheets (Fig. 15.5) and by applying spray techniques (Fig. 15.6) (Recell, Avita Medical, Northridge, CA; Keraheal, MCTTBio, Seoul, South Korea) to deliver either freshly isolated or proliferating epidermal cells to the wound bed.[46-48]

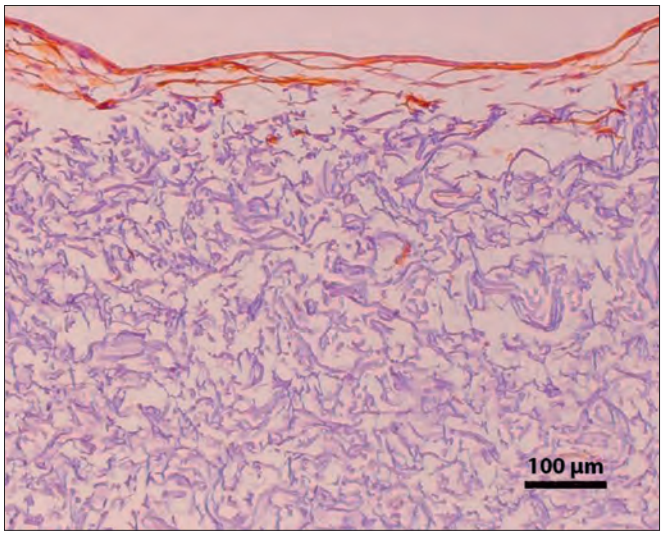

Fig. 15.5 Epidermal cells seeded onto Matriderm dermal matrix.

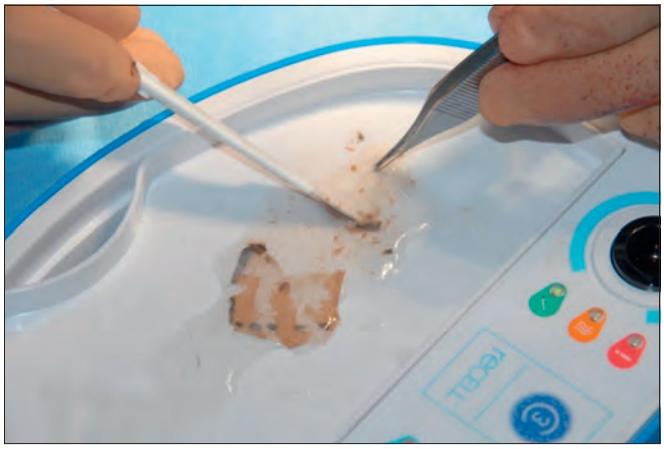

Fig. 15.6 Isolation of epidermal cells using a Recell kit.

DERMAL CONSTRUCTS

Tissues

Virtually all of the characteristics of normal skin that are not related to barrier function are provided by the dermis. These characteristics include flexibility, strength, heat dissipation and conservation, lubrication, and sensation.

A dermal analog that is—in structure at least—closest to the original dermis is based on freeze-dried allogenic dermis. This material is intended to be combined with a thin epithelial autograft at the time of initial wound closure. It is marketed as AlloDerm (LifeCell Corporation, now Acelity, San Antonio, TX).[49,50] Split-thickness allograft skin is obtained from cadaver donors through tissue banks after proper screening for transmissible diseases. Using hypertonic saline, the epithelial elements of the grafts are removed and the remaining dermis is treated in a detergent to inactivate any viruses and the device is freeze-dried. The process is

intended to provide a nonantigenic dermal scaffold, leaving basement membrane proteins (particularly laminin and type IV and VII collagen) intact. The material is rehydrated immediately before placement on wounds with overlying ultrathin epithelial autograft. Clinical experience with this material in burn surgery is limited,[51] but early experiences have been favorable.[52,53] Nevertheless, these products now seem to be used more in breast reconstructive surgery than in acute burns.[54] A similar product, based on allogeneic dermis preserved in glycerol, is Glyaderm (Euro Tissue Bank, Beverwijk, The Netherlands). Also here, antigenicity is reduced by washing out the cells and preserving the original extracellular matrix. Initial studies on burn patients have been performed and reported favorable results.[55]

Dermal Scaffolds

The first dermal substitute used clinically was "artificial skin," also called Integra (IntegraLife, Plainsboro, NJ); it has been used worldwide for several years now for burns as well as reconstructive purposes. This material was developed in the early 1980s by a biomaterials research team from the Massachusetts General Hospital and Massachusetts Institute of Technology.[56] The research team, led by surgeon John Burke from the Massachusetts General Hospital and materials scientist Ionnas Yannas from the Massachusetts Institute of Technology, had the goal of developing a wound covering that would both provide a temporary vapor and bacterial barrier while providing a scaffold for later dermal regeneration. The material was intended to be placed on excised burn wounds. The silicone outer layer serves as a temporary epidermis and is removed after vascular ingrowth into the dermal replacement is completed (usually within 2–3 weeks). The inner layer of this material is a 1- to 2-mm-thick combination of fibers of collagen isolated from bovine tissue and the glycosaminoglycan chondroitin-6-sulfate. To manufacture the device, glycosaminoglycan and collagen fibers are precipitated and then freeze dried and cross-linked by glutaraldehyde. The outer layer of the membrane is 0.009-inch (0.23-mm) -thick polysiloxane polymer with vapor transmission characteristics similar to normal epithelium. This membrane is intended to be placed on freshly excised full-thickness burns and the outer silicone membrane replaced with a thin epithelial autograft 2–3 weeks later.[57] Clinical reports in patients with large burns have been generally favorable,[58-60] although submembrane infection must be watched for. Integra has also been found to be useful in selected burn reconstruction operations (Fig. 15.7).[61]

Whereas Integra is applied in a two-stage operation—first debridement and application of the substitute and 2–3 weeks later removal of the silicone layer and grafting of a split-thickness skin graft—some substitutes can be applied in a one-step procedure. The first dermal substitute that was applied in this way was Matriderm (Medskin Solutions, Billerbeck, Germany). Matriderm consist of bovine collagen fibers mixed with 3% elastin hydrolysate, purified and freeze dried into a dry scaffold that can be placed on the wound in this form immediately or can be prewetted with a saline solution. Clinical results indicate a somewhat retarded take of the graft, reflecting the interpositioning of the unvascularized scaffold between the wound bed and the graft; however, this was compensated by a better outcome in terms of scar quality even after as long as 12 years later (Fig. 15.8).[38] Other scaffolds in this same category are Permacol (a porcine dermal collagen implant, mainly indicated for hernia and abdominal wall repair; Tissue Science Laboratories, Hampshire, UK), Renoskin (Symatèse, Chaponost, France), Pelnac (Smith & Nephew) (both Renoskin and Pelnac are similar to Integra, consisting of a bilayer of collagen with a silicone top layer), and Novomaix (freeze-dried collagen scaffold with elastin fibers; (Matricel, Herzogenrath, Germany). Hyalomatrix (Fidia Advanced Biopolymers, Italy) consists of a bilayer of an esterified hyaluronan beneath a silicone membrane. The scaffold delivers hyaluronan to the wound bed, and the silicone membrane acts as a temporary epidermal barrier.

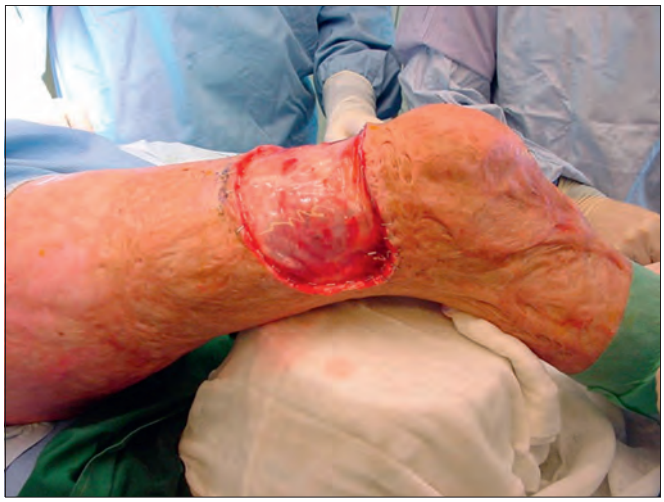

Fig. 15.7 Scar revision using Integra.

CELLULAR DERMAL SUBSTITUTES

Although some cellular constructs are or were (Dermagraft for chronic wound healing, Transcyte for partial-thickness burns; both Smith & Nephew) on the market using dermal cells in a scaffold for improving wound healing, most of these developments are still in the experimental stage. In vivo studies are described using adipose-derived regenerative cells in Integra,[62] and attempts were made to design a new generation of skin substitutes based on nanotechnology using nanocomposite polymers.[63] However, clinical safety and effectivity still need to be demonstrated for this technology.

A limited number of burn patients was already treated with a construct of native horse collagen with cells from a fetal skin bank.[64] Nevertheless, this is not a commercially available product yet. Furthermore, an experimental study Akershoek and colleagues found superior effects of autologous dermal cells over fetal cells when used in a dermal substitute (Novomaix).[65]

The fact that at present cell seeded skin replacement constructs fall into the category of advanced technology medicinal products (ATMPs) made it more difficult to proceed with these developments into clinical application. Production of these constructs should be strictly controlled,

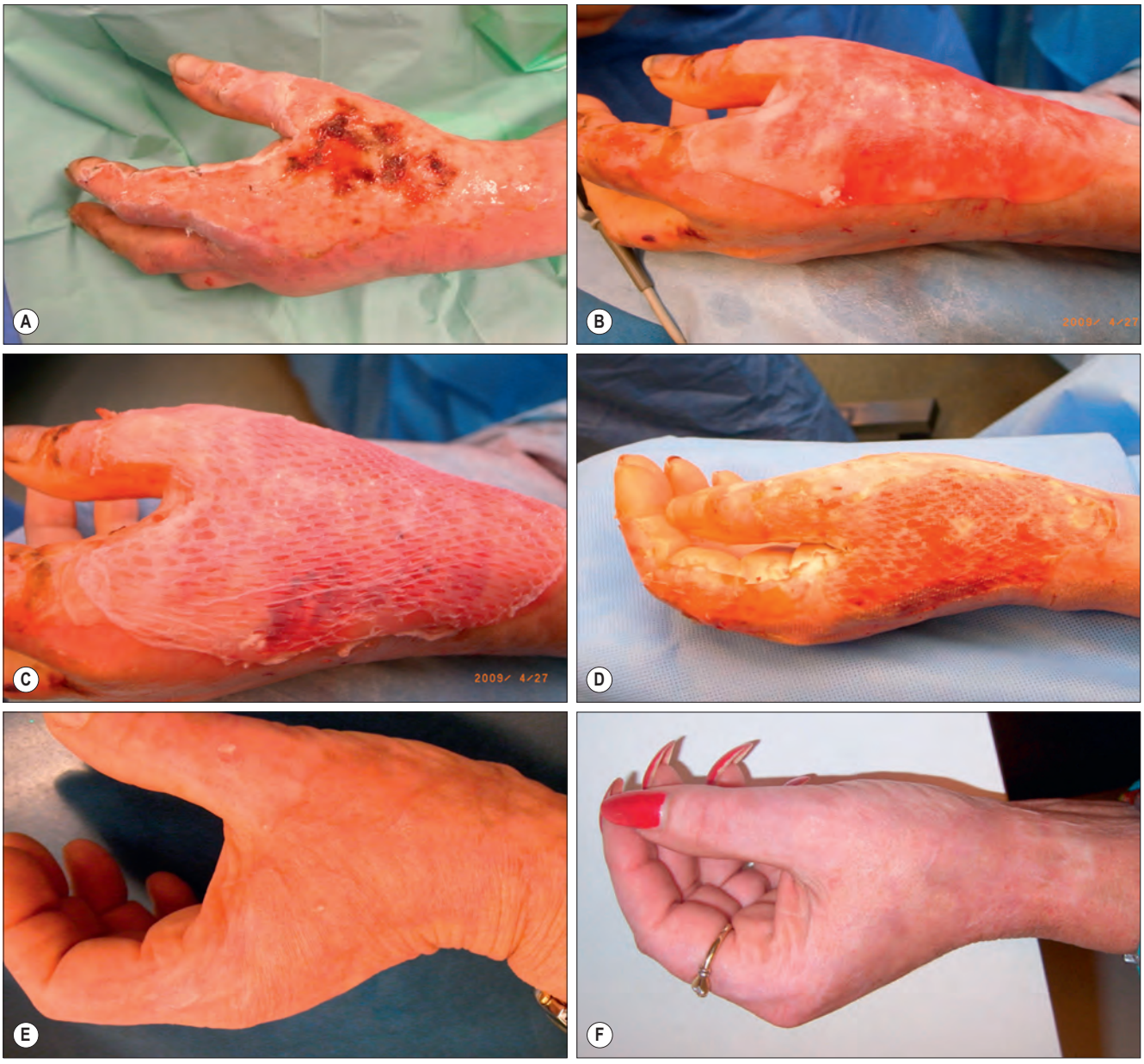

Fig. 15.8 Application and long-term results of Matriderm application. **A,** Full-thickness burn at postburn day (PBD) 3. **B,** Application of Matriderm during surgery, PBD 15. **C,** Application of split-skin mesh graft over Matriderm in a single stage procedure, PBD 15. **D,** Five days after grafting. **E,** Five months postoperatively. **F,** Eighteen months postoperatively.

with clinical-grade ingredients for cell culture media. This aspect stimulated investing in full skin equivalents rather than designing an ATMP for dermal replacement only. For developments in full skin equivalents, see the later discussion.

SUBCUTANEOUS FAT

Although mostly skin is defined as consisting of dermis and epidermis, in recent years, the subcutis has been noted as important for skin function as well. Especially in reconstructive areas, it has become more clear that subcutaneous fat—or the lack of it—plays an essential role in the gliding function of the skin. This is especially important on anatomical locations where the skin is relatively thin, such as the back of the hand and the tibia. In these areas, a scar can easily become attached to underlying tendons or bone if subcutaneous fat is also missing. Recent studies have noted beneficial effects on scar quality of lipo-injection with the patient's own fat, harvested by liposuction.[66–68] Although there is not enough solid clinical evidence yet, the data gathered so far indicate that fat grafting could become a new technique in improving scar quality and outcome after burns. Further research should aim at elucidating the best indications, timing and techniques, and frequencies of application.

Full Skin Substitutes

Ideally, a skin replacement technique would provide immediate replacement of both the dermal and epidermal layers. Combining epithelial cells with a dermal analog in the laboratory seems logical. A completely biological composite skin substitute, culturing human fibroblasts in a dermal matrix, and then growing keratinocytes on this, has been developed by several research groups.[69,70]

The first full composite skin construct to appear on the market was Apligraf (Organogenesis, Canton, MA). It consists of cultured human foreskin–derived neonatal fibroblasts in a bovine type I collagen matrix over which human foreskin–derived neonatal epidermal keratinocytes are then cultured and allowed to stratify. Because the cells are allogeneic, ultimately, the keratinocytes are rejected; therefore, for definite wound closure, an autologous source of keratinocytes needs to be present. Apligraf is therefore mainly used in chronic wound healing and not so much for healing of full-thickness burns.[71]

Another bilayered cellular skin substitute is Orcel (Fortcell Bioscience, Englewood Cliffs, NJ),[72] which contains a layer of cultured human allogeneic neonatal dermal fibroblasts and a layer of cultured human allogeneic neonatal epidermal keratinocytes into a type 1 bovine collagen sponge. Also here, the cells are of allogeneic origin and do not survive for more than 2–3 weeks in a wound. Its working mechanism is thought to be predominantly through the excretion of physiological levels and mix of growth factors and cytokines.

Full skin substitutes that make use of autologous (patient-own) cells have also been described in recent papers.[73-76] Apart from regulatory issues (see later discussion), major problems in the application of these constructs are the long culture times; high costs; and in some cases, the lack of pigment cells. Nevertheless, these are important developments because e in the end, they may lead to novel, clinically applicable truly regenerative full skin analogs, comprising not only dermal and epidermal structures but also vasculature, skin appendages, and even nerves.[77,78]

Regulatory Issues

New developments in regenerative medicine have indicated that the use of living cells in tissue engineered products might prove clinical benefit in terms of promoting wound healing and reducing scar formation.[79] During the past decade, however, new regulations have become effective, designating cell-based therapy as ATMPs. The European Medicines Agency (an agency of the European Union) is dedicated to the scientific evaluation and supervision of market access of medicines. Also, ATMPs fall into this category. Regulation (EC) No. 1394/2007 provides the overall framework on production and use of ATMPs in Europe.[80] In the United States, similar tasks are entrusted to the Food and Drug Administration), where the Office of Cellular, Tissue and Gene Therapies exerts the tasks to evaluate and supervise market access of ATMP products.

According to the EU Regulation No 1394/2007 definition, an ATMP is a "medicine for human use that is based on genes, cells or tissue engineering." A tissue-engineered product may contain or consist of engineered cells or tissues, with the purpose to regenerate, repair, or replace a human tissue, and it may contain viable or nonviable cells or tissues of human or animal origin. Therefore, skin substitutes containing living autologous cells, of dermal, adipose, or epidermal origin are considered as ATMPs and fall under the regulatory issues associated with these. One of the main features of these regulations is that production of ATMPs for human use must take place under good manufacturing practice conditions. For many research laboratories, such conditions are not feasible. Furthermore, a considerable administrative burden is represented by import and export procedures over international borders. Yet given the fact that commercial exploitation of this type of high technological wound treatment is only possible in an international context, these hurdles need to be overcome to allow a successful market position for these products.

Conclusion

Over the past decade, important clinical evidence has been gathered on dermal substitutes, and improvement were achieved in epidermal analogs, both in culture techniques and in application methods. Based on recent reports in preclinical research, we can expect to see further improvements in the next decade in the refinement of full skin equivalents, in incorporation of skin appendages, vasculature, and nerves.

Another area of improvement has been the development of the field of temporary dressings. More synthetic," well-controlled dressings were tested in clinical application. The incorporation of "actives" in these dressings, which was expected previously, was not realized, however. Rather than the addition of single growth factors in wound dressings, the technology of genetic modification might be one of the new clinical developments in the years to come. Cells (e.g., keratinocytes) can be engineered to overexpress platelet-derived growth factor, human growth hormone, insulinlike growth factor 1, and other growth factors.[81,82] On the other hand, mesenchymal stem cells are another tool that could likely lead to innovative technology in burn care.[83] When these can be developed into a readily applicable source for epidermal coverage, the dependence on autologous epidermal cells for wound closure will end.

Nevertheless, there is also an ongoing need for more evidence in clinical science, such as on the comparison of various temporary or permanent scaffolds in promoting wound healing, on the use of growth factors to stimulate the healing process, or on the optimal timing of physical techniques during scar management. Standardized and validated outcome measures should definitely receive more attention and development in clinical evaluation. Patient-reported outcomes can be considered an indispensable part of clinical evaluation. Clinical treatment should therefore focus not only on the treatment itself but also on adequate outcome evaluation of therapy.

Complete references available online at www.expertconsult.inkling.com

References

1. Palmieri TL, et al. A multicenter review of toxic epidermal necrolysis treated in U.S. burn centers at the end of the twentieth century. *J Burn Care Rehabil*. 2002;23(2):87-96.
2. Harr T, French LE. Severe cutaneous adverse reactions: acute generalized exanthematous pustulosis, toxic epidermal necrolysis and Stevens-Johnson syndrome. *Med Clin North Am*. 2010;94(4):727-742, x.
3. Junker JP, et al. Clinical impact upon wound healing and inflammation in moist, wet, and dry environments. *Adv Wound Care (New Rochelle)*. 2013;2(7):348-356.
4. Vloemans AF, et al. Optimal treatment of partial thickness burns in children: a systematic review. *Burns*. 2014;40(2):177-190.
5. Wasiak J, et al. Dressings for superficial and partial thickness burns. *Cochrane Database Syst Rev*. 2013;(3):CD002106.
6. Rashaan ZM, et al. Nonsilver treatment vs. silver sulfadiazine in treatment of partial-thickness burn wounds in children: a systematic review and meta-analysis. *Wound Repair Regen*. 2014;22(4):473-482.
7. Bondoc CC, Burke JF. Clinical experience with viable frozen human skin and a frozen skin bank. *Ann Surg*. 1971;174(3):371-382.
8. Herndon DN. Perspectives in the use of allograft. *J Burn Care Rehabil*. 1997;18(1 Pt 2):S6.
9. Kagan RJ, Robb EC, Plessinger RT. Human skin banking. *Clin Lab Med*. 2005;25(3):587-605.
10. Burke JF, et al. Temporary skin transplantation and immunosuppression for extensive burns. *N Engl J Med*. 1974;290(5):269-271.
11. Sheridan R, Mahe J, Walters P. Autologous skin banking. *Burns*. 1998;24(1):46-48.
12. Vloemans AF, et al. A randomised clinical trial comparing a hydrocolloid-derived dressing and glycerol preserved allograft skin in the management of partial thickness burns. *Burns*. 2003;29(7):702-710.
13. van Baare J, et al. The 1998 Lindberg Award. Comparison of glycerol preservation with cryopreservation methods on HIV-1 inactivation. *J Burn Care Rehabil*. 1998;19(6):494-500.
14. Kesting MR, et al. The role of allogenic amniotic membrane in burn treatment. *J Burn Care Res*. 2008;29(6):907-916.
15. Subrahmanyam M. Amniotic membrane as a cover for microskin grafts. *Br J Plast Surg*. 1995;48(7):477-478.
16. Ganatra MA, Durrani KM. Method of obtaining and preparation of fresh human amniotic membrane for clinical use. *J Pak Med Assoc*. 1996;46(6):126-128.
17. Thomson PD, Parks DH. Monitoring, banking, and clinical use of amnion as a burn wound dressing. *Ann Plast Surg*. 1981;7(5):354-356.
18. Mostaque AK, Rahman KB. Comparisons of the effects of biological membrane (amnion) and silver sulfadiazine in the management of burn wounds in children. *J Burn Care Res*. 2011;32(2):200-209.
19. Song IC, et al. Heterografts as biological dressings for large skin wounds. *Surgery*. 1966;59(4):576-583.
20. Jiong C, et al. Clinical application and long-term follow-up study of porcine acellular dermal matrix combined with autoskin grafting. *J Burn Care Res*. 2010;31(2):280-285.
21. Ersek RA, Hachen HJ. Porcine xenografts in the treatment of pressure ulcers. *Ann Plast Surg*. 1980;5(6):464-470.
22. Chiu T, Burd A. "Xenograft" dressing in the treatment of burns. *Clin Dermatol*. 2005;23(4):419-423.
23. Marvin JA, et al. Improved treatment of the Stevens-Johnson syndrome. *Arch Surg*. 1984;119(5):601-605.
24. Ersek RA, Navarro JA. Maximizing wound healing with silver-impregnated porcine xenograft. *Todays OR Nurse*. 1990;12(12):4-9.
25. Ersek RA, Denton DR. Silver-impregnated porcine xenografts for treatment of meshed autografts. *Ann Plast Surg*. 1984;13(6):482-487.
26. Salisbury RE, et al. Biological dressings for skin graft donor sites. *Arch Surg*. 1973;106(5):705-706.
27. Lou RB, Hickerson WL. The use of skin substitutes in hand burns. *Hand Clin*. 2009;25(4):497-509.
28. Lazic T, Falanga V. Bioengineered skin constructs and their use in wound healing. *Plast Reconstr Surg*. 2011;127(suppl 1):75S-90S.
29. Bacha EA, et al. Staphylococcal toxic shock syndrome in a paediatric burn unit. *Burns*. 1994;20(6):499-502.
30. Tang H, et al. An open, parallel, randomized, comparative, multicenter investigation evaluating the efficacy and tolerability of Mepilex Ag versus silver sulfadiazine in the treatment of deep partial-thickness burn injuries. *J Trauma Acute Care Surg*. 2015;78(5):1000-1007.
31. Gee Kee EL, et al. Randomized controlled trial of three burns dressings for partial thickness burns in children. *Burns*. 2015;41(5):946-955.
32. Vanstraelen P. Comparison of calcium sodium alginate (KALTOSTAT) and porcine xenograft (E-Z DERM) in the healing of split-thickness skin graft donor sites. *Burns*. 1992;18(2):145-148.
33. Blome-Eberwein S, et al. Hydrofiber dressing with silver for the management of split-thickness donor sites: a randomized evaluation of two protocols of care. *Burns*. 2010;36(5):665-672.
34. Brenner M, et al. Management of pediatric skin-graft donor sites: a randomized controlled trial of three wound care products. *J Burn Care Res*. 2015;36(1):159-166.
35. Gardien KL, Middelkoop E, Ulrich MM. Progress towards cell-based burn wound treatments. *Regen Med*. 2014;9(2):201-218.
36. Compton CC, et al. The generation of anchoring fibrils by epidermal keratinocytes: a quantitative long-term study. *Epithelial Cell Biol*. 1995;4(3):93-103.
37. Bloemen MC, et al. Clinical effectiveness of dermal substitution in burns by topical negative pressure: a multicenter randomized controlled trial. *Wound Repair Regen*. 2012;20(6):797-805.
38. Bloemen MC, et al. Dermal substitution in acute burns and reconstructive surgery: a 12-year follow-up. *Plast Reconstr Surg*. 2010;125(5):1450-1459.
39. Rheinwald JG, Green H. Serial cultivation of strains of human epidermal keratinocytes: the formation of keratinizing colonies from single cells. *Cell*. 1975;6(3):331-343.
40. Green H, Kehinde O, Thomas J. Growth of cultured human epidermal cells into multiple epithelia suitable for grafting. *Proc Natl Acad Sci USA*. 1979;76(11):5665-5668.
41. Green H. Cultured cells for the treatment of disease. *Sci Am*. 1991;265(5):96-102.
42. Gallico GG 3rd, et al. Permanent coverage of large burn wounds with autologous cultured human epithelium. *N Engl J Med*. 1984;311(7):448-451.
43. Sheridan RL, Tompkins RG. Cultured autologous epithelium in patients with burns of ninety percent or more of the body surface. *J Trauma*. 1995;38(1):48-50.
44. Rue LW 3rd, et al. Wound closure and outcome in extensively burned patients treated with cultured autologous keratinocytes. *J Trauma*. 1993;34(5):662-667, discussion 667-668.
45. Barret JP, et al. Cost-efficacy of cultured epidermal autografts in massive pediatric burns. *Ann Surg*. 2000;231(6):869-876.
46. Wood F, et al. A prospective randomised clinical pilot study to compare the effectiveness of Biobrane(R) synthetic wound dressing, with or without autologous cell suspension, to the local standard treatment regimen in paediatric scald injuries. *Burns*. 2012;38(6):830-839.
47. Yim H, et al. Clinical study of cultured epithelial autografts in liquid suspension in severe burn patients. *Burns*. 2011;37(6):1067-1071.
48. Lee H. Outcomes of sprayed cultured epithelial autografts for full-thickness wounds: a single-centre experience. *Burns*. 2012;38(6):931-936.
49. Callcut RA, et al. Clinical experience with Alloderm: a one-staged composite dermal/epidermal replacement utilizing processed cadaver dermis and thin autografts. *Burns*. 2006;32(5):583-588.
50. Yim H, et al. The use of AlloDerm on major burn patients: AlloDerm prevents post-burn joint contracture. *Burns*. 2010;36(3):322-328.
51. Wainwright DJ, Bury SB. Acellular dermal matrix in the management of the burn patient. *Aesthet Surg J*. 2011;31(7 suppl):13S-23S.
52. Sheridan RL, Choucair RJ. Acellular allogenic dermis does not hinder initial engraftment in burn wound resurfacing and reconstruction. *J Burn Care Rehabil*. 1997;18(6):496-499.
53. Sheridan R, et al. Acellular allodermis in burns surgery: 1-year results of a pilot trial. *J Burn Care Rehabil*. 1998;19(6):528-530.
54. Skovsted Yde S, Brunbjerg ME, Damsgaard TE. Acellular dermal matrices in breast reconstructions – a literature review. *J Plast Surg Hand Surg*. 2016;1-10.
55. Pirayesh A, et al. Glyaderm((R)) dermal substitute: clinical application and long-term results in 55 patients. *Burns*. 2015;41(1):132-144.
56. Tompkins RG, Burke JF. Progress in burn treatment and the use of artificial skin. *World J Surg*. 1990;14(6):819-824.
57. Tompkins RG, et al. Increased survival after massive thermal injuries in adults: preliminary report using artificial skin. *Crit Care Med*. 1989;17(8):734-740.
58. Jeschke MG, et al. Wound coverage technologies in burn care: novel techniques. *J Burn Care Res*. 2013;34(6):612-620.
59. Sheridan RL, et al. Artificial skin in massive burns – results to 10 years. *Eur J Plast Surg*. 1994;17(2):91-93.

60. Heimbach DM, et al. Multicenter postapproval clinical trial of Integra dermal regeneration template for burn treatment. *J Burn Care Rehabil*. 2003;24(1):42-48.
61. Nguyen DQ, Potokar TS, Price P. An objective long-term evaluation of Integra (a dermal skin substitute) and split thickness skin grafts, in acute burns and reconstructive surgery. *Burns*. 2010;36(1):23-28.
62. Foubert P, et al. Uncultured adipose-derived regenerative cells (ADRCs) seeded in collagen scaffold improves dermal regeneration, enhancing early vascularization and structural organization following thermal burns. *Burns*. 2015;41(7):1504-1516.
63. Chawla R, et al. A polyhedral oligomeric silsesquioxane-based bilayered dermal scaffold seeded with adipose tissue-derived stem cells: in vitro assessment of biomechanical properties. *J Surg Res*. 2014;188(2):361-372.
64. Hohlfeld J, et al. Tissue engineered fetal skin constructs for paediatric burns. *Lancet*. 2005;366(9488):840-842.
65. Akershoek JJ, et al. Cell therapy for full-thickness wounds: are fetal dermal cells a potential source? *Cell Tissue Res*. 2016;364(1):83-94.
66. Byrne M, et al. Early experience with fat grafting as an adjunct for secondary burn reconstruction in the hand: Technique, hand function assessment and aesthetic outcomes. *Burns*. 2016;42(2):356-365.
67. Pallua N, et al. Improvement of facial scar appearance and microcirculation by autologous lipofilling. *J Plast Reconstr Aesthet Surg*. 2014;67(8):1033-1037.
68. Bruno A, et al. Burn scar lipofilling: immunohistochemical and clinical outcomes. *J Craniofac Surg*. 2013;24(5):1806-1814.
69. Boyce ST, Hansbrough JF. Biologic attachment, growth, and differentiation of cultured human epidermal keratinocytes on a graftable collagen and chondroitin-6-sulfate substrate. *Surgery*. 1988;103(4):421-431.
70. Supp DM, Boyce ST. Engineered skin substitutes: practices and potentials. *Clin Dermatol*. 2005;23(4):403-412.
71. Zelen CM, et al. Treatment of chronic diabetic lower extremity ulcers with advanced therapies: a prospective, randomised, controlled, multi-centre comparative study examining clinical efficacy and cost. *Int Wound J*. 2016;13(2):272-282.
72. Still J, et al. The use of a collagen sponge/living cell composite material to treat donor sites in burn patients. *Burns*. 2003;29(8):837-841.
73. Ananta M, Brown RA, Mudera V. A rapid fabricated living dermal equivalent for skin tissue engineering: an in vivo evaluation in an acute wound model. *Tissue Eng Part A*. 2012;18(3-4):353-361.
74. Boyce ST, et al. Cultured skin substitutes reduce requirements for harvesting of skin autograft for closure of excised, full-thickness burns. *J Trauma*. 2006;60(4):821-829.
75. Bottcher-Haberzeth S, et al. Characterization of pigmented dermo-epidermal skin substitutes in a long-term in vivo assay. *Exp Dermatol*. 2015;24(1):16-21.
76. Blok CS, et al. Autologous skin substitute for hard-to-heal ulcers: retrospective analysis on safety, applicability, and efficacy in an outpatient and hospitalized setting. *Wound Repair Regen*. 2013;21(5):667-676.
77. Marino D, et al. Bioengineering dermo-epidermal skin grafts with blood and lymphatic capillaries. *Sci Transl Med*. 2014;6(221):221ra14.
78. Sriwiriyanont P, et al. Characterization of hair follicle development in engineered skin substitutes. *PLoS ONE*. 2013;8(6):e65664.
79. Hirt-Burri N, et al. Biologicals and fetal cell therapy for wound and scar management. *ISRN Dermatol*. 2011;2011:549870.
80. REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 13 November 2007 Official Journal of the European Union, 10/12/2007. Available from: http://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2007_1394/reg_2007_1394_en.pdf. Accessed 26 June 2017.
81. Pham C, et al. Bioengineered skin substitutes for the management of burns: a systematic review. *Burns*. 2007;33(8):946-957.
82. Morgan JR, Yarmush ML. Bioengineered skin substitutes. *Sci Me*. 1997;4:6-15.
83. Malhotra S, et al. Mesenchymal stromal cells as cell-based therapeutics for wound healing. *Stem Cells Int*. 2016;2016:4157934.

16 The Pathophysiology of Inhalation Injury

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Introduction and Epidemiology

It has been more than three decades since Herndon and colleagues' first manuscript on inhalation injury was published.[1] It was initially reported in 1985 that inhalation injury was a major determinant of mortality in severely burned patients.[2]. The standard of care has evolved over time, but inhalation injury still remains a major problem.[3]. Although sepsis is reportedly the most frequent cause of death among burned children,[4], roughly two-thirds of burned patients who have died at the Shriners Hospitals for Children suffer from inhalation injuries.[5] Based on data from 506,628 admissions to burn units from 1988 to 2008, burn patients with inhalation injury are more likely to die than those without inhalation injury (P <0.001).[6] Furthermore when 791 burned patients from 44 hospitals were retrospectively reviewed in 2014, the mortality rate of patients with inhalation injury was 17.9% compared to 0.7% in patients without inhalation injury (P <0.05).[7]

Smoke inhalation causes 5000 to 10,000 deaths annually in the United States and more than 23,000 injuries, including approximately 5000 firefighter injuries.[8] In fact, the United States has the tenth highest fire death rate per million people among industrialized countries.[9] Approximately 15% of burned individuals with over 80% total burned surface area (TBSA) who are admitted to burn centers in the United States have a concomitant smoke inhalation injury.[6] Greater percentages of fire victims who have sustained smoke inhalation are seen in several other countries.[10–13] The lung is a critical organ, and progressive respiratory failure associated with pulmonary edema is a pivotal determinant of mortality.[14–16] Although not as lethal, smoke inhalation alone is a serious problem. According to World Health Organization estimates, more than 4 million people die from household air pollution from cooking with solid fuels (Fig. 16.1).[17]

The inhalation of toxic materials has been of interest for a number of years, particularly because of the use of toxic gases in civilian mass casualty events. In the 1940s, two very large fires focused attention on smoke inhalation in fire accidents. The first was a fire at the Cocoanut Grove nightclub in Boston, Massachusetts, where a large number of people were trapped in a burning building and consequently sustained severe inhalation injury.[18,19] The second disaster occurred in 1947, in Texas City, Texas.[20] A ship loaded with ammonium nitrate fertilizer exploded in the harbor and set off a chain of explosions and fires among 50 refineries and chemical plants, resulting in more than 2000 hospital admissions. Many of the victims were burned and simultaneously inhaled smoke, while many others suffered from smoke inhalation alone. Disasters like those in Boston and Texas led to the establishment of centers for the care of burn victims and research into the pathophysiology of burn injury.

In many ways, the September 11, 2001, disaster at the Pentagon was similar to these two earlier disasters since the burn and inhalation injuries involved combustion of petroleum products. Among the 790 injured survivors of the terrorist attack on the World Trade Center in New York on September 11, 49% suffered from inhalation injury. The situation was the same as in the Pentagon attack in that inhalation injury was seen in some patients who were not burned.[21]

Inhalation injury can be classified as follows: (1) upper airway injury, (2) lower airway injury, (3) pulmonary parenchyma injury, and (4) systemic toxicity. The extent of inhalation damage depends on the fire environment: the ignition source, temperature, and the concentration and solubility of the toxic gases generated. For instance, hot air and smoke chemical compounds usually cause upper airway injury. Water-soluble materials such as acrolein and the other aldehydes damage the proximal airways and set off reactions that inflame in the bronchi and parenchyma, whereas agents with lower water solubility such as chlorine, phosgene, nitrogen oxide, nitrogen dioxide (N_2O_3 or even N_2O_4) are more likely to cause insidious injury.[22]

Pathophysiology

INJURY TO THE OROPHARYNX

Many of the pathophysiological changes occurring after inhalation injury are related to edema formation in the oropharynx, bronchial areas, and parenchyma. This edema results from an increased transvascular fluid flux from vascular beds in these respective tissues. Before discussing the changes that occur in these structures following inhalation injury, a review of the forces responsible for the variables of the Starling-Landis equation should be reviewed[23,24]:

$$J_v = K_f[(P_c - P_{if}) - \sigma(COP_p - COP_{if})]$$

This equation describes the physical forces and physiologic mechanisms that govern fluid transfer between vascular and extravascular compartments. J_v, the transvascular fluid flux, is equal to lymph flow during equilibrium states. As transvascular fluid flux increases, interstitial volume also increases (edema formation) until a new equilibrium with lymph flow occurs. K_f is the filtration coefficient, an index of the total number of pores that are filtering. The number of pores could increase if a larger area of the microcirculation were perfused or if there were more pores per given

Fig. 16.1 An example of direct exposure to smoke as result of open fire using various materials as a fuel.

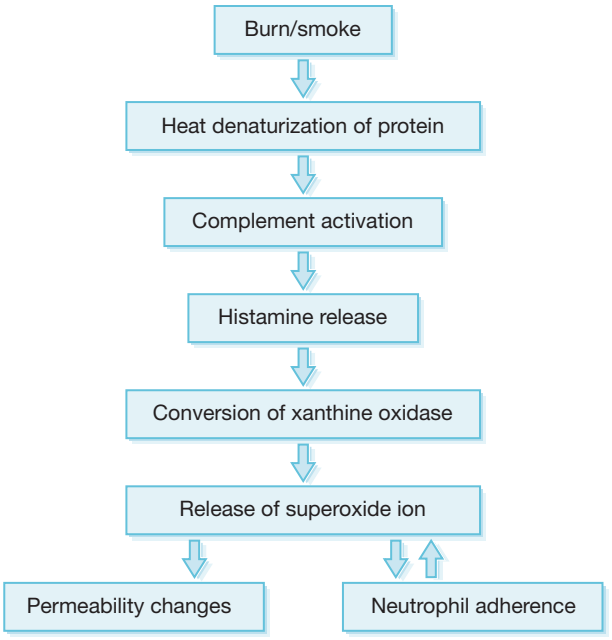

Fig. 16.2 Mechanism for edema formation in the oropharynx.

area of the microcirculation. These pores are the same size as water and electrolytes, as opposed to the larger pores associated with permeability to protein. P_c and P_{if} are the hydrostatic pressures in the microcirculation and interstitial space, respectively. The reflection coefficient, σ, is an index of microvascular permeability to protein. If σ is 1, the membrane is impermeable to protein; when σ is 0, the membrane is completely permeable to protein. COP_p and COP_{if} are the oncotic or colloid osmotic pressures in the plasma and interstitial spaces, respectively.

The major pathophysiology seen in the oropharynx following inhalation injury is induced by microvascular changes similar to those seen with thermal injury in other areas of the body. Heat denatures protein that, in turn, activates complement. Complement activation causes the release of histamine.[25,26] Histamine then causes the formation of xanthine oxidase, an enzyme involved in the breakdown of purines to uric acid.[27] During this conversion, reactive oxygen species (ROS) are released.[28,29] ROS combine with NO, constitutively formed in the endothelium, to form reactive nitrogen species (RNS).[30] The latter produce edema in the burned area by increasing the microvascular pressure and permeability to protein.[31,32] Eicosanoids and proinflammatory cytokines are also released.[33–35] These, along with oxygen free radicals and interleukin-8 (IL-8), attract polymorphonuclear cells to the area.[36] These neutrophils then amplify the release of oxygen radicals, proteases, and other materials into burned areas (Fig. 16.2).

The massive edema occurring in the soft tissue of the oropharynx following burns involves most variables in the Starling equation. There is a large increase in microvascular hydrostatic pressure,[37] a decrease in interstitial hydrostatic pressure,[38] a fall in the reflection coefficient,[37] and an increase in interstitial oncotic pressure.[38,39] The usual treatment for burn resuscitation calls for the administration of large amounts of crystalloid solutions, which has the effect of reducing the plasma oncotic pressure.[40,41] This reduction not only affects the oncotic pressure gradient in the microcirculation, but also has been reported to increase the filtration coefficient.[42,43] The result of this almost complete breakdown in control of the microvascular function and the insult of fluid administration is massive edema. This is probably nowhere more apparent than in soft tissues of the face and oropharynx. The danger to the patient is extreme. The edema may obstruct the airway, making it not only laborious or impossible to breath, but also difficult for the anesthesiologist to intubate the patient (Fig. 16.3A). To avoid this problem, many units prophylactically perform tracheostomies on patients who have evidence of thermal injury to the upper airway on admission. However tracheostomy itself may present problems. The tube may further damage injured areas, especially the larynx.[44] It may be time to reconsider some of these practices. Perhaps some consideration should be given to fluid resuscitation with colloids, which can prevent some of this soft tissue edema and reduce the volume of fluids required for resuscitation.[45,46]

INJURY TO THE TRACHEOBRONCHIAL AREA

With rare exceptions such as inhalation of steam, the injury to the airway is usually from chemicals in smoke. The heat capacity of air is low, and the bronchial circulation is very efficient in warming or cooling airway gases so that most gasses are at body temperature as they pass the glottis.[47] Flames must almost be in direct contact with the airway to induce thermal injury.[48] The chemicals in smoke depend on the materials that are being burned; however, for the most part, the host response is similar. In most instances biological materials such as cotton fabric, wood, grass, or products of these such as cattle feces (commonly used as fuel in developing countries) are the fuel for the fire. Burning of these materials produces ROS and RNS, organic acids, and aldehydes[49] that, upon inhalation, cause damage to the respiratory epithelium. The inhaled chemicals interact with the airway to induce an initial inflammatory response. In sheep that have inhaled cooled cotton smoke, there is

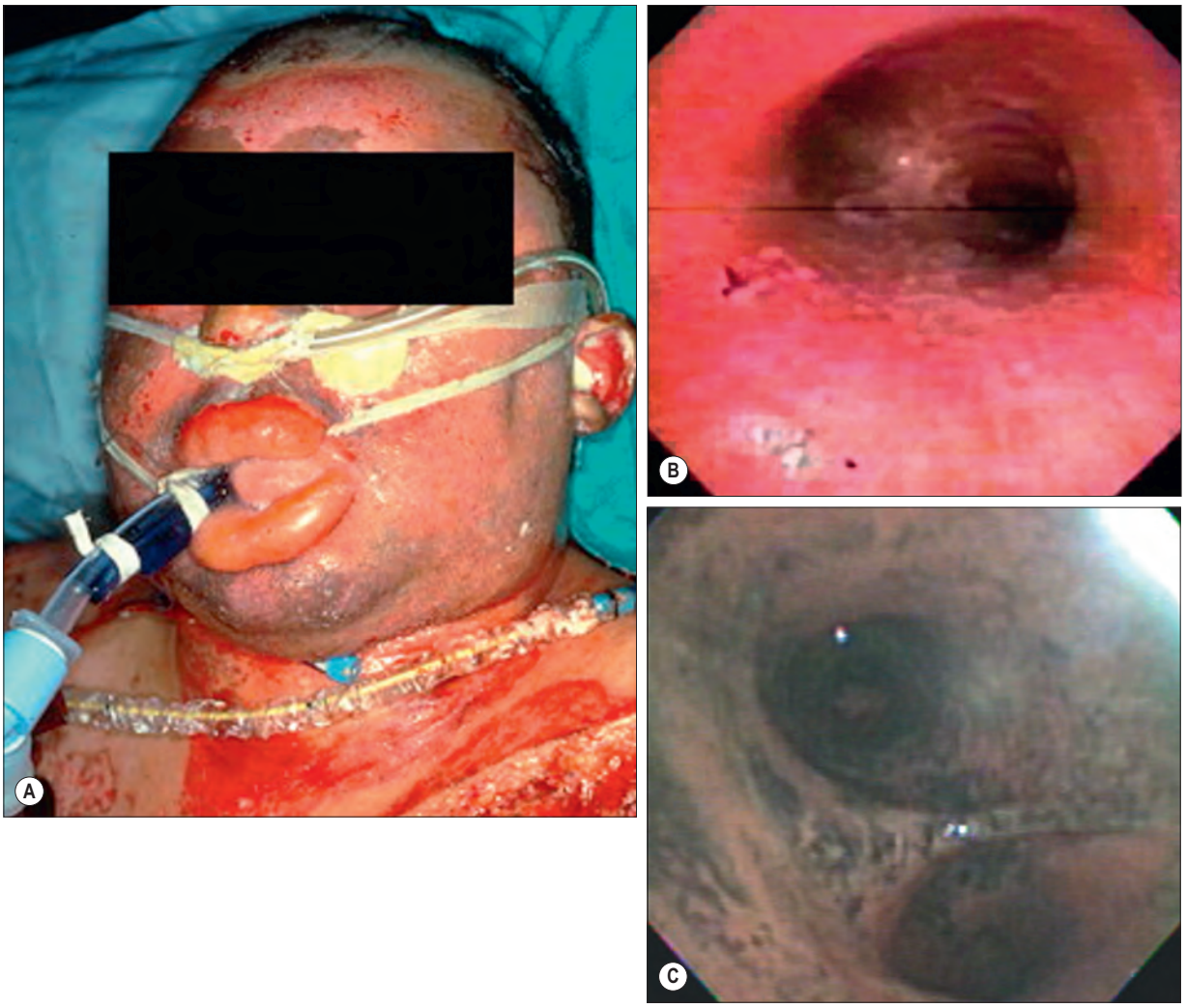

Fig. 16.3 Facial and airway injury after burn and smoke inhalation. **(A)** A facial burn is often associated with thermal injury to the upper airway. **(B)** Hyperemia of airway epithelium. **(C)** Formation of airway obstructive cast. (A is from Cancio LC. Airway management and smoke inhalation injury in the burn patient. *Clin Plast Surg*. 2009;36(4):555–567.)

damage to the tracheobronchial[50,51] and alveolar epithelium. Injury and loss of these cells lead to an intense inflammatory response.[35]

Many of the studies on bronchial circulation following smoke inhalation injury have been performed in sheep because these animals have a single bronchial artery[52] and a single lymphatic draining the lung, thus allowing measurement of pulmonary transvascular fluid flux.[53] In these animals, a 10-fold increase in bronchial blood flow occurs within 20 minutes of smoke inhalation.[54] These same animals demonstrate a sixfold increase in pulmonary transvascular fluid flux and a fall in Pao_2/Fio_2 to 200 or less, but these changes are delayed, occurring around 24 hours after injury. Similar findings have been reported in patients with smoke inhalation alone or a combination of large cutaneous thermal injury and smoke inhalation.[55]

Hyperemia of the airway is such a consistent finding in smoke inhalation that it is used to diagnose the injury.[56,57] Other variables that are used include injury in an enclosed space, singed nasal hair, and soot in sputum. However these latter injuries may be present but the subject may still not develop the signs of pulmonary edema characteristic of inhalation injury. Airway inflammation plays a major role in the overall response to inhalation injury (Fig. 16.3B and C).

As noted, there is a large sustained increase in blood flow in the airway following smoke inhalation.[58] These changes in blood flow are associated with increased bronchial microvascular permeability to protein and small particles[59] and pressure.[60] Simultaneous with changes in bronchial microvasculature function, there is a loss or shedding of the bronchial columnar epithelium.[35,50,61] These changes result in a perfuse transudate with a protein content similar to an ultrafiltrate of the plasma.[62] There are also copious secretions from the goblet cells of the lining and mucosal epithelium.[63] Early in the response, these secretions form a foam material in the airway that many have mistaken for severe pulmonary edema in patients.[64] After several hours the transudate/exudate, exfoliated epithelium, secreted mucus, and inflammatory cells form obstructive materials in the airways.[65] The degree of obstruction at this early stage statistically correlates with decreasing pulmonary function.

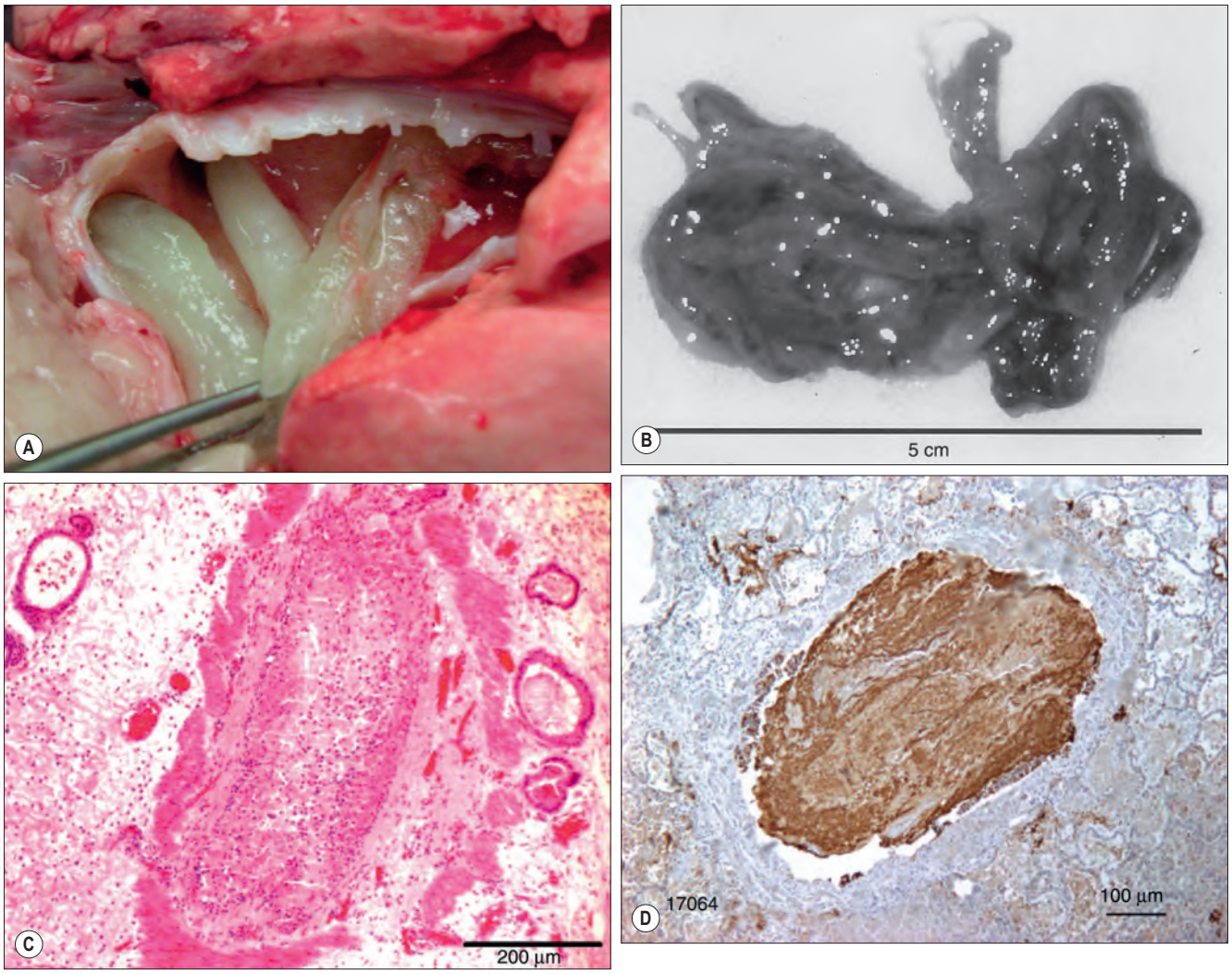

Fig. 16.4 Airway obstructive cast. **(A)** Macroscopic views of an airway obstructive cast in sheep 48 hours after burn and smoke inhalation injury. **(B)** Macroscopic views of an airway cast taken from a patient with burn and smoke inhalation injury by bronchoscope.[69] **(C)** Microscopic views of bronchi totally blocked by obstructive cast in sheep.[35] **(D)** Mucus totally obstructing a bronchiole in a patient after burn and smoke inhalation injury. The tissue had been immunostained for mucin 5B, an upper airway-specific mucin subtype.[66] (B is from Nakae H, Tanaka H, et al. Failure to clear casts and secretions following inhalation injury can be dangerous: report of a case. *Burns* 2001;27(2):189–191; C is from Cox RA, Burke AS, et al. Acute bronchial obstruction in sheep: histopathology and gland cytokine expression. *Exp Lung Res*. 2005;31(9–10):819–837; D is from Cox RA, Mlcak RP, et al. Upper airway mucus deposition in lung tissue of burn trauma victims. *Shock* 2008;29(3):356–361.)

With increasing time after injury, these obstructive materials formed in the upper airway may appear in the lower airway and alveoli.[63,66] This obstructive material is problematic from several stand-points. In some rare instances of severe airway injury these materials can induce total obstruction and are life-threatening (Fig. 16.4).[67–69] Occlusion of some of the bronchi or bronchioles in the setting of high NO production can lead to a loss of hypoxic pulmonary vasoconstriction and thus increased shunt fraction. Loss of hypoxic pulmonary vasoconstriction has been reported with inhalation injury. If single bronchi are occluded while the patient is on a volume-limited ventilator, there may be overstretch, and barotrauma to the alveoli of the nonoccluded portion of the lung can occur. Nebulized anticoagulants have been used to combat the upper airway obstruction that can occur with severe inhalation injury. These are beneficial in reducing cast formation and improving pulmonary performance,[70,71] although their use in the clinical environment has not yet been reported. Airway mucosal edema and luminal obstruction following an inhalation injury occur alongside airway smooth muscle hyperreactivity. Adrenergic[72,73] and antimuscarinic bronchodilator[74] therapies have been shown to be beneficial in reducing ventilatory peak pressure and improving pulmonary function. The initial hyperreactive response of the airways to injury and inflammation is followed by a more long-term pathogenesis of inhalation injury that includes bronchopneumonia.[2] Pneumonia is the leading complication in the critical care of burn victims,[75] with the incidence of pneumonia in a burn patient with inhalation injury being two- to fourfold greater than that seen in burn patients without inhalation injury.[15,76] Conceptually the high incidence of pneumonia in burn patients with inhalation injury is associated with the loss of airway epithelium and the essential properties of these cells in innate defense. Studies that have focused on the repair of the epithelium after burn injury are limited.

In an ovine model with a selected area of smoke injury to the tracheal epithelium, the epithelial repair process was completed at 18 days.[77] Further study by this team of investigators revealed that nebulization of cefazolin and growth factors[78] could improve the rate of airway healing. Because of the effects of pneumonia and inhalation injury on burn patient morbidity and mortality, further studies on the dynamics of airway damage and airway epithelial repair following toxic exposure are needed to improve critical burn care.

The airway is richly innervated with vasomotor and sensory nerve endings.[79] These fibers are known to release neuropeptides that can engender inflammatory responses.[80] Neuropeptides in the upper airway are also involved in mucus secretion, thus their release and interaction with the mucosal gland epithelium can increase the early obstructive pathology that occurs with inhalation injury.[81,82] Neuroinflammation is responsible for pathophysiological changes associated with a number of clinical conditions including tissue injury induced by chemicals.[83,84] Lange and colleagues reported that antagonists to substance P and calcitonin gene-related peptide had a marked effect on this response when administered to sheep and mice that were injured with both burn and smoke inhalation.[51,85] In an ovine model, the combination of burn and smoke inhalation injury caused a 10-fold increase in pulmonary transvascular fluid flux and a reduction of Pa_{O_2}/Fi_{O_2} to 200 or less. These changes were reversed by neuropeptide receptor blocking agents.[85] Released neuropeptides can activate nitric oxide synthase (NOS), have chemokine activity, and change microvascular permeability.[86] The resultant activities lead to the formation of ROS and RNS.[87] Some of the latter are very potent oxidants that can damage DNA.[30] Damage to DNA triggers activation of a DNA repair enzyme, poly(ADP-ribose) polymerase (PARP).[88] This enzyme depletes the cell of high-energy phosphates and causes the activation of nuclear factor-κB (NF-κB)[89,90] NF-κB activation induces upregulation of inducible NOS (iNOS) and IL-8, thus accelerating production of ROS and RNS.[91] NO and 3-nitrotyrosine (an index of RNS), and iNOS mRNA and protein have been reported to be in the airway after smoke inhalation.[87,92] Compounds that catalyze the breakdown of peroxynitrite reduce the response to smoke inhalation. Poly(ADP-ribose) (PAR), the product of the constitutive enzyme PARP, is detectable in airway tissues following smoke inhalation.[87] PARP inhibition prevents PAR formation, NF-κB upregulation, and 3-nitrotyrosine formation.[93] Similarly, Lange and colleagues have reported that compounds that inhibit peroxynitrite by catalyzing its rapid breakdown likewise prevent the formation of these materials.[94] It is interesting to note that mice missing the PARP genes or given a PARP inhibitor will not show the typical inflammatory changes usually observed with asthma.[95] Thus, in many ways, inhalation of smoke may be similar to other forms of airway injury. The fact that the response to inhalation injury is driven by neuroinflammation suggests that the response to smoke from wood or cotton is similar.

INJURY TO THE LUNG PARENCHYMA

As noted earlier, burn and smoke inhalation induce delayed lung parenchymal changes as reflected by reduced Pa_{O_2}/Fi_{O_2}, decreased compliance, and increased edema formation.[96] The delay is dependent on the severity of the airway injury.[49,97] Lung injury is associated with an increased pulmonary transvascular fluid flux.[98] The degree of transvascular fluid is proportional to the duration of smoke exposure[49] and is not caused by carbon monoxide (CO) in the inhalant gas.[99] However the degree of arterial CO is related to severity of inhalation injury.[100] The factors responsible for fluid leak are codified in the Starling-Landis equation.[23,24] The variables of this equation relate fluid movement to pressure and permeability variations. With inhalation of smoke, there is a reduction in the reflection coefficient (permeability to protein), an increase in the filtration coefficient (permeability to small particles), and an increase in pulmonary microvascular pressure.[101,102] Animals exposed to smoke inhalation injury were also noted to have reduced Pa_{O_2}/Fi_{O_2}. These variables are more severely affected when the inhalation is combined with burn injury[103] and show a good relationship to histologic injury scores and changes in transvascular fluid flux.[93] In addition, there is a loss of hypoxic pulmonary vasoconstriction in the injured animals that may help to explain the loss of oxygenation.[104]

As in the oropharynx, injury to the lung parenchyma is associated with PARP activation and 3-nitrotyrosine, and it is markedly reduced by the administration of iNOS or PARP inhibitors.[92]

The venous outflow of the bronchial circulation drains into the pulmonary microcirculation at the precapillary level.[105] Given that initial damage to the airway appeared to drive the pathophysiology of the parenchyma, investigators hypothesized that bronchial blood might deliver cytotoxic materials or cells to the pulmonary microcirculation. To test this hypothesis, several investigators have tied off the bronchial artery of sheep and then exposed the animals to smoke.[59,96,106] Lung parenchymal changes are reduced by this approach, affirming the hypothesis. It has also been shown that increased bronchial blood flow following smoke inhalation injury carries inflammatory mediators to the parenchyma, augmenting the injury process.[107–109] Recent ovine studies demonstrate that nebulized epinephrine (nonspecific adrenergic agonist) has similar effects following smoke inhalation injury: reduced airway blood flow, attenuated pulmonary edema, and reduction in proinflammatory mediators to levels seen in sheep with ablated bronchial circulation.[73,110] The latter observation is of particular clinical importance because the ligation/ablation of bronchial artery is not feasible in clinical practice.

What could be the linkage among the airway, the bronchial venous drainage, and parenchymal injury to the lung? Neutrophils activated in the bronchial circulation flow out into the bronchial venous drainage. Activated polymorphonuclear cells (PMN), especially neutrophils, are stiff. The diameter of neutrophils that have been fixed is approximately 7 μm.[111] Since these cells have been dehydrated in alcohol as part of the fixation process, unfixed cells are much larger, on the order of 12 μm. The pulmonary capillary is small, with an average diameter of 6 μm.[111] Normally, large neutrophils can traverse the pulmonary capillary by changing shape. However, following injury, many of the neutrophils in the bronchial areas have their F-actin activated. As result, these cells are stiff and cannot

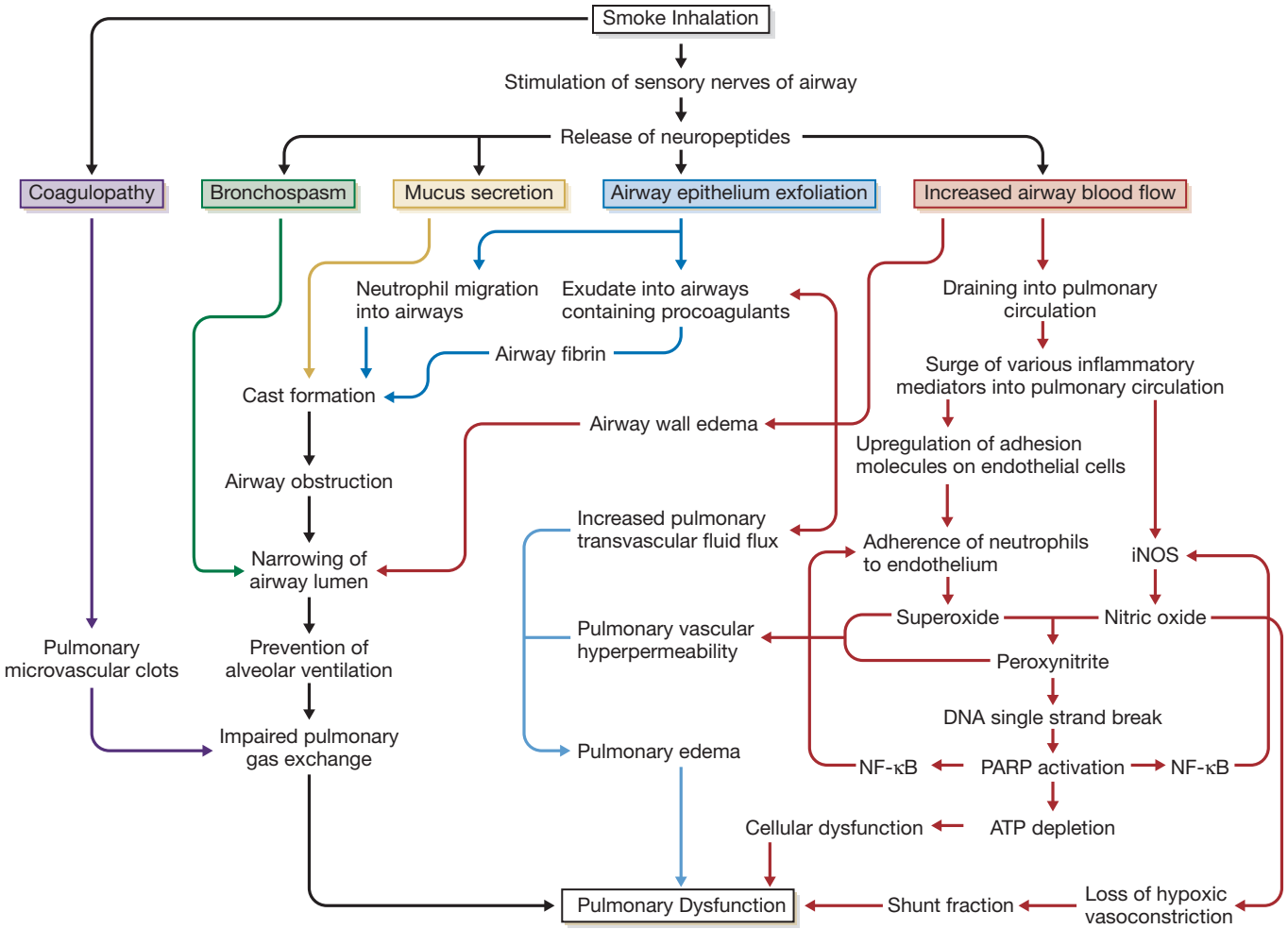

Fig. 16.5 Pathophysiology of burn and smoke inhalation induced acute lung injury. *iNOS*, inducible nitric oxide synthase; *PARP*, poly(ADP-ribose) polymerase. (From Fishman, ed. *Pulmonary diseases and disorders*, 5th edn., vol 2., McGraw-Hill Companies, China. ch. 94. 2015: 1428–1440.)

deform. These stiff cells are carried to the pulmonary microvasculature where they are captured by the narrow pulmonary capillaries. The activated neutrophils release ROS and proteases that damage the parenchyma. The following evidence supports this concept of neutrophil cytotoxicity. Oxidative processes are well established following inhalation injury, with lipid peroxidation and release of proteolytic enzymes following injury.[112–114] Moreover, administration of protease inhibitors or ROS scavengers will reduce the response to smoke inhalation[113,115–117] when activated PMNs lose L-selectin on their surfaces. This L-selectin shedding is prevented by treatment with an L-selectin antibody,[118] which prevents changes in transvascular fluid flux and other aspects of parenchymal damage.[119] Final proof of this hypothesis is provided by studies of how the response to inhalation injury is affected by depleting animals of neutrophils. In these studies of sheep depleted of their leukocytes, a large portion of the response to smoke inhalation was blocked.[120]

Coagulopathy has increasingly been described as a critical complication of burn and smoke inhalation injury. Following burn injury, there is a hypercoagulable state associated with severe deficiency of the potent endogenous anticoagulant antithrombin.[121] In preclinical studies, supplementation with recombinant human antithrombin has been shown to attenuate pulmonary edema, downregulate proinflammatory mediators, and improve pulmonary gas exchange.[71,122] In pilot clinical studies, antithrombin deficiency following cutaneous burn was correlated with TSBA, presence of smoke inhalation, length of ICU and hospital stay, morbidity severity, and mortality.[123–126] Recent unpublished observations showed that of six sheep exposed to smoke inhalation, all developed some degree of pulmonary vascular emboli (clot) observable by computed tomography scan. The pathophysiology of acute lung injury secondary to burn and smoke inhalation injury is summarized in Fig. 16.5.

In addition to exhibiting a depletion of antioxidants as discussed earlier, burn patients are depleted of arginine.[127] When arginine levels are low, NOS produces superoxide rather than NO.[128] Following smoke inhalation, arginase activity is also elevated.[129] This enzyme also depletes arginine by converting it to ornithine.[130] Administration of arginine may assist in reducing the oxidation that occurs with inhalation injury.[131] However the necessity of administering arginine as arginine hydrochloride (because of solubility) limits the amount that may be given intravenously without producing acidosis.

LONG-TERM EFFECTS OF INHALATION INJURY

When earlier editions of this book were published, mortality from inhalation injury was high and the acute inflammatory aspects of the injury were considered a major vector of mortality. Now 85% of our patients survive inhalation injury.[5] Thus the long-term aspects of this injury are of considerable interest. When patients are examined years after burn injury, they demonstrate symptoms of restrictive lung disease and reduced diffusion capacity, both of which are signs of lung fibrosis.[132] At autopsy, both patients and animals reportedly show hyaline membrane and deposition of collagen in their lungs, changes similar to those seen in other forms of acute lung injury.[61,129] As stated earlier, two enzymes compete for arginine: NOS and arginase.[134] NOS forms NO and RNS. Arginase forms ornithine, which is converted into polyamines and proline, leading to the formation of collagen.[135] When NOS is active, it forms N (omega)-hydroxy-nor-L-arginine (NOHA). NOHA is broken down into NO and citrulline. NOHA is a potent inhibitor of arginase.[136,137] Thus, as long as NOS activity is elevated, arginase is inhibited. It has recently been reported that the endogenous NOS inhibitor asymmetric dimethylarginine (ADMA) begins to rise in the lung of sheep following combined burn and smoke inhalation injury.[129] As ADMA increases, NO production falls and tissue levels of collagen increase. The increase in collagen results in hyaline membrane formation and thickening of the alveolar septum that interferes with the diffusion of oxygen into the lung. ADMA is formed in the lung on a regular basis but it is rapidly catabolized by dimethylarginine dimethylaminohydrolase (DDAH).[138,139] DDAH is inactivated by oxidation. Following burn and inhalation injury, lung levels of DDAH fall as markers of oxidation rise, and, as these events occur, levels of ADMA, arginase, and collagen increase.[129] We have previously determined that oxidation is such a serious problem that survival is dependent of the degree of oxidation.[115] In addition, it was recently reported that levels of γ- and α-tocopherol are markedly depleted in thermally injured children.[140] In sheep depleted of α- and γ-tocopherols following burn and smoke exposure, the administration of tocopherol, especially γ- tocopherol, either orally or through nebulization into the airways (more effective) restored not only lung levels of tocopherol, but also normal oxidation status and pulmonary function during the acute phase of injury.[140–146] Preliminary experiments using the long-term model reported by Sousse et al. indicate that the nebulization of γ-tocopherol also reduces collagen deposition; blocks elevation in arginase, proline, and ADMA levels; and restores DDAH levels.

Finally, recent preclinical ovine studies indicate that smoke inhalation causes structural damage in the brain as seen by neuronal and astrocyte death and microhemorrhage (unpublished data). It has previously been reported that smoke-induced oxidative DNA damage in the brain is extensive, and compromised fidelity of DNA repair may underlie neurotoxicity and contribute to delayed death of hippocampal neurons.[147] Furthermore, acute smoke exposure significantly compromises the respiratory capacity of hippocampal mitochondria.[148] These results suggest that fire victims, especially those with smoke inhalation injury, should carefully be monitored for possible nonpulmonary organ damage, including central nervous system (CNS) dysfunction.

The Fire Environment and Toxic Smoke Compounds

Smoke toxicity is an increasing concern because modern industrial products are changing from woods and natural materials toward lighter construction materials, synthetics, and petrochemical-based materials. These materials ignite and burn two to three time hotter and faster than conventional material and, when heated, emit a gas or smoke that is more toxic than natural biological materials. Consequently firefighters have less time to gain control of a fire, and victims are more likely to be incapacitated by breathing toxic gases and to sustain smoke inhalation because they have less time to escape from the burning area.[8] Inhalation injury is caused by steam or toxic inhalants such as fumes, gases, and mists. Fumes consist of small particles with various adherent irritants or cytotoxic chemicals that are dispersed in air. Mists consist of aerosolized irritant or cytotoxic liquids. Smoke consists of a combination of fumes, gases, mists, and hot air. Heat, toxic gases, and low oxygen levels are the most common causes of death in fires. A large variety of toxic gases and chemicals can be generated depending on the fire environment (Table 16.1).

Many of these compounds may act together to increase death, especially CO and hydrogen cyanide (CH).[149,150] A synergism between these compounds has been found to increase tissue hypoxia and acidosis[150] and may also decrease cerebral oxygen consumption and metabolism.[22,151] Hydrogen sulfide would also be predicted to synergize with CO since both cyanide and hydrogen sulfide are inhibitors of mitochondrial cytochrome oxidase. Victims may be incapacitated by the blinding and irritating effects of smoke, as well as by the decreasing oxygen concentration that occurs with combustion and results in progressive hypoxia.

Toxic gases such as CO and cyanide rarely damage the airway, but instead affect gas exchange and produce more systemic effects. Thus it is important to obtain information on the source of the fire and the combustion products generated when treating a fire victim (see Table 16.1). It is also important to know the duration of exposure and the extent to which the fire victim was in an enclosed area since this relates to the dose of toxic materials received.

CARBON MONOXIDE

CO is an odorless, colorless gas that is produced by incomplete combustion of many fuels, especially cellulolytic (cellulose) products such as wood, paper, and cotton.[152] CO toxicity remains one of the most frequent immediate causes of death following smoke-induced inhalation injury. The predominant toxic effect of CO is attributed to its binding to hemoglobin (Hb) to form carboxyhemoglobin (COHb). The affinity of CO for Hb is approximately 200 to 250 times higher than that of oxygen.[153] Inhalation of a 0.1% CO mixture may result in generation of a COHb level as high as 50% of the total Hb. The competitive binding of CO to Hb reduces delivery of oxygen to tissues, leading to severe

Table 16.1 Origin of Selected Toxic Compounds

Gases and Chemicals	Material	Source
Carbon monoxide	Polyvinyl chloride Cellulose	Upholstery, wire/pipe coating, wall, floor, furniture coverings Clothing, fabric Wood, paper, cotton
Cyanide	Wool, silk, cotton, paper, plastic, polymers Polyurethane Polyacrylonitrile Polyamide Melamine resins	Clothing, fabric, blankets, furniture Insulation, upholstery material Appliances, engineering, plastics Carpeting, clothing Household and kitchen goods
Hydrogen chloride	Polyvinyl chloride Polyester	Upholstery, wire/pipe coating, wall, floor, furniture coverings Clothing, fabric
Phosgene	Polyvinyl chloride	Upholstery, wire/pipe coating, wall, floor, furniture coverings
Ammonia	Wool, silk Polyurethane Polyamide Melamine resins	Clothing, fabric, blankets, furniture Insulation, upholstery material Carpeting, clothing Household and kitchen goods
Sulfur dioxide	Rubber	Tires
Hydrogen sulfide	Wool, silk	Clothing, fabric, blankets, furniture
Acrolein	Cellulose Polypropylene Acrylics	Wood, paper, cotton, jute Upholstery, carpeting Aircraft windows, textiles, wall coverings
Formaldehyde	Melamine resins	Household and kitchen goods
Isocyanates	Polyurethane	Insulation, upholstery material
Acrylonitriles	Polyurethane	Insulation, upholstery material

From Prien T, Traber DL. Toxic smoke compounds and inhalation injury: a review. *Burns* 1988;14:451–460.

hypoxia, especially in the most vulnerable organs such as the brain and heart where oxygen extraction is considerably higher than that in most other organs. The oxygen–Hb dissociation curve loses its sigmoid shape and is shifted to the left, thus further impairing tissue oxygen availability.[149,154] In addition, the ability of CO to bind to intracellular cytochromes and to other metalloproteins contributes to CO toxicity. This competitive inhibition with cytochrome oxidase enzyme systems (most notably cytochromes a and P-450) results in an inability of cellular systems to use oxygen.[154,155] Shimazu and his colleagues have shown that extravascular binding of CO to cytochromes and other structures accounts for 10–15% of total body CO stores. This intracellular binding of CO explains the two-compartment elimination of CO from the circulation.[156] Miro and colleagues reported that CO inhibits cytochrome-c oxidase activity in lymphocytes.[157] The electron chain dysfunction induced by CO may cause electron leakage, leading to superoxide production and mitochondrial oxidative stress.[158]

Although smoke inhalation commonly affects the respiratory system, CNS disturbances can also develop. CNS signs can be classified as being related to either acute or delayed toxicity. The veterinary literature contains a few reports on the neurological consequences of smoke inhalation. In dogs, smoke inhalation produces lesions that are consistent with acute CO toxicity. Lesions are confined to the caudate nucleus, globus pallidus, and the substantia nigra bilaterally, as well as the cerebellum, cerebral cortex, and dorsal thalamus. A case report by Kent and colleagues describes the clinicopathological sequelae in acute CO toxicity.[159]

Symptoms and Diagnosis of Carbon Monoxide Poisoning

Symptoms of CO poisoning predominantly manifest in organs and systems with high oxygen utilization. The severity of clinical manifestations varies depending on CO concentration. For instance, CNS symptoms such as headache, confusion, and collapse may occur when the blood COHb level is 40–50%. Symptoms such as unconsciousness, intermittent convulsions, and respiratory failure may occur if the COHb level exceeds 60%, eventually leading to death if exposure continues. The cardiovascular manifestations may result in tachycardia, increase in cardiac output, dysrhythmias, myocardial ischemia, and hypotension depending on severity of poisoning. The correlation between clinical manifestation and severity of CO poisoning is summarized in Table 16.2.

Diagnosis should be based on direct measurement of COHb levels in arterial or venous blood by co-oximetry, taking into account that venous blood underestimates the arterial COHb content.[160] Diagnosis may be facilitated by use of on-site portable breath analyzers. The inability to differentiate oxyhemoglobin from COHb limits the use of a pulse oximeter. The use of blood gas analyzers that estimate sulfur dioxide (SO_2) based on measurement of dissolved PO_2 should also be avoided. Measuring acid–base balance, plasma lactate levels, and bicarbonate is helpful in

Table 16.2 Symptoms and Signs at Varying Concentrations of Carboxyhemoglobin (COHb)

COHb %	Symptoms
0–10	None
10–20	Tightness over forehead, slight headache, dilation of cutaneous blood vessels
20–30	Headache and throbbing in the temples
30–40	Severe headache, weakness, dizziness, dimness of vision, nausea, vomiting, collapse
40–50	As above; greater possibility of collapse, syncope, increased pulse and respiratory rate
50–60	Syncope, increased pulse and respiratory rate, coma, intermittent convulsions, Cheyne-Stokes respirations
60–70	Coma, intermittent convulsions, depressed cardiac and respiratory function, possible death
70–80	Weak pulse, slow respirations, death within hours
80–90	Death in less than 1 h
90–100	Death within minutes

From Einhorn IN. Physiological and toxicological aspects of smoke produced during the combustion of polymeric materials. *Environ Health Perspect*. 1975;11:163–189; and Schulte JH. Effects of mild carbon monoxide intoxication. *Arch Environ Health* 1963;7:524–530.

managing CO poisoning with accompanying lactic or metabolic acidosis. It is important to note that high oxygen concentrations are usually administered to the victim in transit to the hospital, and some delay from cessation of exposure to measurement of CO may limit evaluation of the true extent of exposure.[161] A nomogram has been developed that can relate the COHb levels of a patient to the values that may have been present at the time of smoke inhalation, and this can be used to estimate the true degree of inhalation injury.[100]

HYDROGEN CYANIDE

Hydrogen cyanide (CN), the gaseous form of cyanide, is generated by the combustion of nitrogen- and carbon-containing substances, such as wool, silk, cotton, and paper as well as synthetic substances like plastic and other polymers. Combustion of these materials may produce the rapid and lethal incapacitation of a victim at the fire source.[162] CN is a colorless gas with the odor of bitter almonds; however it is difficult to detect at the site of the fire. CN is cytotoxic mainly owing to its reversible inhibition of cytochrome c oxidase, the thermal oxidase of the respiratory chain, through interaction with the ferric ion of cytochrome a_3.[161] This suppresses cellular oxygenation and causes tissue anoxia. CN also adversely affects a number of other enzyme systems. CN is also toxic by virtue of its combination with essential metal ions, formation of cyanohydrins with carbonyl compounds, and sequestration of sulfur as a thiocyanate.

The importance of CN in smoke inhalation injuries is reflected by a study of residential fires in Paris, France, showing that mean blood CN concentrations in both fire victims who survived (21.6 mol/L) and those who died (116.4 mol/L) were significantly higher than those in control subjects (5.0 mol/L) and that levels in fire victims who died were significantly higher than those in survivors.[163] A study of 144 fire victims in Dallas County, Texas, showed results consistent with the Paris study.[164] Elevated CN concentrations are directly related to the probability of death, suggesting that CN poisoning rather than CO poisoning may be the predominant cause of death in some fire victims. CN also played a greater role in mortality following an aircraft fire at Manchester International Airport in the United Kingdom in 1985. These patients were not severely burned. The large majority (87%) of the 54 individuals who died had potentially lethal levels of CN in their blood, whereas only 21% of these fire victims had COHb levels exceeding 50%. This strongly suggests that, under certain conditions, CN can be a more important determinant of morbidity and mortality following smoke inhalation than CO, which is usually regarded as the primary toxic threat.[8] Smoke is also an often overlooked source of CN exposure in terrorist bombings. Following the first World Trade Center bombing in 1993, traces of CN were found in the vans where the explosion originated. The U.S. Centers for Disease Control and Prevention and the Department of Homeland Security consider CN among the most likely agents of chemical terrorism.[165] CN possesses all attributes of an ideal terrorist weapon: it is plentiful, readily available, and easily obtainable because of its widespread use in industry and laboratories. In addition the use of CN does not require any special knowledge. It is capable of causing mass incapacitation and casualties, and it can cause mass confusion, panic, and social disruption.[166]

Table 16.3 Symptoms of Cyanide Toxicity

Symptoms in Low or Moderate Inhaled Cyanide Concentrations	Symptoms in Moderate or High Inhaled Cyanide Concentrations
Faintness	Prostration
Flushing	Hypotension
Anxiety	Tremors
Excitement	Cardiac arrhythmia
Perspiration	Convulsions
Vertigo	Stupor
Headache	Paralysis
Drowsiness	Coma
Tachypnea	Respiratory depression
Dyspnea	Respiratory arrest
Tachycardia	Cardiovascular collapse

Symptoms and Diagnosis of Cyanide Poisoning

Diagnosis at the fire scene may be difficult. Poisoning may results in CNS, respiratory, and cardiovascular dysfunction due to inhibition of oxidative phosphorylation, depending on the concentration of CN inhalation (Table 16.3).

Electrocardiographic changes such as S-T segment elevation that mimic an acute myocardial infarction[167] may be suggestive. Laboratory findings of anion gap metabolic acidosis and lactic acidemia aid in confirming the diagnosis.[168] Lactic acidosis that is not rapidly responsive to oxygen therapy may be a good indicator for CN poisoning.[100,163] Also, an elevated mixed venous saturation is suggestive of

CN toxicity. CN increases ventilation through carotid body and peripheral chemoreceptor stimulation. Increasing ventilation may augment toxicity in the early stages. Low levels of CN are routinely found in the blood of healthy individuals at levels of 0.02 μg/mL in nonsmokers and 0.04 μg/mL in smokers. Toxicity occurs at a level of 0.1 μg/mL, and at 1.0 μg/mL death is likely.[169] Correlation of blood CN concentrations with clinical symptoms is summarized in Table 16.3.

OTHER TOXIC CHEMICALS

Other toxic chemicals may also substantially contribute to morbidity and mortality in a burn victim. Hydrogen chloride is produced by polyvinyl chloride degradation and causes severe respiratory tract damage and pulmonary edema. Nitrogen oxides may also cause pulmonary edema and a chemical pneumonitis, and they may contribute to cardiovascular depression and acidosis. Aldehydes such as acrolein and acetaldehyde, which are found in wood and kerosene, may further contribute to pulmonary edema and respiratory irritability. Toxic industrial chemicals such as chlorine, phosgene, hydrogen sulfide, and ammonia are of great importance. Because of their widespread availability and high toxicity, there is concern that these chemicals may be used as weapons by terrorists.[165,170]

Phosgene is a colorless, nonflammable, heavier-than-air gas at room temperature and has an odor of newly mown hay. At temperatures lower than 8°C phosgene is an odorless and fuming liquid. The inadequate warning properties of phosgene and the delayed nature of the symptoms that follow exposure make it a potential terrorist weapon.[171,172] Phosgene is only slightly soluble in water, hence its deeper penetration in the pulmonary system. On contact with water it hydrolyzes into carbon dioxide and hydrochloric acid, resulting in direct caustic damage. It also undergoes acylation reactions with amino-, hydroxyl-, and sulfhydryl-groups of cellular macromolecules, resulting in cellular damage and apoptosis.[171,173] Phosgene has delayed effects from 20 minutes up to 48 hours depending on the intensity of exposure. Phosgene inhalation produces severe pulmonary edema. Initially victims develop symptoms of upper airway irritation (eye irritation, rhinorrhea, cough) and then lower respiratory symptoms such as shortness of breath, substernal burning, and chest tightness. The development of overt pulmonary edema within 4 hours of exposure portends a poor prognosis (Table 16.4).

Chlorine is a greenish-yellow gas, an oxidizing agent, and very reactive with water. It has a pungent odor. Upon contact with water chlorine liberates hypochlorous acid, hydrochloric acid, and oxygen free radicals. It causes irritant effects throughout the respiratory tree but mostly in the nasal mucosa and upper airways. It induces cellular damage through its strong oxidizing ability.[174] Phosgene and chlorine gases were extensively used as weapons during World War I.

Ammonia is a colorless gas at room temperature with a very pungent odor. Ammonia readily dissolves in water to form ammonium hydroxide, a very caustic alkaline solution. It causes cutaneous, ocular, and pulmonary injuries. Inhaled ammonia can rapidly produce laryngeal injury and obstruction. It also causes upper tracheobronchial mucosal necrosis with sloughing and severe pulmonary edema.[174]

There are no specific antidotes to counter the toxicity of irritant gases (phosgene, chlorine, and ammonia). Depending on the severity of exposure, supportive therapy such as airway management and ventilation should be provided. Early intubation is required if any significant upper airway symptoms such as stridor are present (Table 16.5).

Table 16.4 Hydrogen Cyanide Concentrations in Air and Associated Symptoms in Humans

HCN Concentration ppm	Symptoms
0.2–5.0	Threshold of odor
10	(TLV-MAC)
18–36	Slight symptoms (headache) after several hours
45–54	Tolerated for 0.5–1 h without difficulty
100	Death in 1 h
110–135	Fatal in 0.5–1 h
181	Fatal in 10 min
280	Immediately fatal

From Einhorn IN. Physiological and toxicological aspects of smoke produced during the combustion of polymeric materials. *Environ Health Perspect*. 1975;11:163–189; and Kimmerle G. Aspects and methodology for the evaluation of toxicological parameters during fire exposure. Polymer Conference Series: Flammability Characteristics of Materials. Salt Lake City: University of Utah, 1973.

Table 16.5 Mean Levels of Airway Obstruction in Uninjured Sheep and 48 h After Burn, Smoke Inhalation, and Combined Smoke Inhalation and Burn Injury

	AIRWAY LEVEL		
Injury	Bronchi	Bronchiole	Terminal Brochioles
Uninjured (n = 5)	2.7 ± 2.4%	1.6 ± 0.9%	0.0 ± 0.0%
Burn alone (n = 6)	4.4 ± 3.5%	2.5 ± 1.5%	0.04 ± 0.1%
Smoke alone (n = 5)	18.1 ± 10.1%*†	8.1 ± 3.0%*†	0.3 ± 0.4%*†
Smoke + Burn (n = 7)	29.3 ± 15.1%*†	1.5 ± 6.7%*†	1.2 ± 1.9%*†

Data are presented as mean ± SD (n, number of animals in each group).
*Significantly different from uninjured animas means, Wilcoxon rank sum test, $P < 0.05$.
†Significantly different from burn injury, Wilcoxon rank sum test, $P < 0.05$. Cox R et al. Am J Respir Cell Mol Biol 29: 295, 2003.

Complete references available online at www.expertconsult.inkling.com

References

1. Herndon DN, Traber DL, et al. The pathophysiology of smoke inhalation injury in a sheep model. *J Trauma*. 1984;24:1044-1051.
2. Herndon DN, Thompson PB, et al. Pulmonary injury in burned patients. *Crit Care Clin*. 1985;1(1):79-96.
3. Saeman MR, Hodgman EI, et al. Epidemiology and outcomes of pediatric burns over 35 years at Parkland Hospital. *Burns*. 2016;42(1):202-208.
4. Williams FN, Herndon DN, et al. The leading causes of death after burn injury in a single pediatric burn center. *Crit Care*. 2009;13(6):R183.
5. Palmieri TL, Warner P, et al. Inhalation injury in children: a 10 year experience at Shriners Hospitals for Children. *J Burn Care Res*. 2009;30(1):206-208.
6. Veeravagu A, Yoon BC, et al. National trends in burn and inhalation injury in burn patients: results of analysis of the nationwide inpatient sample database. *J Burn Care Res*. 2015;36(2):258-265.
7. Chen MC, Chen MH, et al. The impact of inhalation injury in patients with small and moderate burns. *Burns*. 2014;40(8):1481-1486.
8. Alcorta R. Smoke inhalation and acute cyanide poisoning. Hydrogen cyanide poisoning proves increasingly common in smoke-inhalation victims. *JEMS*. 2004;29(8):suppl 6-15, quiz suppl 16-17.
9. *U.S. Department of Security Fire Death Rate Trends: An International Perspective*. Washington, DC: U.S. Department of Health; 2011:12.
10. Kobayashi K, Ikeda H, et al. Epidemiological and outcome characteristics of major burns in Tokyo. *Burns*. 2005;31(suppl 1):S3-S11.
11. Pegg SP. Burn epidemiology in the Brisbane and Queensland area. *Burns*. 2005;31(suppl 1):S27-S31.
12. Song C, Chua A. Epidemiology of burn injuries in Singapore from 1997 to 2003. *Burns*. 2005;31(suppl 1):S18-S26.
13. Tung KY, Chen ML, et al. A seven-year epidemiology study of 12,381 admitted burn patients in Taiwan: using the Internet registration system of the Childhood Burn Foundation. *Burns*. 2005;31(suppl 1):S12-S17.
14. Linares HA. A report of 115 consecutive autopsies in burned children: 1966–80. *Burns*. 1982;8:263-270.
15. Shirani KZ, Pruitt BA Jr, et al. The influence of inhalation injury and pneumonia on burn mortality. *Ann Surg*. 1987;205:82-87.
16. Saffle JR, Sullivan JJ, et al. Multiple organ failure in patients with thermal injury. *Crit Care Med*. 1993;21(11):1673-1683.
17. World Health Organization. Household air pollution and health. 2016. http://www.who.int/mediacentre/factsheets/fs292/en/.
18. Pittman HS, Schatzki R. Pulmonary effects of the Cocoanut Grove fire: a 5 year follow up study. *N Engl J Med*. 1949;241(25):1008.
19. Saffle JR. The 1942 fire at Boston's Cocoanut Grove nightclub. *Am J Surg*. 1993;166(6):581-591.
20. Blocker V, Blocker TJ Jr. The Texas City disaster: a survey of 3000 casualties. *Am J Surg*. 1949;78:756-771.
21. Centers for Disease Control and Prevention. Rapid assessment of injuries among survivors of the terrorist attack on the World Trade Center–New York City, September 2001. *JAMA*. 2002; 287(7):835-838.
22. Haponik EF. Clinical smoke inhalation injury: pulmonary effects. *Occup Med*. 1993;8:430-468.
23. Starling EH. On the absorption of fluids from the connective tissue spaces. *J Physiol*. 1896;19:312-326.
24. Landis EM, Pappenheimer JR. Exchange of substances through the capillary walls. In: Hamilton WF, Dow P, eds. *Handbook of Physiology*. Section 2. Vol. 2. Baltimore, MD: Williams & Wilkins; 1963:961-1034.
25. Oldham KT, Guice KS, et al. Evidence of local complement activation in cutaneous thermal injury in rats. *Prog Clin Biol Res*. 1988;264:421-424.
26. Friedl HP, Till GO, et al. Roles of histamine, complement and xanthine oxidase in thermal injury of skin. *Am J Pathol*. 1989;135:203-217.
27. Schlayer HJ, Laaff H, et al. Involvement of tumor necrosis factor in endotoxin-triggered neutrophil adherence to sinusoidal endothelial cells of mouse liver and its modulation in acute phase. *J Hepatol*. 1988;7:239-249.
28. Granger DN. Role of xanthine oxidase and granulocytes in ischemia-reperfusion injury. *Am J Physiol*. 1988;255:H1269-H1275.
29. Granger DN, McCord JM, et al. Xanthine oxidase inhibitors attenuate ischemia-induced vascular permeability changes in the cat intestine. *Gastroenterology*. 1986;90:80-84.
30. Szabo C, Modis K. Pathophysiological roles of peroxynitrite in circulatory shock. *Shock*. 2010;34(Suppl 1):4-14.
31. Szabo C, Ischiropoulos H, et al. Peroxynitrite: biochemistry, pathophysiology and development of therapeutics. *Nat Rev Drug Discov*. 2007;6(8):662-680.
32. McBride AG, Brown GC. Activated human neutrophils rapidly break down nitric oxide. *FEBS Lett*. 1997;417:231-234.
33. Herndon DN, Abston S, et al. Increased thromboxane B2 levels in the plasma of burned and septic burned patients. *Surg Gynecol Obstet*. 1984;159:210-213.
34. Demling RH, LaLonde C. Topical ibuprofen decreases early postburn edema. *Surgery*. 1987;102:857-861.
35. Cox RA, Burke AS, et al. Acute bronchial obstruction in sheep: histopathology and gland cytokine expression. *Exp Lung Res*. 2005;31(9-10):819-837.
36. Vindenes H, Ulvestad E, et al. Increased levels of circulating interleukin 8 in patients with large burns: relation to burn size and sepsis. *J Trauma*. 1995;39:635-640.
37. Pitt RM, Parker JC, et al. Analysis of altered capillary pressure and permeability after thermal injury. *J Surg Res*. 1987;42:693-702.
38. Lund T. The 1999 Everett Idris Evans memorial lecture. Edema generation following thermal injury: an update. *J Burn Care Rehabil*. 1999;20(6):445-452.
39. Pitkanen J, Lund T, et al. Transcapillary colloid osmotic pressures in injured and non-injured skin of seriously burned patients. *Burns*. 1987;13:198-203.
40. Zetterstrom H, Arturson G. Plasma oncotic pressure and plasma protein concentration in patients following thermal injury. *Acta Anaesthesiol Scand*. 1980;24:288-294.
41. Onarheim H, Reed RK. Thermal skin injury: effect of fluid therapy on the transcapillary colloid osmotic gradient. *J Surg Res*. 1991;50:272-278.
42. Sheng ZY, Tung LY. Neutrophil chemiluminescence in burned patients. *J Trauma*. 1987;27:587-595.
43. Conhaim RL, Harms BA. A simplified two-pore filtration model explains the effects of hypoproteinemia on lung and soft tissue lymph flux in awake sheep. *Microvasc Res*. 1992;44:14-26.
44. Calhoun KH, Deskin RW, et al. Long-term airway sequelae in a pediatric burn population. *Laryngoscope*. 1988;98:721-725.
45. Demling RH, Kramer GC, et al. Effect of nonprotein colloid on postburn edema formation in soft tissues and lung. *Surgery*. 1984;95: 593-602.
46. Brazeal BA, Honeycutt D, et al. Pentafraction for superior resuscitation of the ovine thermal burn. *Crit Care Med*. 1995;23:332-339.
47. Baile EM, Dahlby RW, et al. Role of tracheal and bronchial circulation in respiratory heat exchange. *J Appl Physiol*. 1985;58: 217-222.
48. Moritz AR, Henriques FC, et al. The effect of inhaled heat on the air passages and lungs: an experimental investigation. *Am J Pathol*. 1945;21:311-326.
49. Kimura R, Traber LD, et al. Increasing duration of smoke exposure induces more severe lung injury in sheep. *J Appl Physiol*. 1988;64:1107-1113.
50. Abdi S, Evans MJ, et al. Inhalation injury to tracheal epithelium in an ovine model of cotton smoke exposure. Early phase (30 minutes). *Am Rev Respir Dis*. 1990;142(6 Pt 1):1436-1439.
51. Jacob S, Kraft R, et al. Acute secretory cell toxicity and epithelial exfoliation after smoke inhalation injury in sheep: an electron and light microscopic study. *Toxicol Mech Methods*. 2010;20(8):504-509.
52. Magno MG, Fishman AP. Origin, distribution, and blood flow of bronchial circulation in anesthetized sheep. *J Appl Physiol*. 1982;53:272-279.
53. Staub NC, Bland RD, et al. Preparation of chronic lung lymph fistulas in sheep. *J Surg Res*. 1975;19:315-320.
54. Abdi S, Herndon D, et al. Time course of alterations in lung lymph and bronchial blood flows after inhalation injury. *J Burn Care Rehabil*. 1990;11:510-515.
55. Herndon DN, Barrow RE, et al. Extravascular lung water changes following smoke inhalation and massive burn injury. *Surgery*. 1987;102:341-349.
56. Ramzy PI, Barret JP, et al. Thermal injury. *Crit Care Clin*. 1999;15(2): 333-352, ix.
57. Ramzy PI, Barret JP, Herndon DN. Thermal Injury. *Crit Care Clin*. 1999;15(2):333-352, ix.

58. Stothert JC Jr, Ashley KD, et al. Intrapulmonary distribution of bronchial blood flow after moderate smoke inhalation. *J Appl Physiol*. 1990;69:1734-1739.
59. Hales CA, Barkin P, et al. Bronchial artery ligation modifies pulmonary edema after exposure to smoke with acrolein. *J Appl Physiol*. 1989;67:1001-1006.
60. Hinder F, Matsumoto N, et al. Inhalation injury increases the anastomotic bronchial blood flow in the pouch model of the left ovine lung. *Shock*. 1997;8:131-135.
61. Linares HA, Herndon DN, et al. Sequence of morphologic events in experimental smoke inhalation. *J Burn Care Rehab*. 1989;10:27-37.
62. Barrow RE, Morris SE, et al. Selective permeability changes in the lungs and airways of sheep after toxic smoke inhalation. *J Appl Physiol*. 1990;68:2165-2170.
63. Cox RA, Burke AS, et al. Airway obstruction in sheep with burn and smoke inhalation injuries. *Am J Respir Cell Mol Biol*. 2003;29(3 Pt 1):295-302.
64. Mathru M, Venus B, et al. Noncardiac pulmonary edema precipitated by tracheal intubation in patients with Injury. *Crit Care Med*. 1983;11:804-806.
65. Herndon DN, Traber LD, et al. Etiology of the pulmonary pathophysiology associated with inhalation injury. *Resuscitation*. 1986;14:43-59.
66. Cox RA, Mlcak RP, et al. Upper airway mucus deposition in lung tissue of burn trauma victims. *Shock*. 2008;29(3):356-361.
67. Pietak SP, Delahaye DJ. Airway obstruction following smoke inhalation. *Can Med Assoc J*. 1976;115(4):329-331.
68. Desai MH, Rutan RL, et al. Managing smoke inhalation injuries. *Postgrad Med*. 1989;86(8):69-70, 73-66.
69. Nakae H, Tanaka H, et al. Failure to clear casts and secretions following inhalation injury can be dangerous: report of a case. *Burns*. 2001;27(2):189-191.
70. Enkhbaatar P, Cox RA, et al. Aerosolized anticoagulants ameliorate acute lung injury in sheep after exposure to burn and smoke inhalation. *Crit Care Med*. 2007;35(12):2805-2810.
71. Enkhbaatar P, Esechie A, et al. Combined anticoagulants ameliorate acute lung injury in sheep after burn and smoke inhalation. *Clin Sci*. 2008;114(4):321-329.
72. Palmieri TL, Enkhbaatar P, et al. Continuous nebulized albuterol attenuates acute lung injury in an ovine model of combined burn and smoke inhalation. *Crit Care Med*. 2006;34(6):1719-1724.
73. Lange M, Hamahata A, et al. Preclinical evaluation of epinephrine nebulization to reduce airway hyperemia and improve oxygenation after smoke inhalation injury. *Crit Care Med*. 2011;39(4):718-724.
74. Jonkam C, Zhu Y, et al. Muscarinic receptor antagonist therapy improves acute pulmonary dysfunction after smoke inhalation injury in sheep. *Crit Care Med*. 2010;38(12):2339-2344.
75. National Burn Repository. 2014 National Burn Repository report of data from 2004–2013. 2014.
76. de La Cal MA, Cerda E, et al. Pneumonia in patients with severe burns: a classification according to the concept of the carrier state. *Chest*. 2001;119(4):1160-1165.
77. Barrow RE, Wang CZ, et al. Cellular sequence of tracheal repair in sheep after smoke inhalation injury. *Lung*. 1992;170(6):331-338.
78. Barrow RE, Wang CZ, et al. Growth factors accelerate epithelial repair in sheep trachea. *Lung*. 1993;171(6):335-344.
79. Perez Fontan JJ. On lung nerves and neurogenic injury. *Ann Med*. 2002;34(4):226-240.
80. Fontan JJ, Cortright DN, et al. Substance P and neurokinin-1 receptor expression by intrinsic airway neurons in the rat. *Am J Physiol Lung Cell Mol Physiol*. 2000;278(2):L344-L355.
81. Kuo HP, Rohde JA, et al. Capsaicin and sensory neuropeptide stimulation of goblet cell secretion in guinea-pig trachea. *J Physiol*. 1990;431:629-641.
82. Shimura S, Sasaki T, et al. Neuropeptides and airway submucosal gland secretion. *Am Rev Respir Dis*. 1991;143(3 Pt 2):S25-S27.
83. Sluka KA, Willis WD, et al. The role of dorsal root reflexes in neurogenic inflammation. *Pain Forum*. 1995;4:141-149.
84. Hagains CE, Trevino LA, et al. Contributions of dorsal root reflex and axonal reflex to formalin-induced inflammation. *Brain Res*. 2010;1359:90-97.
85. Lange M, Enkhbaatar P, et al. Role of calcitonin gene-related peptide (CGRP) in ovine burn and smoke inhalation injury. *J Appl Physiol*. 2009;107(1):176-184.
86. Kraneveld AD, Nijkamp FP. Tachykinins and neuro-immune interactions in asthma. *Int Immunopharmacol*. 2001;1(9-10):1629-1650.
87. Saunders FD, Westphal M, et al. Molecular biological effects of selective neuronal nitric oxide synthase inhibition in ovine lung injury. *Am J Physiol Lung Cell Mol Physiol*. 2010;298(3):L427-L433.
88. Szabo C. Poly (ADP-ribose) polymerase activation and circulatory shock. *Novartis Found Symp*. 2007;280:92-103, discussion 103-107, 160-104.
89. Espinoza LA, Smulson ME, et al. Prolonged poly(ADP-ribose) polymerase-1 activity regulates JP-8-induced sustained cytokine expression in alveolar macrophages. *Free Radic Biol Med*. 2007;42(9):1430-1440.
90. Hassa PO, Covic M, et al. The enzymatic and DNA binding activity of PARP-1 are not required for NF-kappa B coactivator function. *J Biol Chem*. 2001;276(49):45588-45597.
91. Virag L. Poly(ADP-ribosyl)ation in asthma and other lung diseases. *Pharmacol Res*. 2005;52(1):83-92.
92. Soejima K, Traber LD, et al. Role of nitric oxide in vascular permeability after combined burns and smoke inhalation injury. *Am J Respir Crit Care Med*. 2001;163:745-752.
93. Shimoda K, Murakami K, et al. Effect of poly(ADP ribose) synthetase inhibition on burn and smoke inhalation injury in sheep. *Am J Physiol Lung Cell Mol Physiol*. 2003;285(1):L240-L249.
94. Lange M, Szabo C, et al. Beneficial pulmonary effects of a metalloporphyrinic peroxynitrite decomposition catalyst in burn and smoke inhalation injury. *Am J Physiol Lung Cell Mol Physiol*. 2010;300(2):L167-L175.
95. Boulares AH, Zoltoski AJ, et al. Gene knockout or pharmacological inhibition of poly(ADP-ribose) polymerase1 prevents lung inflammation in a murine model of asthma. *Am J Respir Cell Mol Biol*. 2003;28(3):322-329.
96. Soejima K, Schmalstieg FC, et al. Pathophysiological analysis of combined burn and smoke inhalation injuries in sheep. *Am J Physiol Lung Cell Mol Physiol*. 2001;280:L1233-L1241.
97. Ashley KD, Herndon DN, et al. Systemic blood flow to sheep lung: comparison of flow probes and microspheres. *J Appl Physiol*. 1992;73:1996-2003.
98. Traber DL, Schlag G, et al. Pulmonary edema and compliance changes following smoke inhalation. *J Burn Care Rehabil*. 1985;6:490-494.
99. Sugi K, Theissen JL, et al. Impact of carbon monoxide on cardiopulmonary dysfunction after smoke inhalation injury. *Circ Res*. 1990;66:69-75.
100. Clark CJ, Campbell D, et al. Blood carboxyhaemoglobin and cyanide levels in fire survivors. *Lancet*. 1981;1:1332-1335.
101. Isago T, Fujioka K, et al. Derived pulmonary capillary pressure changes after smoke inhalation in sheep. *Crit Care Med*. 1991;19:1407-1413.
102. Isago T, Noshima S, et al. Analysis of pulmonary microvascular permeability after smoke inhalation. *J Appl Physiol*. 1991;71:1403-1408.
103. Sakurai H, Soejima K, et al. Inhibition of lung permeability changes after burn and smoke inhalation by an anti-interleukin-8 antibody in sheep. *Surg Today*. 2009;39(5):399-406.
104. Westphal M, Cox RA, et al. Combined burn and smoke inhalation injury impairs ovine hypoxic pulmonary vasconstriction. Crit Care Med. In press.
105. Charan NB, Turk GM, et al. Gross and subgross anatomy of bronchial circulation in sheep. *J Appl Physiol*. 1984;57:658-664.
106. Efimova O, Volokhov AB, et al. Ligation of the bronchial artery in sheep attenuates early pulmonary changes following exposure to smoke. *J Appl Physiol*. 2001;88:888-893.
107. Sakurai H, Johnigan R, et al. Effect of reduced bronchial circulation on lung fluid flux after smoke inhalation in sheep. *J Appl Physiol*. 1998;84(3):980-986.
108. Hamahata A, Enkhbaatar P, et al. Effect of ablated bronchial blood flow on survival rate and pulmonary function after burn and smoke inhalation in sheep. *Burns*. 2009;35(6):802-810.
109. Morita N, Enkhbaatar P, et al. Impact of bronchial circulation on bronchial exudates following combined burn and smoke inhalation injury in sheep. *Burns*. 2011;37(3):465-473.
110. Lopez E, Fujiwara O, et al. Nebulized epinephrine limits pulmonary vascular hyperpermeability to water and protein in ovine with burn and smoke inhalation injury. *Crit Care Med*. 2016;44(2):e89-e96.
111. Doerschuk CM, Beyers N, et al. Comparison of neutrophil and capillary diameters and their relation to neutrophil sequestration in the lung. *J Appl Physiol*. 1993;74:3040-3045.

112. Traber DL, Herndon DN, et al. The pulmonary lesion of smoke inhalation in an ovine model. *Circ Shock*. 1986;18:311-323.
113. Niehaus GD, Kimura R, et al. Administration of a synthetic antiprotease reduces smoke-induced lung injury. *J Appl Physiol*. 1990;69: 694-699.
114. Youn YK, LaLonde C, et al. Oxidants and the pathophysiology of burn and smoke inhalation injury. *Free Radic Biol Med*. 1992;12:409-415.
115. Nguyen TT, Cox CS, et al. Free radical activity and loss of plasma antioxidants, vitamin E, and sulfhydryl groups in patients with burns: the 1993 Moyer Award. *J Burn Care Rehabil*. 1993;14:602-609.
116. Nguyen TT, Herndon DN, et al. Effect of manganous superoxide dismutase on lung fluid balance after smoke inhalation injury. *Proc Am Burn Assoc*. 1993;25:31.
117. Nguyen TT, Cox CS Jr, et al. Effects of manganese superoxide dismutase on lung fluid balance after smoke inhalation. *J Appl Physiol*. 1995;78:2161-2168.
118. Schenarts PJ, Schmalstieg FC, et al. Effects of an L-selectin antibody on the pulmonary and systemic manifestations of severe smoke inhalation injuries in sheep. *J Burn Care Rehab*. 2000;21:229-240.
119. Sakurai H, Schmalstieg FC, et al. Role of L-selectin in physiological manifestations after burn and smoke inhalation injury in sheep. *J Appl Physiol*. 1999;86(4):1151-1159.
120. Basadre JO, Sugi K, et al. The effect of leukocyte depletion on smoke inhalation injury in sheep. *Surgery*. 1988;104:208-215.
121. Garcia-Avello A, Lorente JA, et al. Degree of hypercoagulability and hyperfibrinolysis is related to organ failure and prognosis after burn trauma. *Thromb Res*. 1998;89(2):59-64.
122. Rehberg S, Yamamoto Y, et al. Antithrombin attenuates vascular leakage via inhibiting neutrophil activation in acute lung injury. *Crit Care Med*. 2013;41(12):e439-e446.
123. Kowal-Vern A, Walenga JM, et al. Prothrombin fragment 1.2 and modified antithrombin as predictors of disseminated intravascular coagulation and thrombotic risk in thermal injury. *J Burn Care Res*. 2013;34(4):459-464.
124. Kowal-Vern A, Walenga JM, et al. The impact of antithrombin (H) concentrate infusions on pulmonary function in the acute phase of thermal injury. *Burns*. 2001;27(1):52-60.
125. Niedermayr M, Schramm W, et al. Antithrombin deficiency and its relationship to severe burns. *Burns*. 2007;33(2):173-178.
126. Lavrentieva A, Kontakiotis T, et al. The efficacy of antithrombin administration in the acute phase of burn injury. *Thromb Haemost*. 2008;100(2):286-290.
127. Yu YM, Ryan CM, et al. Arginine and ornithine kinetics in severely burned patients: increased rate of arginine disposal. *Am J Physiol Endocrinol Metab*. 2001;280:E509-E517.
128. Xia Y, Roman LJ, et al. Inducible nitric-oxide synthase generates superoxide from the reductase domain. *J Biol Chem*. 1998;273:22635-22639.
129. Sousse LE, Yamamoto Y, et al. Acute lung injury-induced collagen deposition is associated with elevated asymmetric dimethylarginine and arginase activity. *Shock* 2010;35(3):282-288.
130. Maarsingh H, Pera T, et al. Arginase and pulmonary diseases. *Naunyn Schmiedebergs Arch Pharmacol*. 2008;378(2):171-184.
131. Murakami K, Enkhbaatar P, et al. L-arginine attenuates acute lung injury after smoke inhalation and burn injury in sheep. *Shock*. 2007;28(4):477-483.
132. Mlcak R, Desai MH, et al. Lung function following thermal injury in children – an 8-year follow up. *Burns*. 1998;24:213-216.
133. Ipaktchi K, Mattar A, et al. Attenuating burn wound inflammation improves pulmonary function and survival in a burn-pneumonia model. *Crit Care Med*. 2007;35(9):2139-2144.
134. Morris SM Jr. Recent advances in arginine metabolism: roles and regulation of the arginases. *Br J Pharmacol*. 2009;157(6):922-930.
135. Prosser FH, Wahl LM. Involvement of the ornithine decarboxylase pathway in macrophage collagenase production. *Arch Biochem Biophysics*. 1988;260:218-225.
136. Tenu JP, Lepoivre M, et al. Effects of the new arginase inhibitor N(omega)-hydroxy-nor-L-arginine on NO synthase activity in murine macrophages. *Nitric Oxide*. 1999;3(6):427-438.
137. Bratt JM, Franzi LM, et al. Arginase enzymes in isolated airways from normal and nitric oxide synthase 2-knockout mice exposed to ovalbumin. *Toxicol Appl Pharmacol*. 2009;234(3):273-280.
138. Smith CL, Birdsey GM, et al. Dimethylarginine dimethylaminohydrolase activity modulates ADMA levels, VEGF expression, and cell phenotype. *Biochem Biophys Res Commun*. 2003;308(4):984-989.
139. Zakrzewicz D, Eickelberg O. From arginine methylation to ADMA: a novel mechanism with therapeutic potential in chronic lung diseases. *BMC Pulm Med*. 2009;9:5.
140. Traber MG, Leonard SW, et al. α-Tocopherol adipose tissue stores are depleted after burn injury in pediatric patients. *Am J Clin Nutr*. 2010;92(6):1378-1384.
141. Morita N, Shimoda K, et al. Vitamin E attenuates acute lung injury in sheep with burn and smoke inhalation injury. *Redox Rep*. 2006;11(2):61-70.
142. Morita N, Traber MG, et al. Aerosolized alpha-tocopherol ameliorates acute lung injury following combined burn and smoke inhalation injury in sheep. *Shock*. 2006;25(3):277-282.
143. Traber MG, Shimoda K, et al. Burn and smoke inhalation injury in sheep depletes vitamin E: kinetic studies using deuterated tocopherols. *Free Radic Biol Med*. 2007;42(9):1421-1429.
144. Hamahata A, Enkhbaatar P, et al. gamma-Tocopherol nebulization by a lipid aerosolization device improves pulmonary function in sheep with burn and smoke inhalation injury. *Free Radic Biol Med*. 2008;45(4):425-433.
145. Shimoda K, Nakazawa H, et al. Plasma and tissue vitamin E depletion in sheep with burn and smoke inhalation injury. *Burns*. 2008;34(8):1137-1141.
146. Traber DL, Traber MG, et al. Tocopherol as treatment for lung injury associated with burn and smoke inhalation. *J Burn Care Res*. 2009;30(1):164-165.
147. Chen L, Lee HM, et al. Accumulation of oxidatively generated DNA damage in the brain: a mechanism of neurotoxicity. *Free Radic Biol Med*. 2007;42(3):385-393.
148. Lee HM, Reed J, et al. Impaired mitochondrial respiration and protein nitration in the rat hippocampus after acute inhalation of combustion smoke. *Toxicol Appl Pharmacol*. 2009;235(2):208-215.
149. Prien T, Traber DL. Toxic smoke compounds and inhalation injury: a review. *Burns*. 1988;14:451-460.
150. Moore SJ, Ho IK, et al. Severe hypoxia produced by concomitant intoxication with sublethal doses of carbon monoxide and cyanide. *Toxicol Appl Pharmacol*. 1991;109:412-420.
151. Pitt BR, Radford EP, et al. Interaction of carbon monoxide and cyanide on cerebral circulation and metabolism. *Arch Environ Health*. 1979;34:345-349.
152. Terrill JB, Montgomery RR, et al. Toxic gases from fires. *Science*. 1978;200(4348):1343-1347.
153. Smith RP. Toxic responses of the blood. In: Klaassen CD, Amdur MO, Doull J, eds. *Casarett and Doull's Toxicology, the Basic Science of Poisons*. New York: MacMillan; 1986:223-244.
154. West JB. *Pulmonary Pathophysiology: The Essentials*. Baltimore, MD: Lippincott Williams & Wilkins; 2003.
155. Goldbaum LR, Orellano T, et al. Mechanism of the toxic action of carbon monoxide. *Ann Clin Lab Sci*. 1976;6:372-376.
156. Shimazu T, Ikeuchi H, et al. Half-life of blood carboxyhemoglobin after short-term and long-term exposure to carbon monoxide. *J Trauma*. 2000;49(1):126-131.
157. Alonso JR, Cardellach F, et al. Reversible inhibition of mitochondrial complex IV activity in PBMC following acute smoking. *Eur Respir J*. 2004;23(2):214-218.
158. Miro O, Alonso JR, et al. Oxidative damage on lymphocyte membranes is increased in patients suffering from acute carbon monoxide poisoning. *Toxicol Lett*. 1999;110(3):219-223.
159. Kent M, Creevy KE, et al. Clinical and neuropathological findings of acute carbon monoxide toxicity in chihuahuas following smoke inhalation. *J Am Anim Hosp Assoc*. 2010;46(4):259-264.
160. Westphal M, Morita N, et al. Carboxyhemoglobin formation following smoke inhalation injury in sheep is interrelated with pulmonary shunt fraction. *Biochem Biophys Res Commun*. 2003;311(3): 754-758.
161. Charnock EL, Meehan JJ. Postburn respiratory injuries in children. *Pediatr Clin North Am*. 1980;27:661-676.
162. Purser DA, Grimshaw P, et al. Intoxication by cyanide in fires: a study in monkeys using polyacrylonitrile. *Arch Environ Health*. 1984;39:394-400.
163. Baud FJ, Barriot P, et al. Elevated blood cyanide concentrations in victims of smoke inhalation. *N Engl J Med*. 1991;325:1761-1766.
164. Silverman SH, Purdue GF, et al. Cyanide toxicity in burned patients. *J Trauma*. 1988;28:171-176.
165. Hinton HL. *Combating Terrorism: Observations on the Threat of Chemical and Biological Terrorism. U.G.A*. Washington DC: Office of National Security and International Affairs Division; 1999.

166. Eckstein M. Cyanide as a chemical terrorism weapon. *JEMS*. 2004;29(8):suppl 22-31.
167. Smith PW, Crane R, et al. Effects of exposure to carbonmonoxide and hydrogen cyanide. In: *Physiological and Toxological Aspects of Combustion Products*. Washington DC: National Academy of Science; 1976:75-78.
168. Morocco AP. Cyanides. *Crit Care Clin*. 2005;21(4):691-705.
169. Becker CE. The role of cyanide in fires. *Vet Human Toxicol*. 1985;27:487-490.
170. Hughart JL, Bashor MM. Industrial Chemicals and Terrorism: Human Health Threat Analysis, Mitigation Prevention. AFTSAD Registry. Washington, DC: US Public Health Service; n.d.
171. Author. USAMRICD. Pulmonary agents. In: *US Army Medical Research Institute of Chemical Defence, Medical Management of Chemical Casualties Handbook*. Aberdeen, MA: USAMRICD; 2000:18-34.
172. Author. Medical management for phosgene. In: *Managing Hazardous Material Incidents*. Atlanta, GA: US Department of Health and Human Services; 2001.
173. Borak J, Diller WF. Phosgene exposure: mechanisms of injury and treatment strategies. *J Occup Environ Med*. 2001;43(2):110-119.
174. Burns TR, Mace JL, et al. Ultrastructure of acute ammonia toxicity in the human lung. *Am J Forensic Med Pathol*. 1985;6(3):204-210.

17 Diagnosis and Treatment of Inhalation Injury

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Introduction

Inhalation injury is a nonspecific term that refers to damage to the respiratory tract or pulmonary parenchyma by heat or chemical irritants carried into the airways during respiration.

Along with total body surface area (TBSA) burned and age, inhalation injury is one of the three features most associated with mortality following thermal insult.[1] Issues related to diagnosis and management of inhalation injury have been most recently reviewed by Walker et al.[2]

Inhalation injury may occur in conjunction with cutaneous burns or in isolation. The severity of injury varies depending on the chemical composition of the agent(s) inhaled, the intensity of exposure, and pre-existing comorbidities. There are three basic classes of inhalation injury: direct thermal injury, tissue damage due to inhalation of chemical irritants, and systemic effects of inhaled toxins. The upper airway serves as an efficient heat exchanger that protects lower structures from extremes of heat or cold. Reflex laryngeal closure also protects subglottic areas. As a result, direct thermal injury is generally restricted to the upper airway and rarely involves subglottic structures.[3] Exceptions are the inhalation of steam, due to the much higher specific heat of water vapor, and blast injuries that can force hot gases past the glottic opening. Inhaled irritants are generally present in smoke as a mixture of gases, fumes, and mists, and the chemical composition of smoke produced from various fuels has been described. Fumes consist of particles of various size dispersed in gases. Mists are aerosolized liquids. The intensity of exposure along with the size and chemical composition of these particles and droplets determines how far distally they will migrate in the respiratory tract and, thus, the nature of the tissue injury.[4] Large particles and droplets of lipid-soluble liquids are more likely to adhere to airway surfaces and do not reach as far distally as smaller particles and more water-soluble droplets. Systemic toxicity may occur when toxins such as carbon monoxide (CO) or cyanide are present in the inhaled gases.

The reported incidence of inhalation injuries has varied greatly over time and from region to region. Smith and others reported 19.6% incidence among burn patients in the United States.[5] In Israel Haik and colleagues found as few as 1.9% in association with burns,[6] whereas Luo and others found 8.01% in China.[7] Regional differences are to be expected as a result of differences in local customs, building materials, and other factors.

The presence of inhalation injury is clinically significant for a variety of reasons, as listed in Box 17.1. Inhalation injury has been found to be an independent risk factor for mortality.[8,9] It is also associated with hemodynamic instability because volume requirements for resuscitation may be increased by as much as 50% when cutaneous burns are accompanied by inhalation injury.[10,11] Parenchymal injury from inhaled irritants or hot gases can lead to impaired gas exchange, pneumonia, and acute respiratory distress syndrome (ARDS). When severe, these changes increase the risk of multiorgan failure and mortality. After recovery from inhalation injury pulmonary function disorders may persist due to pulmonary fibrosis or bronchiectasis.[12] Improvements in the survival of patients with inhalation injury have been attributed to better overall burn outcomes, improved ventilator management, and improved management of pneumonias.[7]

Improvements in the care of cutaneous burns have outpaced advancements in the treatment of inhalation injuries. There are several reasons for this disparity. The treatment of pulmonary parenchymal injury is inherently more complex than treatment for cutaneous burns. Necrotic skin can be excised and replaced with substitute materials or autografted skin, and healing can be observed directly. In contrast, treatment of injured lung involves measures to prevent further injury to allow host mechanisms to repair injured tissues. Healing of pulmonary injury is followed more indirectly by observations of blood gas exchange and radiographs. Inhalation injury results both from direct effects of heat and chemical irritants as well as from indirect effects from an inflammatory response to the initial insult. Despite extensive studies, these processes are incompletely understood and no specific therapies have been identified.

Because inhalation injury has such broad and critical clinical implications, it is important that it be diagnosed as early as possible. Early diagnosis can be accomplished by recognition of risk factors revealed by the history and physical examination and confirmed by diagnostic procedures.

Diagnosis

There is no consensus on the diagnostic criteria for inhalation injury. In the clinical setting the diagnosis is a relatively subjective judgment based on history and physical examination, often confirmed by additional diagnostic procedures such as bronchoscopy. One of the reasons for the lack of consensus for early diagnosis is that much of the impaired pulmonary function following inhalation injury results from obstruction of small airways and an inflammatory response to the initial direct injury. These changes develop over a period of days after injury. In addition, it is our clinical impression that progressive respiratory failure is not always proportional to the intensity of smoke exposure.[13] It is also possible for thermally injured patients to experience acute lung injury from the systemic effects of the

Box 17.1 Clinical Significance of Inhalation Injury

- Increased mortality
- Airway closure secondary to oropharyngeal edema
- Increased resuscitation fluid requirements
- Impaired pulmonary gas exchange
- Pneumonia
- Risk of systemic inflammatory response syndrome and multiorgan failure
- Chronic pulmonary dysfunction
- Laryngeal damage

inflammatory response to severe cutaneous burns.[14] Thus it is not uncommon to see acute lung injury in children with large scald burns when inhalation of hot or caustic gases did not occur.[15] This makes it difficult to determine what component of respiratory failure is due to inhalation injury and what component is an effect of systemic inflammation associated with large cutaneous burns.

On initial presentation, patients with inhalation injury may have relatively normal gas exchange as evaluated by arterial blood gas analysis, and the chest radiograph is often normal.[16] In the absence of evidence of respiratory distress it is important to recognize features from the history and physical examination that reveal risk factors for inhalation injury. Normal gas exchange and chest radiograph on admission do not rule out significant inhalation injury. Early diagnosis is important to recognize the potential for airway compromise, manage fluid resuscitation, and to recognize systemic toxicity that may lead to permanent neurological deficits if not promptly treated.

History pertinent to the diagnosis of inhalation injury includes information regarding the mechanism of injury and the intensity of exposure. Mechanisms of injury that carry significant risk of inhalation injury include not only exposure to smoke from a fire, but blast injury that can force hot gases past the larynx, steam burns that can not only burn the upper airway but carry heat to structures below the larynx, and exposure to caustic fumes, as occurs in some industrial accidents. Information regarding the mechanism of injury also includes the source of combustion, which could identify specific chemical irritants. The history can also provide information regarding the intensity of exposure. Duration of exposure is an important determinant of intensity of exposure. When a victim's avoidance behavior is impaired, as when trapped in an enclosed space, intoxicated, unconscious, or in the case of extremes of age, exposure to injurious inhalants is increased.

History of the mechanism of injury is especially important in the case of scalds due to ingestion of hot liquids. Although patients may appear asymptomatic initially, oropharyngeal scalds have led to delayed fatal airway occlusion. Intraoral scalds can present in a manner similar to epiglottitis.[17] The larynx should be examined for evidence of compromise in all patients who present with significant risk (either by history or physical exam) of intraoral scald.

The physical examination can reveal additional risk factors for inhalation injury. We guard our face vigorously, and the presence of burns to the face or singed eyebrows or nasal hair implies a very intense exposure to heat. When gases hot enough to burn tissue are near the airway inlet it suggests that oropharyngeal or nasopharyngeal structures may also suffer thermal injury. Soot deposits on the face and carbonaceous sputum suggests inhalation of smoke. Physical examination may reveal signs and symptoms such as stridor, hoarseness, drooling, and dysphagia that are considered classic evidence of thermal injury to the oropharynx. Presence of these findings, however, does not always indicate that tracheal intubation is necessary.[18] However, as described below, when patients are considered at risk for upper airway thermal injury and occlusion, a priority is to evaluate the upper airway for impending occlusion that may be prevented by early tracheal intubation.

In addition to the history and physical examination, there are diagnostic tools that may be used to confirm a diagnosis of inhalation injury or to follow the progression of injury. Since manifestations of respiratory dysfunction may be delayed after inhalation injury, pulse oximetry and arterial blood gas analysis are insensitive indicators of lung injury during the initial stages. Despite this, it is important to employ these tools as soon as possible. Early impairment of gas exchange is an ominous sign of severe injury and requires early and aggressive intervention. Diagnosis of CO or cyanide toxicity may be facilitated by blood gas analysis. It is also important to have baseline values to judge progress.

Lee and O'Connel assessed the chest radiographs of 45 patients admitted to their hospital following injury in an enclosed space fire.[19] Of those patients, 33 had abnormal findings consistent with inhalation injury. They suggested that the initial radiograph is an important predictor of injury and need for mechanical support of respiration. However, Wittram and Kenny examined admission chest radiographs over a 3-year period for all patients requiring ventilatory support for inhalation injury.[16]. Out of 25 patients, 12 had normal initial chest radiographs despite ultimately requiring mechanical ventilation. The initial chest radiograph is considered an insensitive early indicator of parenchymal injury after smoke inhalation. Although an admission chest radiograph should be obtained in all patients suspected of inhalation injury a normal study does not rule out the possibility of significant pulmonary injury.[16]

Flexible fiberoptic bronchoscopy was early recognized as a powerful tool in the diagnosis of inhalation injury.[20] Fiberoptic bronchoscopy allows direct visualization of tissue damage to the upper airway and bronchi from heat and chemical irritants. This procedure can quickly and reliably identify patients with upper airway compromise who will benefit from intubation and, at the same time, avoid intubation of patients who will not benefit.[21] Bronchoscopic evidence of inhalation injury includes soot deposits, erythema, edema (as indistinct tracheal rings and/or blunting of the carina), mucosal blisters and erosions, hemorrhages, and bronchorrhea (Fig. 17.1). Flexible fiberoptic bronchoscopy has been considered the gold standard for diagnosis of inhalation injury and is often used to confirm the diagnosis of inhalation injury.[22] However, Hunt noted that, in some cases, bronchoscopy performed soon after injury may not show mucosal injury.[20] In addition, because acute lung injury and tracheobronchitis can be a result of systemic inflammation due to cutaneous burns,[14,23] endoscopic

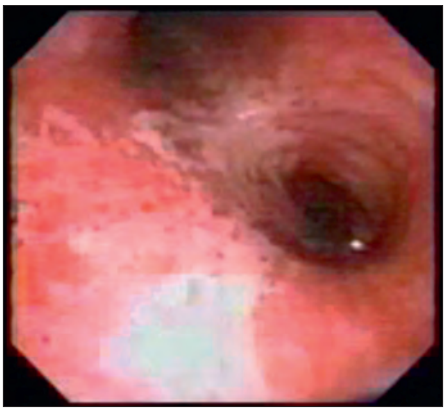

Fig. 17.1 Bronchoscopic view of the trachea from a patient with smoke inhalation injury. Note generalized inflammation and erythema. Edema is manifest as indistinct tracheal rings and blunting of the carina. There are patchy areas of denuded mucosa and a fibrinous exudate is forming at the carina

changes after 36–48 hours may be caused by mechanisms other than inhalation of chemical irritants. As an example, a small fraction of young pediatric patients with large scald injuries develop acute lung injury and require mechanical ventilation.[15] Bronchoscopic examination of these patients can reveal inflammatory changes characteristic of smoke inhalation. Moreover, although fiberoptic bronchoscopy can definitively identify tissue damage from inhalation injury, it has been recognized that the observed changes are relatively proximal and may be more severe than more peripheral parenchymal injuries.[24] As a result, a bronchoscopic diagnosis of inhalation injury does not always identify which patients will experience progressive respiratory dysfunction.

Numerous attempts have been made to grade severity of inhalation injury based on bronchoscopic findings in order to identify patients who may need increased levels of support regarding airway management, respiratory support, or increased volume of fluid during the initial resuscitation. In their retrospective study, Hassan et al. found that mortality among patients with inhalation injury correlated with severity of bronchoscopic findings.[25] However, Spano and colleagues also performed a retrospective review to evaluate the effectiveness of bronchoscopy to predict outcomes for patients with inhalation injuries.[26] They used an abbreviated injury score (AISD INH) introduced by Endorph and Gameli[27] that grades the severity of bronchoscopic findings associated with smoke inhalation injury. They also reviewed the three previous studies that specifically compared the AIS INH with clinical outcome.[27–29] All these studies found trends that were suggestive of poorer clinical outcome in patients with more severe bronchoscopic changes, but these trends were not statistically significant. Spano et al. suggested that further studies to allow refinement in descriptions of severity grades will be needed before bronchoscopic evaluation produces reliable prognostic information.[26]

It is generally accepted that patients with smoke inhalation injury require increased fluid volume for resuscitation of cutaneous burns.[10,11,30] Increases of up to 40–50% have been observed.[10] While this has been a fairly consistent observation, the value of bronchoscopy in predicting increased fluid needs has been inconsistent. Endorf and Gamelli found that an initial P:F ratio of less than 350 was a more reliable predictor of increased fluid requirements than was diagnosis of inhalation injury by bronchoscopy.[27] In their patients, fluid requirements during initial resuscitation were not correlated with severity of findings at initial bronchoscopy. Cancio and colleagues found that diagnosis of inhalation injury per se was not related to increased fluid needs but that mechanical ventilation was related.[30] They suggested that mechanical ventilation may be a surrogate variable for more severe inhalation injury, and this could explain its closer correlation with fluid needs. These observations reinforce the possibility that findings of bronchoscopy are relatively proximal and may not always reflect the severity of more distal parenchymal injury. Need for mechanical ventilation and decreased P:F are more dependent on parenchymal injury and therefore may be more accurate predictors of inhalation injury.

Mackie and colleagues have offered an alternative mechanism for increased fluid requirements in burn patients who also have inhalation injury.[31] They found that ventilated patients with burns but no inhalation injury required more fluid than did patients with similar burns but who did not receive mechanical ventilation. Fluid balance was not significantly affected in patients who also had burns, inhalation injury, and were mechanically ventilated. Mackie suggests that positive pressure ventilation increases intrathoracic pressure, which impairs venous return to the heart. More intravenous fluid is then required to maintain cardiac preload. These findings are consistent with a greater effect of mechanical ventilation on fluid balance than inhalation injury.[32]

Although bronchoscopy does not reliably predict respiratory failure, endoscopic assessment of the upper airway has been found to be highly useful in identifying patients with glottic or supraglottic changes who would benefit from early intubation. Just as important, this exam also helps avoid unnecessary intubations that expose patients to serious risk without benefit.[21]

Radionuclide studies represent an additional tool that has been used to provide evidence of pulmonary injury distal to the more proximal views permitted by flexible bronchoscopy. Intravenously administered xenon-133 is excreted by the lungs and exhaled. Delayed clearance of xenon-133 is a sensitive indicator of inhalation injury.[33] Lung scintigraphy using technetium-99 aerosol inhalation has also been used to identify areas of pulmonary dysfunction in patients with respiratory dysfunction after smoke inhalation. Delayed clearance and inhomogeneous lung distribution of radioactivity are evidence of injury.[34] These studies are sensitive indicators of inhalation injury, but interpretation can be confounded by pre-existing lung disease, and it may be difficult to perform these studies in critically ill burn patients.

The poor correlation of clinical outcome with severity of bronchoscopic findings in patients with smoke inhalation injury has led some clinicians to evaluate the possibility that chest computed tomography (CT) could provide more accurate prognostic information. CT can reveal regional differences in structural changes that impair pulmonary function, such as atelectasis, consolidation, and fibrosis, more effectively than chest radiographs. Yamamura and

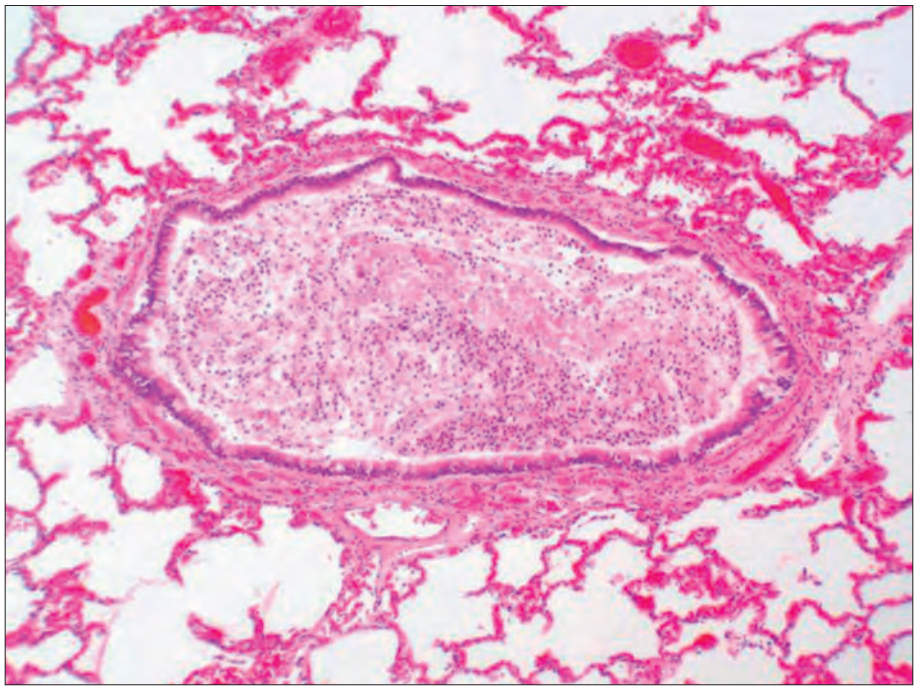

Fig. 17.2 Small airway occluded by inflammatory exudate in a patient who had a smoke inhalation injury.

others used admission chest CT to measure bronchial wall thickness in patients with suspected inhalation injury.[35] Increased bronchial wall thickness was associated with total number of ventilator days, ICU days, and pneumonia. Oh and colleagues obtained CT scans shortly after admission for patients at risk for smoke inhalation. A grading system was used to provide a score for each CT scan based on interstitial markings, ground-glass opacification, and consolidation. This score was compared with clinical outcomes described as a composite endpoint based on pneumonia, ALI/ARDS, and mortality. Injury detected by bronchoscopy alone was associated with an 8.3-fold increase in the composite score, while the combination of bronchoscopic evidence of inhalation injury and a high CT score was associated with a 12.7-fold increase in the composite endpoint. The authors were cautiously optimistic that with additional clinical experience and refinement of image analytical techniques, CT scans alone or in combination with bronchoscopic evaluation may provide more accurate early prognosis for patients with smoke inhalation injury. The risks of taking an acutely ill patient to the CT scanner were also acknowledged.

Pathophysiology of Pulmonary Insufficiency with Inhalation Injury

As stated earlier, except in special cases such as inhalation of steam, injury to airways below the larynx and pulmonary parenchyma nearly always results from chemical irritation rather than thermal injury. A number of reviews are available to describe the pathophysiology of pulmonary failure associated with smoke inhalation.[4,36,37] Chemicals inhaled with smoke, as well as carbon particles coated with irritants, are deposited in the airways. Aqueous secretions of the mucosa dissolve these irritants, and the respiratory mucosa is bathed in relatively concentrated caustic solutions. The initial response to this insult is direct injury to the respiratory epithelium, resulting in hyperemia, edema, increased mucous secretions, impaired ciliary clearance, and bronchoconstriction. Work in experimental animals has also demonstrated an early separation of ciliated respiratory epithelial cells from the basement membrane. This results in denuded areas of the airways and explains the copious formation of protein-rich exudate. Fibrin casts tenaciously adherent to the airway surfaces are formed from this exudate.

Much of the morbidity associated with smoke inhalation is also the result of the inflammatory response to the early direct effect of chemical irritants. The inflammatory response to smoke inhalation is similar to the injury produced by aspiration of acidic gastric contents. The direct injury to tissues from the initial insult causes local accumulation of inflammatory cells and initiation of a cascade of inflammatory mediators that exacerbate and sustain tissue damage (see later discussion). Airways become blocked by edema, bronchoconstriction, fibrin casts, necrotic debris, and inflammatory infiltrate (Fig. 17.2). Degraded surfactant causes alveolar instability and collapse. These changes result in impaired hypoxic pulmonary vasoconstriction and areas of atelectasis and in post-obstruction sequestration of material that provides a medium for bacterial growth and risk of pneumonia. Impaired function of alveolar macrophages slows the removal of these materials and facilitates the development of infection. Pulmonary compliance is reduced, which can greatly increase the work of breathing or require higher ventilator pressures and associated risk of ventilator-induced lung injury.

As a result of these changes pulmonary gas exchange is impaired. Atelectasis due to airway obstruction increases dead space and shunt to an extent, but the impaired gas exchange due to smoke inhalation appears to be primarily a ventilation–perfusion imbalance.[38] It has been suggested that this mechanism of pulmonary dysfunction is fundamentally different from other types of ARDS.[22] Other etiologies of ARDS, such as sepsis, involve disruption of the pulmonary capillary membrane and alveolar flooding, resulting primarily in true shunt. This distinction can influence the ventilator strategies employed. Patients with respiratory failure due to smoke inhalation injury have small airway obstruction, and care should focus on pulmonary toilet together with recruiting and stabilizing alveoli, which tend to collapse. By contrast, in ARDS due to other etiologies the strategy is to concentrate on avoiding ventilator-induced lung injury. In some burn centers this is a rationale for the use of high-frequency percussive ventilation. Just as the bronchi are the focus of the diagnosis of inhalation injury, it is also the focus of its pathology.[39] The hyperemia and edema that are seen in the airway and which are so important for the diagnosis of inhalation injury are the result of an almost 20-fold increase in bronchial blood flow.[40,41]

Following the airway injury, there are changes in the lung parenchyma. There is a release of the chemokine interleukin (IL)-8 and an influx of neutrophils into the airway and alveoli. Reactive oxygen (ROS) and nitrogen species (RNS) are formed.[42] One of the latter, peroxynitrite, damages DNA. DNA damage results in activation of poly-(ADP ribose) polymerase (PARP).[43] Poly-(ADP ribose) protects the damaged DNA but also activates the nuclear factor (NF)-κB.[44] This causes the formation of the inducible form of nitric oxide synthase (NOS) and additional release of IL-8, attracting and activating additional neutrophils and forming more reactive nitrogen and oxygen species.[45] The oxidation, nitration, and nitrosation of lung tissues results in membrane damage, edema formation, and impaired oxygen diffusion.[46,47] Alveoli that are not ventilated are not perfused with blood because alveolar hypoxia causes pulmonary vasoconstriction. NO released by NOS causes a loss of hypoxic pulmonary vasoconstriction, leading to perfusion of unventilated alveoli and thus a fall in arterial oxygen saturation.[48]

In experimental animals ablation of the bronchial blood flow will prevent most of the pathophysiology involved in inhalation injury to the pulmonary parenchyma.[39,49,50] These changes in bronchial blood flow are not associated with heat. They can be produced in experimental animals by smoke that has been cooled to body temperature.[41] As mentioned earlier, the blood flow to the airway is so effective in cooling or heating inhaled air that it is almost impossible for heat carried by dry gases to reach the bronchi.[3,51] These changes in blood flow also appear to be independent of the chemical composition of smoke because they are mediated by neuroinflammation. We have reported that, following insufflation of smoke into deeply anesthetized sheep, the airway blood flow increased 10-fold, but, after administration of an inhibitor of the neuropeptide calcitonin gene-related peptide (CGRP), the smoke-induced hyperemia was markedly reduced.[52] Neuropeptides (peptides released from nerves within the lung tissue) induce vasodilatation by causing activation of NOS, leading to the formation of NO. It has also been reported that an inhibitor of the neuro isoform of NOS would block the hyperemia and much of the pathophysiology mentioned earlier, including the loss of hypoxic pulmonary vasoconstriction.[53,54] These findings have led us to the following hypothesis: the chemicals in smoke activate sensory nerves to release neuropeptides that activate neuronal NOS1 to release NO and superoxide to form peroxynitrite, which damages DNA, activating PARP, which stimulates NF-κB, which in turn will up-regulate the inducible form of NOS (iNOS), leading to massive formation of ROS and RNS, tissue damage, and hypoxia and dyspnea. Some of the activated polymorphonuclear cells that escape from the pulmonary and bronchial circulation into the systemic circulation are carried to systemic organs, promoting multiorgan system damage.

Treatment

Currently there are no specific therapeutic interventions for inhalation injury, and treatment consists of supportive modalities. However, if systemic toxicity is suspected (i.e., cyanide or CO), there are specific interventions recommended. When mechanical ventilation is required, measures should be taken to minimize ventilator-induced lung injury. Surveillance cultures and other measures should be initiated to allow early recognition and treatment of pulmonary infection.

Treatment should begin at the scene of injury. Pulmonary function must be supported in coordination with care of cutaneous burns and other possible injuries. The history along with a rapid physical examination can identify victims at risk of inhalation injury as well as respiratory insufficiency and other indications for early intervention. Initially special attention must be given to the airway evaluation. There are many potential indications for early and even prophylactic intubation in victims of serious burn injury (Box 17.2). Early hypoxemia due to impaired gas exchange after inhalation injury is an ominous sign, and those with respiratory distress that is not corrected by supplemental oxygen may require intubation. Patients unable to protect their airway owing to diminished mental status due to injury or intoxication should be intubated to prevent aspiration. It is recommended that, even in the absence of inhalation injury, those with large full-thickness burns covering 30–40% or more of their total body surface area (TBSA) should be intubated because of the risk of associated hemodynamic instability.[55] Another indication for early prophylactic intubation is the risk of upper airway occlusion due

Box 17.2 Indications for Early Tracheal Intubation after Inhalation Injury

- Extensive burns over face and neck
- Overt signs and symptoms of airway obstruction by edema
- Inability to protect airway from aspiration
- Significant toxicity from carbon monoxide or cyanide
- Respiratory failure
- Hemodynamic instability

Box 17.3 Risks of Unnecessary Tracheal Intubation of Burned Patients

- Impairs communication with patient (impairs history and consent)
- Urgent attempts are more likely to fail or cause injury
- Facial burns make it difficult to secure the endotracheal tube, and unintended extubations are common
- Acute burn patients often require heavy sedation when intubated, which increases morbidity associated with unintended extubation
- A translaryngeal endotracheal tube can exacerbate a laryngeal injury

to edema from thermal injury. In some patients with burns to the face and neck or after inhalation of hot gases or steam, early intubation can be life-saving. Training supported by the American Burn Association has encouraged early tracheal intubation in patients at risk for airway occlusion. However, intubation is not a benign intervention, and there is growing recognition of the associated risks. Eastman and colleagues at the Parkland Burn Center published a retrospective study of pre-burn center intubations of burn victims.[56] This was in response to what may have been a preventable death of a burn victim intubated prior to hospitalization. Out of 879 burn patients intubated before admission to hospital, 11.9% were extubated on the day of admission. In addition, 41.1% were extubated within 48 hours of injury. It is unlikely that pathological changes requiring intubation would resolve so quickly. These findings suggest that many patients may have been exposed to the risks of intubation without commensurate benefit. Box 17.3 lists risks associated with unnecessary tracheal intubations. Intubation is especially dangerous during transportation outside a hospital. These patients require deep sedation to avoid unplanned extubation. With extubation during transport, impaired respiratory drive due to sedation may cause dangerous hypoventilation. The risk is even greater when muscle relaxants are used during transport.

Otolaryngologists at the Baltimore Regional Trauma Center used spirometry (flow–volume loops) and flexible fiberoptic bronchoscopy to prospectively evaluate indications for intubation in patients at risk of inhalation injury.[21] They reported that of 11 patients who were admitted to the emergency department with evidence of inhalation injury, six met their institutional criteria for intubation. However, when these patients were examined by fiberoptic bronchoscopy, no significant airway compromise was observed, and they were managed safely and effectively without intubation. The high negative predictive value of normal flow–volume loops for airway compromise in patients with inhalation injury that they also observed had been previously reported by Haponik et al.[57]

Madnani and colleagues have also demonstrated that the presence of signs and symptoms that have been considered classic evidence of inhalation injury does not always predict the need for tracheal intubation.[18] Further evaluation is needed to avoid morbidity associated with unnecessary intubations. When burn victims first present, the history and physical examination can identify those who are in significant respiratory distress or who have other indications for immediate endotracheal intubation. For other patients with risk factors for inhalation injury but who may only be experiencing mild distress, spirometry (flow–volume loops) and/or endoscopic evaluation can be used to identify those who have impending airway compromise and will more likely benefit from early prophylactic intubation. Those who do not require early intubation can be observed and repeat evaluations performed if their clinical condition changes. An algorithm for airway management in burn patients is illustrated in Fig. 17.3.

Another potential complication of inhalation injury requiring early attention is systemic toxicity from CO and/or cyanide. Intoxication should be considered in all patients suspected of significant exposure to smoke. The predominant toxic effect of CO is to prevent binding of oxygen to hemoglobin by the formation of carboxyhemoglobin (COHb). CO has an affinity for hemoglobin approximately 200 times that of oxygen. CO can also prevent cellular utilization of oxygen by binding to mitochondrial cytochromes. Early symptoms include headache, nausea, dizziness, and lowered mental status. Diagnosis requires direct measurement of COHb. Conventional pulse oximetry will not distinguish between oxyhemoglobin and COHb. COHb can be measured by arterial or venous CO oximetry or pulse CO oximetry.[58]

Increased oxygen partial pressure will speed elimination of CO. Oxygen supplementation by face mask is usually sufficient, but in more severe cases (COHb >15%) it may be necessary to provide 100% oxygen via an endotracheal tube. Hyperbaric oxygen has also been used to treat CO poisoning, but there is no consensus on the indications, treatment parameters, or outcome benefits.[59] Moreover, hyperbaric facilities are not widely available.

Cyanide is another toxic component of smoke, especially when the fuel is composed of certain plastic products. Cyanide causes cellular anoxia by binding to mitochondrial cytochromes and preventing intracellular oxygen utilization. Arterial oxygen partial pressures are not reduced by cyanide. Clinical signs of hypoxia despite adequate arterial oxygen tension or metabolic acidosis despite apparently adequate oxygen delivery suggest cyanide toxicity. The earlier treatment is initiated, the more likely it will be successful. Supplemental oxygen can cause nonenzymatic oxidation of reduced cytochromes, displace cytochrome oxidase, and potentiate the effects of administered antidotes. Pharmacological intervention includes methemoglobin generators such as nitrates (amyl nitrite 0.2 mL by inhalation, or sodium nitrite 10 mL of 3% solution intravenous for adults and 0.13–0.33 mL/kg of 3% solution for children) and dimethylaminophenol (3.25 mg/kg) to increase methemoglobin levels. Methemoglobin competes with cytochrome oxidase for cyanide. Caution is required because excessive levels of methemoglobin lead to decreased oxygen-carrying ability of hemoglobin and may cause toxicity. Some agents can bind cyanide directly. Dicobalt edetate (20 mL of 15% solution for adults or 0.3–0.5 mL/kg of 15% solution for pediatric patients) has a rapid effect but carries a risk of toxicity. Hydroxocobalamin (adults 5–10 g or children 70 mg/kg) is the precursor of vitamin B_{12} and has been shown to be safe, with few side effects. Sulfur donors such as sodium thiosulfate (adults 25 mL of 50% solution or children 1.65 mL/kg of 25% solution) accentuate the body's

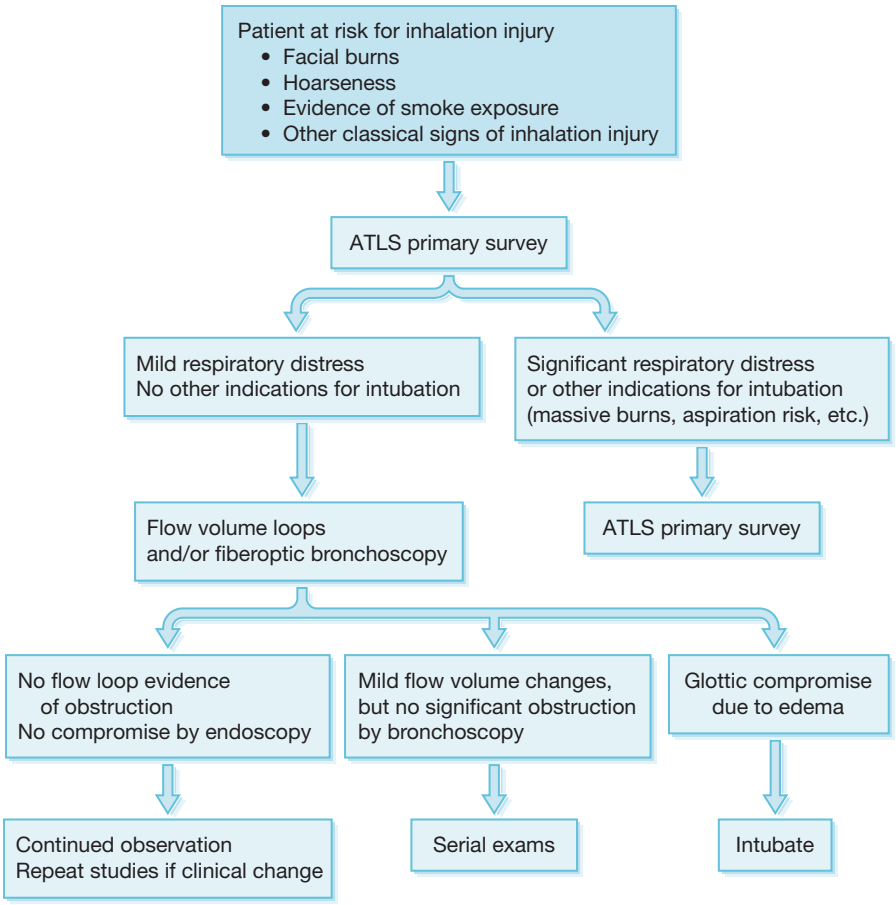

Fig. 17.3 An algorithm to assist airway management decisions in patients at risk for inhalation injury.

enzymatic conversion of cyanide to thiocyanate in the presence of the mitochondrial enzyme rhodanese, reducing its toxicity and increasing elimination.[60]

As mentioned earlier, inhalation injury has been consistently observed to significantly increase fluid requirements for resuscitation of patients with cutaneous burns.[10] The presence of an inhalation injury might intuitively be viewed as an indication to restrict fluids to avoid pulmonary edema. In fact, fluid restriction has been found to exacerbate pulmonary capillary leak and increase lung lymph formation in sheep that have sustained cutaneous burns and smoke inhalation injury.[61] Although it is important to avoid fluid overload in all patients, including those with inhalation injury, inadequate fluid resuscitation can also cause further injury to the lungs of patients with inhalation injury.[62] A combination of cutaneous burns and inhalation injury reduces the margin for error in managing fluid resuscitation. It becomes more difficult to reach a balance where sufficient volume is administered for resuscitation but not so much that it drives up filling pressures, which may increase transudation from pulmonary capillaries that already have increased permeability.

Supplemental humidified oxygen should be used for patients suspected of having inhalation injury. The humidification helps prevent inspissation of the airway secretions. The head of the bed should be placed at a 30- to 45-degree angle to reduce upper airway edema and limit the effect of pressure from abdominal contents on the diaphragm. Meticulous pulmonary hygiene is a vital component of the management of inhalation injury. Frequent airway suctioning, chest physiotherapy including percussive and coughing techniques, and early mobilization all help clear debris and prevent build-up of secretions, which can cause airway obstruction, atelectasis, and predispose to the development of pneumonia.[63,64] Care should be taken when suctioning to avoid hypoxia and bradycardia. Preoxygenation and suctioning for short periods of 10–15 sec can reduce the incidence of these problems. Postural drainage can be useful, although sometimes skin graft location and fragility impede use of this technique.[65] Percussive and vibratory techniques such as high-frequency chest wall oscillation also help clear mucoid secretions.[65,66] It is also important to maintain good nutritional status in these patients.

Inhalation of smoke produces damage to the airways resulting in sloughing of epithelial cells, increased microvascular permeability, and a dramatic increase in bronchial blood flow.[41] As a result, the airways are flooded with plasma exudate and cellular debris. This mix combines with mucus to form a fibrinocellular cast or pseudomembrane that partially or completely obstructs airways. This process is exacerbated by an intense inflammatory infiltrate. In an attempt to disrupt this sequence, Desai and colleagues administered

aerosolized heparin and N-acetylcysteine to slow formation of fibrin and thin mucous secretions in pediatric patients with smoke inhalation injury.[67] They observed a decrease in atelectasis, frequency of re-intubations, and mortality. Treatment with aerosolized heparin is utilized in many burn centers because it is intuitively attractive and does not affect systemic coagulation. The preclinical and clinical evidence of the effectiveness of inhaled anticoagulants for the treatment of smoke inhalation has been reviewed by Miller et al.[68] At the time of writing there were reports of improved survival in experimental animals and in patients, along with improved oxygenation, ventilation, and attenuation of markers of lung injury when smoke inhalation injury is treated with nebulized heparin or other anticoagulants in various protocols, but no large prospective studies have been done in burn patients. More recently, in a prospective randomized trial of 214 mechanically ventilated non-burn ICU patients, Bandeshe et al.[69] examined regular saline nebulization against unfractionated sodium heparin (5000 iU/2 mL four times daily) and found no difference in terms of the development of ventilator-associated pneumonia (VAP) or amount of secretions. They concluded that nebulized heparin cannot be recommended for prophylaxis against VAP or to hasten recovery from pneumonia in patients receiving mechanical ventilation.

When chest physiotherapy and pharmacological agents still fail to facilitate expectoration of secretions or ameliorate cast formation, fiberoptic bronchoscopy can be effective for removal of secretions and also to obtain microbiological specimens through bronchoalveolar lavage in suspected cases of pneumonia. Attempts to replace surfactant have also been studied but are not in widespread clinical use. Antibiotics are indicated for suspected or proven pulmonary infection.[64,70]

Mechanical ventilation is indicated when the signs of respiratory failure are either present or imminent. Indications include impaired gas exchange due to pulmonary parenchymal injury, decreased pulmonary compliance, or impending collapse of effort due to fatigue. Burns involving the head and neck may make intubation technically difficult. In these circumstances avoidance of muscle relaxants and the use of an intubation technique that maintains spontaneous ventilation is safest. The flexible fiberoptic bronchoscope is well suited to this task. A nasal endotracheal tube may be preferable for patient comfort, oral hygiene, and stability. A nasal endotracheal tube can be secured by a nasal septal bridle, which is much more secure than tape or ligatures over burned skin and prevents irritation of wounds and disruption of grafts.

Currently there is no consensus on the ideal mode of mechanical ventilation for burn patients. The intricacies of mechanical ventilation in burn patients have been reviewed previously.[22,71–73] Recommendations by the American Thoracic Society (ATS) and the American College of Chest Physicians[74] can generally be applied to the population of mechanically ventilated burn patients: minimize the time the patient is on the ventilator; conduct a spontaneous breathing trial with inspiratory pressure augmentation (5–8 cm H_2O) rather than without (using a T-piece or continuous positive airway pressure [CPAP]); and, for acutely hospitalized patients who have been mechanically ventilated for more than 24 hours, protocolized rehabilitation directed toward early mobilization. In the adult burn population, especially those with inhalation injury and at high risk for extubation failure who have been receiving mechanical ventilation for more than 24 hours and who have passed a spontaneous breathing trial, extubation to preventive noninvasive ventilation is recommended.

The aim is to provide adequate ventilation to maintain airway and alveolar patency without exacerbating the pulmonary injury by overdistension or barotrauma. Ventilation with low tidal volumes (≤ 7 mL/kg) is now generally accepted as a routine practice in patients with acute lung injury, and most burn centers have adopted this approach to reduce ventilator-induced injury. In patients with inhalation injury the small airways may be narrowed by edema and bronchospasm, which increases airway resistance and hence airway pressures during mechanical ventilation. Under these circumstances it is often difficult to provide adequate ventilation of patients with inhalation injury with tidal volumes of less than 7 mL/kg. How this strategy applies to patients with inhalation injury has not been established.[75] Permissive hypercapnia has been found to be a safe technique to assist in limiting airway pressures in burn patients.[76,77] This allows lower airway pressures and smaller tidal volumes to be used when ventilating the patient and is well tolerated when gradual in onset and the pH is kept higher than 7.2–7.25.

A common ventilation strategy is to determine the level of positive end-expiratory pressure (PEEP) by using a pressure–volume curve. This helps maintain alveolar patency and reduces trauma caused by the shear forces imparted as alveoli collapse and are re-expanded with each breath. The lower inflection point of the pressure–volume curve of a mechanical breath is where the slope of the lower curve begins to increase and is the airway pressure below which the alveoli collapse. The PEEP value can be set just above this pressure. Fio_2 should be weaned down as tolerated to reduce oxygen-related complications. The Pao_2 can be maintained between 80 and 100 mm Hg, although values of 65–70 mm Hg can support adequate tissue oxygenation.

Conventional mechanical ventilation is either volume- or pressure-controlled. Volume-controlled ventilation delivers a consistent tidal volume and minute ventilation to the lungs, but this can result in increased airway pressures depending on the compliance of the lungs. Pressure-controlled ventilation limits the inflating pressure used, but the tidal volume then varies depending on compliance and inspiratory time.[77] High-frequency percussive ventilation (HFPV) is a ventilatory mode that delivers subtidal breaths at a high frequency along with tidal, low-frequency breaths.[78] HFPV has become a preferred mode of ventilation in some burn centers.[22] Proponents suggest that HFPV allows gas exchange at lower peak and mean pressures and may also dislodge and facilitate the removal of secretions and debris in the airways. It appears to be associated with decreased work of breathing, improved oxygenation (higher Pao_2/Fio_2 ratios), and lower peak pressures.[79,80] Pediatric patients at our hospital (SBH-Galveston) managed with HFPV also had a significant reduction in the incidence of pneumonia compared to a conventionally ventilated control group.[80]

High-frequency oscillatory ventilation (HFOV) uses a reciprocating diaphragm to deliver respiratory rates in the

range of 3 to 15 Hz (up to 900 breaths/min) through a standard endotracheal tube. This rate is so fast that the airway pressure merely oscillates around a constant mean airway pressure. A retrospective review of HFOV in severely burned pediatric patients showed significant, early, and sustained improvement in oxygenation.[81]

Airway pressure release ventilation (APRV) is a pressure-controlled time-cycled mode of ventilation that also allows spontaneous breathing during the ventilatory cycle without changing the preset pressure settings.[82] Recruitment of alveoli and oxygenation occur at a high-pressure setting, and ventilation occurs by controlled releases to the lower pressure. The mechanical inspiratory phase can be prolonged to achieve higher mean airway pressures without high peak airway pressures. It has so far shown promising results in trauma patients and pediatric patients with mild to moderate lung disease. Comparable or superior oxygenation values were achieved while using lower peak airway pressures.[83] This mode may be useful in the burn population as a means to ventilate while reducing barotrauma.

Although it has become standard practice to use tidal volumes of 7 mL/kg or less when ventilating patients with acute lung injury or ARDS in order to avoid further damage to the lung, it is occasionally difficult to maintain adequate gas exchange with these small tidal volumes. The hypermetabolic state associated with major burns produces larger amounts of CO_2 that require higher minute ventilation to excrete. A certain amount of permissive hypercapnia can be tolerated safely,[76] which facilitates the use of lower tidal volumes to an extent, but an additional feature of the pathophysiology of inhalation injury is the small airway narrowing by edema, bronchospasm, inflammatory infiltrate, fibrinous exudate, and sloughed epithelium. These small airway changes can require higher pressures to support ventilation. Sousse and colleagues did a retrospective comparison of clinical outcomes of patients with inhalation who were ventilated with high tidal volumes (15 mL/kg) with patients after a change in practice to lower tidal volumes (9 mL/kg). In this retrospective study with historical controls, high tidal volumes were associated with decreased ventilator days, atelectasis, and ARDS. The incidence of pneumothorax was increased with high tidal volumes.[84] Further experience is needed before the use of higher tidal volumes becomes a generally accepted practice.

Mechanical ventilation should be weaned as the patient's condition improves and discontinued as soon as it is no longer necessary. During the weaning process, the Fio_2, PEEP, and rate should be reduced as tolerated until the patient is capable of supporting respiratory requirements without assistance. Criteria for a trial of extubation include ability to protect the airway (awake and relatively alert), cough and deep breath (negative inspiratory pressure >25 cm H_2O), adequate minute ventilation (tidal volume 6 mL/kg and respiratory rate adequate without hypercarbia or tachypnea), adequate oxygenation (Pao_2 >60 mm Hg on Fio_2 ≤0.4), and hemodynamic stability (no vasoactive infusions other than lower dose of dobutamine). The presence of acidemia is a relative contraindication to a trial of extubation, and the decision should take into consideration the patient's physiological reserve and the etiology of the metabolic disturbance. The decision to extubate must also take into consider the metabolic state and burn-related decrease in strength of the patient. Increased generation of CO_2 must be matched by increased minute ventilation and respiratory effort. Work of breathing is often also increased by poor pulmonary compliance and diaphragmatic elevation due to hepatomegaly.[85] At the same time skeletal muscle wasting and decreased strength are also products of the hypermetabolic and catabolic state.[86] If the patient's physiological reserve is marginal it may be best to carefully weigh the risks and benefits of extubation to decide if it is best to continue mechanical ventilation. Once the patient is extubated, supplemental, humidified oxygen should be provided, and the patient should be carefully observed for any signs of respiratory compromise that might necessitate re-intubation.

Extracorporeal membrane oxygenation (ECMO) is a technique that can be used in patients with severe respiratory failure, in which the patient's blood is circulated through an extracorporeal cardiopulmonary bypass circuit that facilitates gas exchange through a semipermeable membrane.[87] While this is taking place, much lower ventilatory pressures and a low Fio_2 can be used to allow the lung to heal without the additional complications of mechanical ventilation. Anticoagulation is necessary during treatment, which makes surgical care of burn wounds difficult. Asmussen et al. have published a meta-analysis of experimental and clinical evidence available for the use of ECMO for treatment of hypoxemic respiratory failure associated with burn and smoke inhalation injury.[88] Interpretation of these data and evaluation of the effectiveness of ECMO in burn patients are limited by the small number of studies and patients. In addition, Asmussen and colleagues point out that those available studies with designs suitable for comparison were performed over a long time period during which ECMO techniques and equipment have varied greatly. This, along with absence of control groups, further complicates comparisons of outcomes. As a result, the available literature is insufficient to provide guidelines. Further experience and research with these improved techniques and equipment is necessary.

Opinions on the use of tracheostomy in burn patients are divided and have fluctuated over the years. The most common indication is a need for prolonged mechanical ventilation. This allows removal of the translaryngeal endotracheal tube, which reduces the chance of laryngeal injury and provides a more secure airway. When multiple surgical treatments are predicted, a tracheostomy tube obviates the need for repeated intubation for each procedure. When prolonged mechanical ventilation is needed, patient comfort can also be enhanced with a tracheostomy, and pulmonary toilet is facilitated. Owing to high rates of pulmonary contamination with burn wound bacterial flora and mortality, tracheostomy was discouraged in the past.[89] More recently, with advances in burn care, several studies have found that the risk of pneumonia is not increased by tracheostomy in burn patients.[90,91] As a result, many burn centers routinely perform tracheostomy not only in patients who require prolonged ventilation but in those with extensive burns who will require multiple anesthetics for surgical procedures. In studies involving small groups of patients, tracheostomy has been used without complications.[91] Tracheostomy is an invasive procedure, however, and in larger

patient populations there is a risk of significant morbidity. Saffle et al. found that burn patients treated with conventional ventilation were extubated sooner than those randomized to early tracheostomy.[92] Because clinical outcomes were otherwise not different between groups, it appears that there was no significant benefit of the more invasive tracheostomy. In the absence of clear evidence of benefit, the use of tracheostomy in burn patients remains a matter of clinical judgment, but, in each case, the risk of potential complications should be considered in the decision.

Potential Future Therapeutic Strategies

The pathophysiological processes described offer the possibility for future development of numerous pharmacological interventions. One of the most obvious areas for treatment would be the use of antioxidants. Burned patients are immensely depleted of antioxidants, especially vitamin E.[93,94] In this clinical scenario ROS and RNS play major roles in organ damage in addition to mediation of the pathophysiology.[47] Nebulization of γ-tocopherol, a form of vitamin E that scavenges both ROS and RNS, has been shown to be beneficial.[95,96] On the other hand, inhibitors of NOS1,[54,97] NOS2,[98] and PARP,[99] as well as compounds that catalyze the breakdown of peroxynitrite, have also been shown to be effective in reversing the acute changes in pathophysiology.[42,45,98,99]

Recently there have been reports that hydrogen sulfide may have therapeutic benefits in lung injury.[100] We have tested hydrogen sulfide in both murine and ovine models of burn injury and found therapeutic benefit.[101,102] As we have learned more about the pathophysiology and treatment of inhalation injury, there have been more survivors. Examination of these individuals several years after injury showed that many had evidence of excessive deposition of collagen in their lungs.[103] Perhaps initial treatment of patients might have an important effect on long-term pathophysiology. This is certainly an area for future investigation. NOS, the enzyme that plays a major role in the acute aspects of injury, has the amino acid arginine as its substrate, as does arginase, the enzyme that is the basis of collagen deposition.[104] Thus inhibition of NOS could make more arginine available for the arginase, and hence increase collagen deposition. In a consensus conference, the faculty from the Shriners Hospitals met to discuss potential therapies for inhalation injury.[105–108] Clinical trials will be necessary before the effectiveness of these novel interventions is established.

Long-Term Changes in Pulmonary Function

Although the pathophysiology associated with the acute phase of inhalation injury has been studied extensively both clinically and through experimental models, the same cannot be said for the long-term alterations in pulmonary function that occur in the months and years following a burn and inhalation injury. Palmieri has discussed some of the theoretical reasons why it is difficult to evaluate the long-term clinical effects of inhalation injuries related to burns.[109] Any study of long-term changes in pulmonary function after inhalation injury must distinguish between changes due to the effects of inhaled irritants at the time of injury and those that result from ventilator-induced lung injury or acute lung injury due to the systemic inflammatory response syndrome (SIRS) or sepsis. In addition, outcomes may change over time due to alterations in clinical management. Massive burn injury also impairs muscle mass and strength along with chest wall compliance, which can affect respiratory effort even in the absence of inhalation injury. As Palmieri has pointed out, none of the previous reports of long-term pulmonary changes after inhalation injury relates the degree of acute pulmonary insult to the long-term changes.[109] Pre-existing lung disease was also not considered in previous studies. Most studies involved relatively small groups of patients studied at different times and by different means, which makes it difficult to compare results between studies. In a more recent Canadian review of ARDS incidence in 162 mechanically ventilated burn patients, Cartotto et al.[110] found a significant correlation of development of ARDS with the size of burn injury, size of full-thickness injury, and the duration of intubation, but not with the incidence of inhalation injury. The authors concluded that ARDS develops early after burn and that the extent of full-thickness burn predicted development of moderate to severe ARDS. Increasing severity of ARDS based upon the Berlin definition was associated with a significantly greater duration of mechanical ventilation and a trend toward higher mortality.

One way post-injury pulmonary function has been shown to be manifest is by a hyperactive or bronchospastic condition of the airways. This was shown to persist for at least 6 months in one study, along with inflammatory changes in the bronchial mucosa and elevated inflammatory cytokine tumor necrosis-α (TNF-α), interferon (IFN-γ), and interleukin (IL)-2 levels in serum and bronchioalveolar lavage fluid. The majority of subjects, however, had normal pulmonary function tests.[111]

Longer-term studies have in some cases shown the development of obstructive and restrictive patterns on pulmonary function testing, indicating that normal lung function may not always be regained following recovery from inhalation injury.[103,112,113] In a pediatric burn cohort, no difference in exercise tolerance was noted between children who had sustained an inhalation injury and those who had not. However, those children who had had an inhalation injury achieved their goal with a significantly higher respiratory rate and had a higher incidence of abnormal lung function.[113] Conversely an adult study found no evidence of altered respiratory function after inhalation injury or any significant exercise intolerance in those tested.[114]

Damage to the larynx by inhaled toxins and thermal injury, and also by intubation as a treatment for inhalation injury or upper airway edema, is common and can result in persistent hoarseness, dysphonia, or even exercise intolerance due to dyspnea on exertion. Injury to the laryngeal mucosa can cause scarring that can affect the flexibility and vibratory capacity of the vocal cords and also their ability to open and close properly. Laryngeal morbidity can be severe, as seen in Fig. 17.4. As a result, voice production may be affected, and this may not resolve without

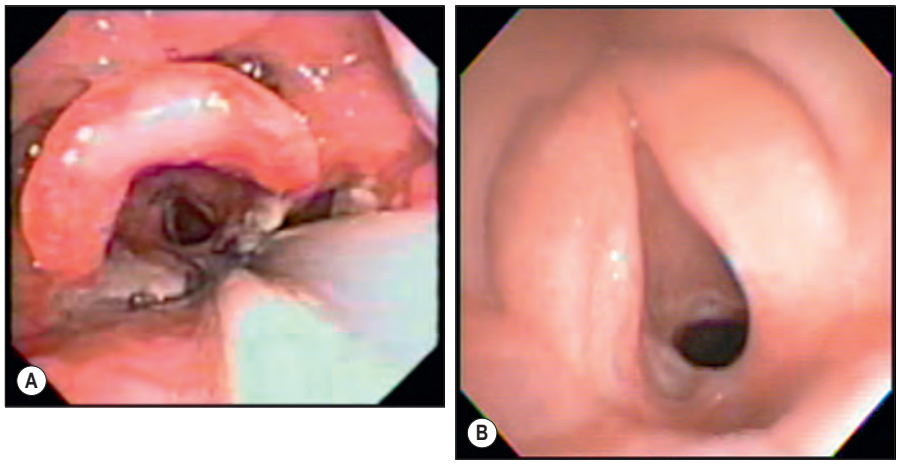

Fig. 17.4 (A) Thermal necrosis of laryngeal structures as seen in this photograph is an indication for tracheostomy to minimize laryngeal injury. A tracheostomy was performed on this patient soon after admission, and, after recovery from his burns and decannulation of his trachea, his voice was normal. **(B)** Thermal and mechanical injury to the larynx can result in posterior glottic scars and webs, as in this endoscopic image. Early diagnosis of injury can facilitate care to minimize long-term effects.

treatment. Some of the phonation problems can be helped by voice therapy, and some of the laryngeal scarring may be amenable to surgical or laser excision.[115] It is important to recognize laryngeal injuries as early as possible. When recognized, tracheostomy can help minimize exacerbation of the injury from a translaryngeal airway. Consultation with a laryngologist may make such interventions more timely.

Complete references available online
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References

1. Colohan SM. Predicting prognosis in thermal burns with associated inhalational injury: a systematic review of prognostic factors in adult burn victims. *J Burn Care Res*. 2010;31(4):529-539.
2. Walker PF, Buehner MF, Wood LA, et al. Diagnosis and management of inhalation injury: an updated review. *Crit Care*. 2015;19:351.
3. Moritz AR, Henriques FC, McLean R. The effects of inhaled heat on the air passages and lungs: an experimental investigation. *Am J Pathol*. 1945;21(2):311-331.
4. Demling RH. Smoke inhalation lung injury: an update. *Eplasty*. 2008;8:e27.
5. Smith DL, Cairns BA, Ramadan F, et al. Effect of inhalation injury, burn size, and age on mortality: a study of 1447 consecutive burn patients. *J Trauma*. 1994;37(4):655-659.
6. Haik J, Liran A, Tessone A, et al. Trauma burns in Israel: demographic, etiologic and clinical trends, 1997–2003. *Isr Med Assoc J*. 2007;9(9):659-662.
7. Luo G, Peng Y, Yuan Z, et al. Inhalation injury in southwest China – the evolution of care. *Burns*. 2010;36(4):506-510.
8. Shirani KZ, Pruitt BA Jr, Mason AD Jr. The influence of inhalation injury and pneumonia on burn mortality. *Ann Surg*. 1987; 205(1):82-87.
9. Palmieri TL. Inhalation injury: research progress and needs. *J Burn Care Res*. 2007;28(4):549-554.
10. Navar PD, Saffle JR, Warden GD. Effect of inhalation injury on fluid resuscitation requirements after thermal injury. *Am J Surg*. 1985;150(6):716-720.
11. Dai NT, Chen TM, Cheng TY, et al. The comparison of early fluid therapy in extensive flame burns between inhalation and noninhalation injuries. *Burns*. 1998;24(7):671-675.
12. Tasaka S, Kanazawa M, Mori M, et al. Long-term course of bronchiectasis and bronchiolitis obliterans as late complication of smoke inhalation. *Respiration*. 1995;62(1):40-42.
13. Woodson LC. Diagnosis and grading of inhalation injury. *J Burn Care Res*. 2009;30(1):143-145.
14. Steinvall I, Bak Z, Sjoberg F. Acute respiratory distress syndrome is as important as inhalation injury for the development of respiratory dysfunction in major burns. *Burns*. 2008;34(4):441-451.
15. Mosier MJ, Peter T, Gamelli RL. Need for mechanical ventilation in pediatric scald burns: why it happens and why it matters. *J Burn Care Res*. 2016;37(1):e1-e6.
16. Wittram C, Kenny JB. The admission chest radiograph after acute inhalation injury and burns. *Br J Radiol*. 1994;67(800):751-754.
17. Dye DJ, Milling MA, Emmanuel ER, Craddock KV. Toddlers, teapots, and kettles: beware intraoral scalds. *BMJ*. 1990;300(6724):597-598.
18. Madnani DD, Steele NP, de Vries E. Factors that predict the need for intubation in patients with smoke inhalation injury. *Ear Nose Throat J*. 2006;85(4):278-280.
19. Lee MJ, O'Connell DJ. The plain chest radiograph after acute smoke inhalation. *Clin Radiol*. 1988;39(1):33-37.
20. Hunt JL, Agee RN, Pruitt BA Jr. Fiberoptic bronchoscopy in acute inhalation injury. *J Trauma*. 1975;15(8):641-649.
21. Muehlberger T, Kunar D, Munster A, Couch M. Efficacy of fiberoptic laryngoscopy in the diagnosis of inhalation injuries. *Arch Otolaryngol Head Neck Surg*. 1998;124(9):1003-1007.
22. Cancio LC. Airway management and smoke inhalation injury in the burn patient. *Clin Plast Surg*. 2009;36(4):555-567.
23. Zak AL, Harrington DT, Barillo DJ, et al. Acute respiratory failure that complicates the resuscitation of pediatric patients with scald injuries. *J Burn Care Rehabil*. 1999;20(5):391-399.
24. Haponik EF. Diagnosis, impact, and classification of inhalation injury. In: Haponik EF, ed. *Respiratory Injury: Smoke Inhalation and Burns*. New York: McGraw-Hill; 1990:17-45.
25. Hassan Z, Wong JK, Bush J, Bayat A, Dunn KW. Assessing the severity of inhalation injuries in adults. *Burns*. 2010;36(2):212-216.
26. Spano S, Hanna S, Li Z, Wood D, Cartotto R. Does bronchoscopic evaluation of inhalation injury severity predict outcome? *J Burn Care Res*. 2016;37(1):1-11.
27. Endorf FW, Gamelli RL. Inhalation injury, pulmonary perturbations, and fluid resuscitation. *J Burn Care Res*. 2007;28(1):80-83.
28. Albright JM, Davis CS, Bird MD, et al. The acute pulmonary inflammatory response to the graded severity of smoke inhalation injury. *Crit Care Med*. 2012;40(4):1113-1121.
29. Mosier MJ, Pham TN, Park DR, et al. Predictive value of bronchoscopy in assessing the severity of inhalation injury. *J Burn Care Res*. 2012;33(1):65-73.
30. Cancio LC, Chavez S, Alvarado-Ortega M, et al. Predicting increased fluid requirements during the resuscitation of thermally injured patients. *J Trauma*. 2004;56(2):404-413, discussion 413-414.
31. Mackie DP, Spoelder EJ, Paauw RJ, Knape P, Boer C. Mechanical ventilation and fluid retention in burn patients. *J Trauma*. 2009;67(6):1233-1238, discussion 1238.
32. Mackie DP. Inhalation injury or mechanical ventilation: which is the true killer in burn patients? *Burns*. 2013;39(7):1329-1330.
33. Moylan JA Jr, Wilmore EW, Mouton DE, Pruitt BA Jr. Early diagnosis of inhalation injury using 133 xenon lung scan. *Ann Surg*. 1972;176(4):477-484.
34. Lin WY, Kao CH, Wang SJ. Detection of acute inhalation injury in fire victims by means of technetium-99m DTPA radioaerosol inhalation lung scintigraphy. *Eur J Nucl Med*. 1997;24(2):125-129.
35. Yamamura H, Morioka T, Hagawa N, Yamamoto T, Mizobata Y. Computed tomographic assessment of airflow obstruction in smoke inhalation injury: relationship with the development of pneumonia and injury severity. *Burns*. 2015;41(7):1428-1434.
36. Demling RH. Smoke inhalation injury. *New Horiz*. 1993;1(3):422-434.
37. Rehberg S, Maybauer MO, Enkhbaatar P, et al. Pathophysiology, management and treatment of smoke inhalation injury. *Expert Rev Respir Med*. 2009;3(3):283-297.
38. Shimazu T, Yukioka T, Ikeuchi H, et al. Ventilation-perfusion alterations after smoke inhalation injury in an ovine model. *J Appl Physiol*. 1996;81(5):2250-2259.
39. Traber DL, Hawkins HK, Enkhbaatar P, et al. The role of the bronchial circulation in the acute lung injury resulting from burn and smoke inhalation. *Pulm Pharmacol Ther*. 2007;20(2):163-166.
40. Abdi S, Herndon D, McGuire J, Traber L, Traber DL. Time course of alterations in lung lymph and bronchial blood flows after inhalation injury. *J Burn Care Rehabil*. 1990;11(6):510-515.
41. Stothert JC Jr, Ashley KD, Kramer GC, et al. Intrapulmonary distribution of bronchial blood flow after moderate smoke inhalation. *J Appl Physiol*. 1990;69(5):1734-1739.
42. Lange M, Szabo C, Enkhbaatar P, et al. Beneficial pulmonary effects of a metalloporphyrinic peroxynitrite decomposition catalyst in burn and smoke inhalation injury. *Am J Physiol Lung Cell Mol Physiol*. 2011;300(2):L167-L175.
43. Lange M, Connelly R, Traber DL, et al. Time course of nitric oxide synthases, nitrosative stress, and poly(ADP ribosylation) in an ovine sepsis model. *Crit Care*. 2010;14(4):R129.
44. Espinoza LA, Smulson ME, Chen Z. Prolonged poly(ADP-ribose) polymerase-1 activity regulates JP-8-induced sustained cytokine expression in alveolar macrophages. *Free Radic Biol Med*. 2007;42(9):1430-1440.
45. Saunders FD, Westphal M, Enkhbaatar P, et al. Molecular biological effects of selective neuronal nitric oxide synthase inhibition in ovine lung injury. *Am J Physiol Lung Cell Mol Physiol*. 2010;298(3): L427-L436.
46. Lange M, Enkhbaatar P, Nakano Y, Traber DL. Role of nitric oxide in shock: the large animal perspective. *Front Biosci (Landmark Ed)*. 2009;14:1979-1989.
47. Rehberg S, Maybauer MO, Maybauer DM, et al. The role of nitric oxide and reactive nitrogen species in experimental ARDS. *Front Biosci (Schol Ed)*. 2010;2:18-29.
48. Westphal M, Cox RA, Traber LD, et al. Combined burn and smoke inhalation injury impairs ovine hypoxic pulmonary vasoconstriction. *Crit Care Med*. 2006;34(5):1428-1436.
49. Efimova O, Volokhov AB, Iliaifar S, Hales CA. Ligation of the bronchial artery in sheep attenuates early pulmonary changes following exposure to smoke. *J Appl Physiol*. 2000;88(3):888-893.
50. Hamahata A, Enkhbaatar P, Sakurai H, Nozaki M, Traber DL. Sclerosis therapy of bronchial artery attenuates acute lung injury induced by burn and smoke inhalation injury in ovine model. *Burns*. 2010;36(7):1042-1049.
51. Baile EM, Dahlby RW, Wiggs BR, Pare PD. Role of tracheal and bronchial circulation in respiratory heat exchange. *J Appl Physiol*. 1985;58(1):217-222.
52. Lange M, Enkhbaatar P, Traber DL, et al. Role of calcitonin gene-related peptide (CGRP) in ovine burn and smoke inhalation injury. *J Appl Physiol*. 2009;107(1):176-184.
53. Westphal M, Enkhbaatar P, Schmalstieg FC, et al. Neuronal nitric oxide synthase inhibition attenuates cardiopulmonary dysfunctions after combined burn and smoke inhalation injury in sheep. *Crit Care Med*. 2008;36(4):1196-1204.

54. Enkhbaatar P, Connelly R, Wang J, et al. Inhibition of neuronal nitric oxide synthase in ovine model of acute lung injury. *Crit Care Med*. 2009;37(1):208-214.
55. Cancio LC, Batchinsky AI, Dubick MA, et al. Inhalation injury: pathophysiology and clinical care proceedings of a symposium conducted at the Trauma Institute of San Antonio, San Antonio, TX, USA on 28 March 2006. *Burns*. 2007;33(6):681-692.
56. Eastman AL, Arnoldo BA, Hunt JL, Purdue GF. Pre-burn center management of the burned airway: do we know enough? *J Burn Care Res*. 2010;31(5):701-705.
57. Haponik EF, Meyers DA, Munster AM, et al. Acute upper airway injury in burn patients. Serial changes of flow-volume curves and nasopharyngoscopy. *Am Rev Respir Dis*. 1987;135(2):360-366.
58. Piatkowski A, Ulrich D, Grieb G, Pallua N. A new tool for the early diagnosis of carbon monoxide intoxication. *Inhal Toxicol*. 2009;21(13):1144-1147.
59. Kealey GP. Carbon monoxide toxicity. *J Burn Care Res*. 2009;30(1): 146-147.
60. Klassen CD. Nonmetallic envornmental toxicants. In: Hardman JG, Limbird LE, Gilman AG, eds. *Goodman & Gilman's the Pharmacological Basis of Therapeutics*. New York: McGraw Hill; 2001:1892-1893.
61. Herndon DN, Traber DL, Traber LD. The effect of resuscitation on inhalation injury. *Surgery*. 1986;100(2):248-251.
62. Herndon DN, Barrow RE, Linares HA, et al. Inhalation injury in burned patients: effects and treatment. *Burns Incl Therm Inj*. 1988;14(5):349-356.
63. Herndon DN, Thompson PB, Traber DL. Pulmonary injury in burned patients. *Crit Care Clin*. 1985;1(1):79-96.
64. Desai MH, Rutan RL, Herndon DN. Managing smoke inhalation injuries. *Postgrad Med*. 1989;86(8):69-70, 73-76.
65. Silverberg R, Johnson J, Gorga D, Nagler W, Goodwin C. A survey of the prevalence and application of chest physical therapy in U.S. burn centers. *J Burn Care Rehabil*. 1995;16(2 Pt 1):154-159.
66. Koga T, Kawazu T, Iwashita K, Yahata R. Pulmonary hyperinflation and respiratory distress following solvent aspiration in a patient with asthma: expectoration of bronchial casts and clinical improvement with high-frequency chest wall oscillation. *Respir Care*. 2004;49(11):1335-1338.
67. Desai MH, Mlcak R, Richardson J, Nichols R, Herndon DN. Reduction in mortality in pediatric patients with inhalation injury with aerosolized heparin/N-acetylcystine [correction of acetylcystine] therapy. *J Burn Care Rehabil*. 1998;19(3):210-212.
68. Miller AC, Elamin EM, Suffredini AF. Inhaled anticoagulation regimens for the treatment of smoke inhalation-associated acute lung injury: a systematic review. *Crit Care Med*. 2014;42(2):413-419.
69. Bandeshe H, Boots R, Dulhunty J, et al. Is inhaled prophylactic heparin useful for prevention and Management of Pneumonia in ventilated ICU patients?: The IPHIVAP investigators of the Australian and New Zealand Intensive Care Society Clinical Trials Group. *J Crit Care*. 2016;34:95-102.
70. Sheridan RL. Airway management and respiratory care of the burn patient. *Int Anesthesiol Clin*. 2000;38(3):129-145.
71. Dries DJ. Key questions in ventilator management of the burn-injured patient (first of two parts). *J Burn Care Res*. 2009;30(1):128-138.
72. Dries DJ. Key questions in ventilator management of the burn-injured patient (second of two parts). *J Burn Care Res*. 2009;30(2):211-220.
73. Chung KK, Rhie RY, Lundy JB, et al. A survey of mechanical ventilator practices across burn centers in North America. *J Burn Care Res*. 2016;37(2):e131-e139.
74. Schmidt GA, Girard TD, Kress JP, et al. Liberation from mechanical ventilation in critically ill adults: executive summary of an official American College of Chest Physicians/American Thoracic Society Clinical Practice Guideline. *Chest*. 2017;151(1):160-165.
75. Peck MD, Koppelman T. Low-tidal-volume ventilation as a strategy to reduce ventilator-associated injury in ALI and ARDS. *J Burn Care Res*. 2009;30(1):172-175.
76. Sheridan RL, Kacmarek RM, McEttrick MM, et al. Permissive hypercapnia as a ventilatory strategy in burned children: effect on barotrauma, pneumonia, and mortality. *J Trauma*. 1995;39(5):854-859.
77. McCall JE, Cahill TJ. Respiratory care of the burn patient. *J Burn Care Rehabil*. 2005;26(3):200-206.
78. Allan PF, Osborn EC, Chung KK, Wanek SM. High-frequency percussive ventilation revisited. *J Burn Care Res*. 2010;31(4):510-520.
79. Moncrief JA. Complications of burns. *Ann Surg*. 1958;147(4): 443-475.
80. Cortiella J, Mlcak R, Herndon D. High frequency percussive ventilation in pediatric patients with inhalation injury. *J Burn Care Rehabil*. 1999;20(3):232-235.
81. Greathouse ST, Hadad I, Zieger M, et al. High-frequency oscillatory ventilators in burn patients: experience of Riley Hospital for Children. *J Burn Care Res*. 2012;33(3):425-435.
82. Daoud EG, Farag HL, Chatburn RL. Airway pressure release ventilation: what do we know? *Respir Care*. 2012;57(2):282-292.
83. Dart BW, Maxwell RA, Richart CM, et al. Preliminary experience with airway pressure release ventilation in a trauma/surgical intensive care unit. *J Trauma*. 2005;59(1):71-76.
84. Sousse LE, Herndon DN, Andersen CR, et al. High tidal volume decreases adult respiratory distress syndrome, atelectasis, and ventilator days compared with low tidal volume in pediatric burned patients with inhalation injury. *J Am Coll Surg*. 2015;220(4):570-578.
85. Barrow RE, Hawkins HK, Aarsland A, et al. Identification of factors contributing to hepatomegaly in severely burned children. *Shock*. 2005;24(6):523-528.
86. Hart DW, Wolf SE, Chinkes DL, et al. Determinants of skeletal muscle catabolism after severe burn. *Ann Surg*. 2000;232(4):455-465.
87. Thompson JT, Molnar JA, Hines MH, Chang MC, Pranikoff T. Successful management of adult smoke inhalation with extracorporeal membrane oxygenation. *J Burn Care Rehabil*. 2005;26(1):62-66.
88. Asmussen S, Maybauer DM, Fraser JF, et al. Extracorporeal membrane oxygenation in burn and smoke inhalation injury. *Burns*. 2013;39(3):429-435.
89. Eckhauser FE, Billote J, Burke JF, Quinby WC. Tracheostomy complicating massive burn injury. A plea for conservatism. *Am J Surg*. 1974;127(4):418-423.
90. Coln CE, Purdue GF, Hunt JL. Tracheostomy in the young pediatric burn patient. *Arch Surg*. 1998;133(5):537-539, discussion 539-540.
91. Palmieri TL, Jackson W, Greenhalgh DG. Benefits of early tracheostomy in severely burned children. *Crit Care Med*. 2002;30(4):922-924.
92. Saffle JR, Morris SE, Edelman L. Early tracheostomy does not improve outcome in burn patients. *J Burn Care Rehabil*. 2002;23(6):431-438.
93. Nguyen TT, Cox CS, Traber DL, et al. Free radical activity and loss of plasma antioxidants, vitamin E, and sulfhydryl groups in patients with burns: the 1993 Moyer Award. *J Burn Care Rehabil*. 1993;14(6):602-609.
94. Traber MG, Leonard SW, Traber DL, et al. *Am J Clin Nutr*. 2010;35(3):474-483.
95. Morita N, Shimoda K, Traber MG, et al. *Redox Rep*. 2006;11(2):61-70.
96. Hamahata A, Enkhbaatar P, Kraft ER, et al. gamma-Tocopherol nebulization by a lipid aerosolization device improves pulmonary function in sheep with burn and smoke inhalation injury. *Free Radic Biol Med*. 2008;45(4):425-433.
97. Lange M, Hamahata A, Enkhbaatar P, et al. Beneficial effects of concomitant neuronal and inducible nitric oxide synthase inhibition in ovine burn and inhalation injury. *Shock*. 2011;35(6):626-631.
98. Enkhbaatar P, Murakami K, Shimoda K, et al. Inducible nitric oxide synthase dimerization inhibitor prevents cardiovascular and renal morbidity in sheep with combined burn and smoke inhalation injury. *Am J Physiol Heart Circ Physiol*. 2003;285(6):H2430-H2436.
99. Shimoda K, Murakami K, Enkhbaatar P, et al. Effect of poly(ADP ribose) synthetase inhibition on burn and smoke inhalation injury in sheep. *Am J Physiol Lung Cell Mol Physiol*. 2003;285(1):L240-L249.
100. Szabo C. Hydrogen sulphide and its therapeutic potential. *Nat Rev Drug Discov*. 2007;6(11):917-935.
101. Esechie A, Kiss L, Olah G, et al. Protective effect of hydrogen sulfide in a murine model of acute lung injury induced by combined burn and smoke inhalation. *Clin Sci*. 2008;115(3):91-97.
102. Esechie A, Enkhbaatar P, Traber DL, et al. Beneficial effect of a hydrogen sulphide donor (sodium sulphide) in an ovine model of burn- and smoke-induced acute lung injury. *Br J Pharmacol*. 2009;158(6):1442-1453.
103. Mlcak R, Desai MH, Robinson E, Nichols R, Herndon DN. Lung function following thermal injury in children–an 8-year follow up. *Burns*. 1998;24(3):213-216.
104. Sousse LE, Yamamoto Y, Enkhbaatar P, et al. Acute lung injury-induced collagen deposition is associated with elevated asymmetric dimethylarginine and arginase activity. *Shock*. 2011;35(3):282-288.
105. Enkhabaatar P, Herndon DN, Traber DL. Use of nebulized heparin in the treatment of smoke inhalation injury. *J Burn Care Res*. 2009;30(1):159-162.

106. Palmieri TL, Enkhbaatar P, Sheridan R, Traber DL, Greenhalgh DG. Studies of inhaled agents in inhalation injury. *J Burn Car Res*. 2009;30(1):169-171.
107. Palmieri TL, Warner P, Mlcak RP, et al. Inhalation injury in children: a 10 year experience at Shriners Hospitals for Children. *J Burn Care Res*. 2009;30(1):206-208.
108. Traber DL, Traber MG, Enkhbaatar P, Herndon DN. Tocopherol as treatment for lung injury associated with burn and smoke inhalation. *J Burn Care Res*. 2009;30(1):164-165.
109. Palmieri TL. Long term outcomes after inhalation injury. *J Burn Care Res*. 2009;30(1):201-203.
110. Cartott R, Li Z, Hanna S, et al. The acute respiratory distress syndrome (ARDS) in mechanically ventilated burn patients: an analysis of risk factors, clinical features, and outcomes using the Berlin ARDS definition. *Burns*. 2016;42(7):1423-1432.
111. Park GY, Park JW, Jeong DH, Jeong SH. Prolonged airway and systemic inflammatory reactions after smoke inhalation. *Chest*. 2003;123(2):475-480.
112. McElroy K, Alvarado MI, Hayward PG, et al. Exercise stress testing for the pediatric patient with burns: a preliminary report. *J Burn Care Rehabil*. 1992;13(2 Pt 1):236-238.
113. Desai MH, Mlcak RP, Robinson E, et al. Does inhalation injury limit exercise endurance in children convalescing from thermal injury? *J Burn Care Rehabil*. 1993;14(1):12-16.
114. Bourbeau J, Lacasse Y, Rouleau MY, Boucher S. Combined smoke inhalation and body surface burns injury does not necessarily imply long-term respiratory health consequences. *Eur Respir J*. 1996;9(7):1470-1474.
115. Casper JK, Clark WR, Kelley RT, Colton RH. Laryngeal and phonatory status after burn/inhalation injury: a long term follow-up study. *J Burn Care Rehabil*. 2002;23(4):235-243.

18 Respiratory Care

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Introduction

The multitude of respiratory complications caused by smoke inhalation, flame burns, and their treatment epitomize the clinical challenges that confront health care workers. Smoke inhalation injury and its sequelae impose demands on the practitioners who play a central role in its clinical management. These demands may range from intubation and resuscitation of victims in the emergency room to assistance with diagnostic bronchoscopies, performance of pulmonary function studies, monitoring of arterial blood gases, airway maintenance, chest physiotherapy, and mechanical ventilator management.[1] Additional demands are placed on the practitioners in the rehabilitation phase in determining disability or limitations diagnosed by pulmonary function studies or cardiopulmonary stress testing. It is imperative that a well-organized, protocol-driven approach to respiratory care of the burn patient be utilized so that improvements can be made and the morbidity and mortality associated with inhalation injury can be reduced (Box 18.1). This chapter provides an overview of the common hands-on approaches to the treatment of inhalation injury, with emphasis on mucociliary clearance techniques, pharmacologic adjuncts, mechanical ventilation, infection control, and the late complications associated with inhalation injury.

Bronchial Hygiene Therapy

Airway clearance techniques are an essential component of respiratory management of patients with smoke inhalation. *Bronchial hygiene therapy* is a term used to describe several of the modalities intended to accomplish this goal. Therapeutic coughing, chest physiotherapy, bronchial drainage and positioning, percussion and vibration, early ambulation, airway suctioning, and therapeutic bronchoscopy have been effective in the removal of retained secretions.

THERAPEUTIC COUGHING

Therapeutic coughing functions to promote airway clearance of excess mucus and fibrin casts in the tracheal bronchial tree. Impairing the cough mechanism may result in retained secretions, bronchial obstruction, atelectasis, and/or pneumonia. A cough can either be a reflex or a voluntary action. The mechanisms of a cough include:

a. a deep inspiration,
b. the closure of the glottis,
c. contraction of the muscles in the chest wall, abdomen, and pelvic floor,
d. opening of the glottis, and
e. a rapid expulsive exhalation phase.

During a cough, alveolar, pleural, and subglottic pressures may rise as much as 200 cm H_2O. A failure of the cough mechanism may be due to an impairment of any step in the sequence described. When this occurs, it is necessary to perform techniques which are used to improve the cough.

Series of Three Coughs

The patient is asked to start a small breath and small cough, followed by a bigger breath and harder cough, and finally a very deep breath and hard cough. This technique is particularly effective for postoperative patients who tend to splint from pain.[2]

Tracheal Tickle

The respiratory therapist places their index and middle finger flat in the patient's sternal notch and gently massages inward in a circular fashion over the trachea. This is most effective with obtunded patients or with patients recovering from anesthesia.[2]

Cough Stimulation

Patients with artificial airways cannot cough normally since a tube is placed either between their vocal cords (endotracheal tube) or below their cords (tracheostomy). Adequate pressure cannot be built up without the cords in close proximity. A cough may be stimulated by inflating the cuff on the tube, giving a large and rapid inspiration with the manual resuscitation bag, holding the breath for 1–2 s, and rapidly allowing the bag to release and exhalation to ensue. This technique is normally performed by two persons, and it is made more effective with one therapist performing vibration and chest compressions from the time of the inspiratory hold all during exhalation.[2] Cough and deep breathing exercises are encouraged every 2 h to aid in removing retained secretions.

CHEST PHYSIOTHERAPY

The definition of chest physiotherapy has progressed to gravity-assisted bronchial drainage with chest percussion and vibrations. Studies have shown that the combination of techniques are effective in secretion removal.[3–6]

Bronchial Drainage/Positioning

Bronchial drainage/positioning is a therapeutic modality that uses gravity-assisted positioning designed to improve pulmonary hygiene in patients with inhalation injury or retained secretions. Studies have shown that a patient's

Box 18.1 Inhalation Injury Treatment Protocol

- Titrate humidified oxygen to maintain SaO_2s >90%
- Cough, deep breath exercises every 2 h
- Turn patient side to side every 2 h
- Chest physiotherapy every 4 h
- Aerosolize 3 cc of 20% N-acetylcysteine every 4 h with a bronchodilator
- Alternate aerosolizing 5000 units of heparin with 3 cc of normal saline every 4 h
- Nasotracheal suctioning as needed
- Early ambulation on postoperative day 5
- Sputum cultures for intubated patients every M-W-F
- Pulmonary function studies prior to discharge and at outpatient visits
- Patient/family education regarding inhalation injury
- The protocol is continued for 7 days.

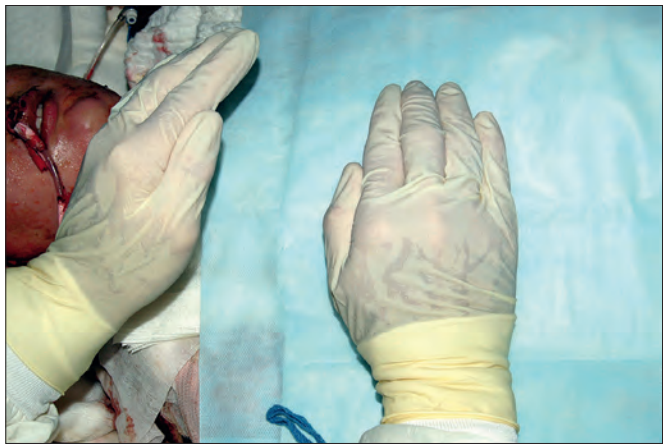

Fig. 18.2 Chest physiotherapy techniques.

Fig. 18.1 Patient positioning for secretion mobilization.

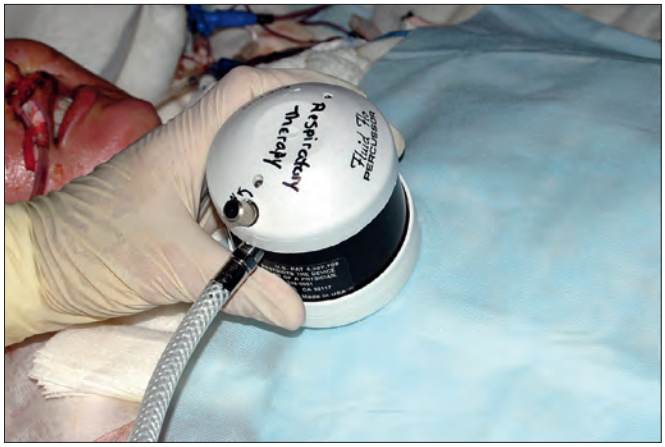

Fig. 18.3 Gentle mechanical chest vibrations.

arterial oxygenation may fall during bronchial drainage/positioning.[7] Therefore, it is common practice in intensive care units to turn patients side to side every 2 h to aid in mobilizing secretions (Fig. 18.1).

Percussion

Percussion aids in the removal of secretions from the tracheal bronchial tree. It is performed by cupping the hand to allow a cushion of air to enter between the therapist's hand and the patient. If this is done properly, a popping sound will be heard when the patient is percussed. There should be a towel between the patient and the therapist's hand in order to prevent irritation of the skin.[8] Percussion is applied over the surface landmarks of the bronchial segments that are being drained. The hands rhythmically and alternately strike the chest wall. Incisions, skin grafts, and bony prominences should be avoided during percussion (Fig. 18.2).

Vibration/Shaking

Vibration/shaking is a movement used to move loose secretions to larger airways so that they can be coughed up or removed by suctioning. Vibration involves the rapid shaking of the chest wall during exhalation. The percussor vibrates the thoracic cage by placing both hands over the percussed areas and vibrating into the patient, isometrically contracting or tensing the muscles of their arms and shoulders. Mechanical vibrations have been reported to be clinically effective. Gentle mechanical vibration may be indicated for patients who cannot tolerate manual percussion (Fig. 18.3). Chest physiotherapy techniques should be used every 2–4 h for patients with retained secretions.

EARLY AMBULATION

Early ambulation is another effective means of preventing respiratory complications. Patients routinely should be helped out of bed on postoperative days 3–5, and they should be encouraged to ambulate and sit in a chair. With the appropriate use of analgesics, even patients on continuous mechanical ventilation can be helped out of bed and into a chair (Fig. 18.4). The rocking chair (Fig. 18.5) has several beneficial effects:

- the patient can breathe with regions of the lungs that are normally hyperventilated,
- muscular strength and tone are preserved, and
- contractions are prevented and exercise tolerance is maintained.[9]

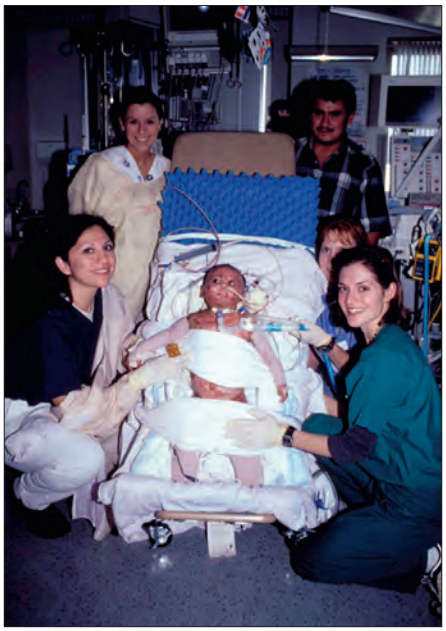

Fig. 18.4 Early ambulation.

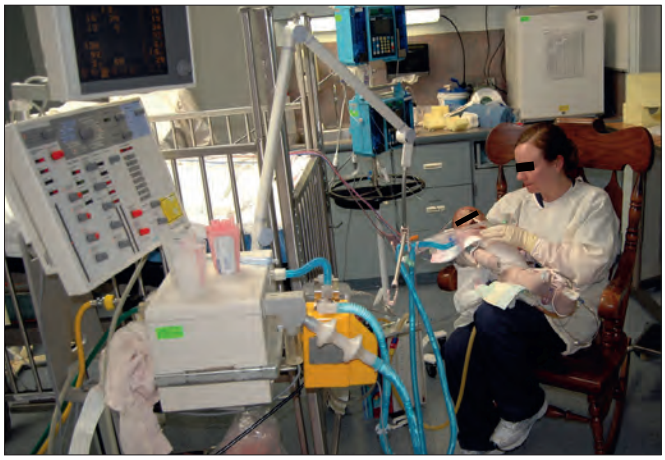

Fig. 18.5 Patient up out of bed, secretions being mobilized by rocking, and chest physiotherapy techniques.

AIRWAY SUCTIONING

Airway suctioning is another method of clearing an airway. Normal bronchial hygiene is usually accomplished by the mucociliary escalator process. When these processes are not effective in maintaining a clear airway, tracheobronchial suctioning is recommended.[10–13] Nasotracheal suctioning is intended to remove accumulated secretions and other foreign material from the trachea that cannot be removed by the patient's spontaneous cough or by less invasive procedures. Nasotracheal suctioning refers to the insertion of a suction catheter through the nasal passages and pharynx into the trachea in order to aspirate secretions or foreign material.

The first step in this process is to hyperoxygenate the patient with 100% oxygen. The patient should be positioned in the Fowler's position, and the catheter slowly advanced through the nares to a point just above the larynx. The operator then listens for air sounds at the proximal end of the catheter. When airflow is felt to be strongest and respiratory sounds are loudest, the tip of the catheter is immediately above the epiglottis. On inspiration, the catheter is advanced into the trachea. After the vocal cords have been passed, a few deep breaths are allowed and the patient is reoxygenated. Suction begins while the catheter is slowly withdrawn from the trachea. The patient should not be suctioned for more than 15 s without being reoxygenated.

Suctioning is not without potential hazards.[14,15] Complications include irritation of the nasotracheal mucosa with bleeding, abrupt drops in P_{O_2}, vagal stimulation, and bradycardia. Preoxygenating and limiting suction time have been shown to decrease or eliminate the fall in the P_{O_2}.[12–14] Sputum cultures should be performed for microbiological identification when they are clinically indicated.

THERAPEUTIC BRONCHOSCOPY

When all other techniques fail to remove secretions, the use of the fiberoptic bronchoscope may be beneficial. In addition to its diagnostic functions, bronchoscopy retains important therapeutic applications. The fiberoptic bronchoscope is small in diameter, flexible, and has a steerable tip that can be maneuvered into the fourth- or fifth-order bronchi for examination or specimen removal. Copious secretions encountered in patients with inhalation injury may require repeated bronchoscopic procedures when more conservative methods are unsuccessful.

PHARMACOLOGIC ADJUNCTS

Bronchodilators can be helpful in select cases. Inhalation injury to the lower airways results in a chemical tracheobronchitis, which can produce wheezing and bronchospasms. Most drugs used in the management of bronchospasms are believed to control bronchial muscle tone. Aerosolized sympathomimetic are effective in two ways: they cause bronchial muscle relaxation, and they stimulate mucociliary clearance. A newer compound of note is metaproterenol, which is available as a cartridge inhaler, as an aerosolized liquid, as a tabular oral medication, or as a syrup. The recommended oral dose is 10–20 mg every 6–8 h, or 1–2 puffs every 3–4 h as an inhaled bronchodilator with a duration of action of 1–5 h.[16]

Albuterol can also be aerosolized or be administered orally or parenterally. Albuterol is available in a metered cartridge inhaler, and its standard dose is 1–2 puffs three to four times daily. Aerosolized albuterol has a duration of action of approximately 4–6 h.[17]

Racemic epinephrine is used as an aerosolized topical vasoconstrictor, bronchodilator, and secretion bond breaker. The vasoconstrictive action of racemic epinephrine is useful in reducing mucosal and submucosal edema within the walls of the pulmonary airways. A secondary bronchodilator action serves to reduce potential spasms of the smooth muscles of the terminal bronchioles. Water, employed as a diluent for racemic epinephrine, serves to lower both adhesive and cohesive forces of the retained endobronchial secretions, thus serving as a bond-breaking vehicle. Racemic epinephrine has also been used for the treatment of

postextubation stridor.[18] Its mode of action is thought to be related to the vasoconstrictive activity, with the resultant decrease in mucosal edema. Aerosolized treatments may be given every 2 h as long as the heart rate is not increased.

Hypertonic saline offers a theoretically more effective form of mucokinetic therapy. The deposition of hypertonic droplets on the respiratory mucosa causes the osmotic attraction of fluids from the mucosal blood vessels and tissues into the airway. Thus, a "bronchorrhea" is induced. The watery solution helps dilute the respiratory tract secretions and increase their bulk, thereby augmenting expectoration. Furthermore, there is evidence that hypertonic saline has a direct effect on the mucoprotein DNA complexes, and, by reducing the cohesive intramolecular forces, the salt helps reduce the viscous properties of the mucoid fluid.[19] Excessive use of hypertonic saline is not recommended because burn patients cannot tolerate the sodium load and may develop edema.

Oxandrolone is a synthetic testosterone analog that has been shown to significantly reduced hypermetabolism and significantly increased height percentile, bone mineral content, lean body mass, and strength in pediatric burn patients.[20] Recently, it has been shown that pediatric patients treated with oxandrolone for 1 year had significantly higher maximum voluntary ventilation compared to untreated patients. [21] Also, during maximal exercise, the subjects treated with oxandrolone had a significantly higher maximal ventilation (V_{EMax}).[21] The administration of oxandrolone may be used as an agent in the future to improve lung function in burned patients.

Aerosolized acetylcysteine is a powerful mucolytic agent in use in respiratory care. Acetylcysteine contains a thiol group; the free sulfhydryl radical of this group is a strong reducing agent which ruptures the disulfide bonds that give stability to the mucoprotein network. Agents that break down these disulfide bonds produce the most effective mucolysis.[22] Of note, acetylcysteine is an irritant to the respiratory tract. It can cause mucosal changes, and it may induce bronchospasms. For this reason, patients are evaluated for signs of bronchospasms, and a bronchodilator may be added if necessary. Acetylcysteine has proved to be effective in combination with aerosolized heparin for the treatment of inhalation injury in animal studies.[23]

Last, heparin and acetylcysteine combinations have been used as scavengers for the free oxygen radicals produced when alveolar macrophages are activated either directly by chemicals in smoke or by one or more of the compounds in the arachidonic oxidative cascade.[24] Animal studies have shown an increased P/F ratio, decreased peak inspiratory pressures, and a decreased amount of fibrin cast formation with the heparin and acetylcysteine combination therapy.[25] In a retrospective review, Desai et al. have shown that the use of heparin and N-acetylcysteine is effective in pediatric patients with inhalation injury.[26] Results indicated a significant decrease in the reintubation rates, the incidence of atelectasis, and improved mortality for patients treated with the combined therapy. Therefore, a standard treatment for patients with inhalation injury may include 5000–10,000 units of heparin and 3 mL normal saline nebulized every 4 h, alternating with 3–5 mL of 20% acetylcysteine for 7 days. This ensures that the patient receives an aerosolized treatment every 2 h. Baseline and daily clotting analyses are recommended for the entire length of the aerosolized treatments.

Mechanical Ventilation

Over the past 30 years, and particularly over the past decade, there has been an increase in new ventilation techniques that present alternatives for the treatment of patients with smoke inhalation. Unfortunately, although the number of options available to the clinician has appeared to increase, randomized and placebo-controlled clinical trials defining the specific role for each mode of ventilation and comparing them to other modes of ventilation have not been forthcoming. The recommendations from the American College of Chest Physicians Consensus Conference on Mechanical Ventilation serve as general guidelines.[27] The consensus concludes:

- The clinician should choose a ventilator mode that has been shown to be capable of supporting oxygenation and ventilation and that the clinician has experience in using.
- An acceptable oxygen saturation should be targeted.
- Based primarily on animal data, a plateau pressure of greater than 35 cm H_2O is cause for concern. However, with clinical conditions that are associated with a decreased chest wall compliance, plateau pressures greater than 35 cm H_2O may be acceptable.
- To accomplish the goal of limiting plateau pressures, P_{CO_2} values should be permitted to rise (permissive hypercapnia) unless other contraindications exist that demand a more normal P_{CO_2} or pH.
- Positive end-expiratory pressure (PEEP) is useful in supporting oxygenation. An appropriate level of PEEP may be helpful in preventing lung damage. The level of PEEP required should be established by empirical trials and reevaluated on a regular basis.
- Large tidal volumes (10–12 mL/kg) with PEEP may be needed to improve oxygenation if the use of protective ventilation strategies becomes ineffective. Peak flow rates should be adjusted as needed to satisfy patient inspiratory needs.[57] Care must be taken to avoid the consequences of utilizing high ventilator pressures if large tidal volumes are required.

Animal studies showed a reduction in ventilator-induced injury with a reduction in plateau pressures to 35 cm H_2O by increasing PEEP and decreasing tidal volume.[28] A number of clinical trials have been conducted to support this treatment strategy.[29–31] A meta-analysis of these trials was conducted by the Cochrane Anesthesia Review Group in 2007.[32] It showed a reduction in mortality and duration of mechanical ventilation with the use of plateau pressure at less than 30 cm H_2O and tidal volume at less than 7 mL/kg body weight. In light of this evidence, the tidal volumes used when initiating mechanical ventilation should be 6–8 mL/kg of predicted body weight. If the patient becomes obstructed with fibrin cast and presents with an acute increase in P_{CO_2} and decrease in Pa_{O_2}, the clinician should first provide aggressive pulmonary toilet, then consider changing over to volume ventilation with higher tidal volumes. If ventilation continues to worsen, tidal volumes

of 10–12 mL/kg may be needed to provide adequate mechanical ventilation.[57]

MODES OF VENTILATION

Control Mode

In the control mode of ventilation, the ventilator automatically cycles at a rate selected by the operator. The ventilator will cycle regardless of the patient's needs or desire for a breath, but it guarantees a minimum level of minute ventilation in the sedated or paralyzed patient. This mode of ventilation is often utilized in patients with acute respiratory distress syndrome (ARDS) because of the high peak pressures needed to achieve adequate chest expansion. The major disadvantage with this mode is that the patient cannot cycle the ventilator; thus, the minute ventilation must be set appropriately.

Assist-Control Mode

In the assist-control mode of ventilation, every breath is supported by the ventilator and a back-up control rate is set. The tidal volume, inspiratory flow rate, flow waveform, sensitivity, and control rate are set.[33–35] The advantages include that assist-control ventilation combines the security of controlled ventilation with the possibility of synchronizing the breathing pattern of the patient and ventilator, and it ensures ventilation support during each breath. Disadvantages are as follows:

- Excessive patient work occurs in case of inadequate peak flow or sensitivity settings, especially if the ventilator drive of the patient is increased,[33–35]
- It is often poorly tolerated in awake, nonsedated subjects, and it can require sedation to insure synchrony of patient and ventilator,
- It can cause respiratory alkalosis, and
- It may worsen air trapping with patients with chronic obstructed lung disease (COPD).[26]

Synchronized Intermittent Mandatory Ventilation

Synchronized intermittent mandatory ventilation (SIMV) combines a preset number of ventilator-delivered mandatory breaths of the present tidal volume with the facility for intermittent patient-generated spontaneous breaths.[36,37] The advantages are as follows:

- The patient is able to perform a variable amount of respiratory work, and the security of a preset mandatory level of ventilation is maintained,
- SIMV allows for variation in the level of partial ventilation support from near total ventilation support to spontaneous breathing, and
- It can be used as a weaning tool.

Disadvantages include:

- Hyperventilation with respiratory alkalosis,
- Excessive work of breathing due to the presence of a poorly responsive demand valve, suboptimal ventilation circuits, or inappropriate flow delivery could occur, and
- In each case, extra work is imposed on the patient during spontaneous breaths.

Pressure Control Mode

In pressure-controlled ventilation all breaths are time- or patient-triggered, pressure-limited, and time-cycled. The length of inspiration, pressure level, and back-up rate are set by the operator. The tidal volume is based on the compliance and resistance of the patient's lungs, the ventilator system, and the preset pressure.

Pressure Support Ventilation

Pressure support ventilation (PSV) is a pressure-targeted, flow-cycled mode of ventilation in which each breath must be patient-triggered. It is used both as a mode of ventilation during stable ventilation support periods and as a weaning method.[37–41] It is primarily designed to assist spontaneous breathing; thus, the patient must have an intact respiratory drive.

Advantages include:

- It is generally considered a comfortable mode of ventilation for most patients,
- Pressure support reduces the work of breathing,
- It can be used to overcome airway resistance caused by the endotracheal tube, and
- Pressure support may be useful in patients who are difficult to wean.

Disadvantages include:

- The tidal volume is not controlled and it is dependent on respiratory mechanics, cycling frequency, and synchrony between the patient and ventilator, and
- Pressure support may be poorly tolerated in some patients with high airway resistances because of the preset high initial flow rates.

ALTERNATE MODES OF VENTILATION

During the past decade, a new concept of ventilation has emerged in the treatment of ARDS patients. In severe cases of ARDS, only a small part of the lung parenchyma remains accessible to gas delivered by mechanical ventilation.[42,43] As a consequence, tidal volumes of greater than 10 mL/kg may overexpand and injure the remaining normally aerated lung parenchyma. High airway pressures may result in overdistension and local hyperventilation of more compliant parts of the lung. Overdistension of lungs in animals has been shown to produce diffuse alveolar damage.[44–46] This is the primary reason that alternative modes of ventilation, which are all based on a reduction of end-inspiratory airway pressures and/or tidal volumes delivered to the patient, have been developed and are used by many clinicians caring for patients with severe forms of acute or chronic respiratory failure. The following four alternative modes of ventilation will be discussed: high-frequency ventilation, high-frequency percussive ventilation, airway pressure release ventilation, and volumetric diffusive ventilation.

High-Frequency Ventilation

High-frequency ventilation (HFV) is the administration of small tidal volumes of 1–3 mL/kg at high frequencies of

100–3000 cpm.[47] This mode of ventilation is based on a marked reduction in tidal volumes and airway pressures, and it has the greatest potential for reducing pulmonary barotraumas. There are a number of different types of high-frequency ventilation techniques. The two most common are high-frequency jet ventilation (HFJV) and high-frequency percussive ventilation (HFPV).

HFJV is the only high-frequency mode routinely used to ventilate patients with ARDS, and it is primarily used in Europe.[27] This type of ventilation uses a brief jet of gas at a high frequency. Comparative data concerning the advantages of HFJV over conventional ventilation are limited. There is no agreement, however, that HFJV is better than conventional mechanical ventilation in ARDS.[48]

HFPV has shown some promise in the ventilation of patients with inhalation injury.[49–51] HFPV refers to ventilation utilizing the Volume Diffusive Respiration (VDR) ventilator, and it oscillates between the inspiratory and expiratory airway pressures. Clinical studies indicate that this mode of ventilation may aid in reducing pulmonary barotrauma.[49,50] In a retrospective study, Cortiella et al. have shown a decreased incidence of pneumonia, peak inspiratory pressure, and an improved P/F ratio in children ventilated with the use of HFPV compared to controls.[52] In the first prospective randomized study of HFPV, Mlcak et al. have shown a significant decrease in the peak inspiratory pressures needed to ventilate pediatric patients with inhalation injury.[53] No significant differences were found for incidence of pneumonia, P/F ratios, or mortality.

Based on clinical experience, the following guidelines are suggested for initial set-up of the HFPV in children (Table 18.1). The pulsatile flow (PIP) rate should be set at 20 cm H_2O, the pulse frequency (high rate) should be set between 500 and 600, and the low respiratory rate should be set between 15 and 20. Oscillatory PEEP levels should be initially set at approximately 3 cm H_2O, and demand PEEP should be set at 2 cm H_2O. Ventilator settings are adjusted based on the patient's clinical condition and blood gas values. To improve oxygenation, the ventilator can be switched to a more diffusive mode (increased pulse frequency); to eliminate carbon dioxide, the ventilator can be switched to a more convective mode (decreased pulse frequency). With HFPV, subtidal volumes are delivered in a progressive stepwise fashion until a preset oscillatory equilibrium is reached, and exhalation is passive.

Clinicians must be familiar with each technique used and its possible limitations. There must be adequate humidification of the respiratory gases or severe necrotizing tracheobronchitis can occur. Special delivery devices for providing adequate humidification during HFV are required. It is not clear when and how it should be used following inhalation injury.[54] As the methodology for HFPV evolves, it is anticipated that HFPV will play a larger role in the care of select mechanical ventilation-dependent populations.[55]

Airway Pressure Release Ventilation

Airway pressure release ventilation (APRV) is a pressure-regulated mode of ventilation support that allows for time-cycled decreases in pressure to facilitate CO_2 elimination. This mode allows spontaneous breathing while limiting airway pressures; therefore, it may limit the amount of sedatives or neuromuscular blocking agents needed. APRV is a protective ventilator strategy that uses inverse ratio ventilation at two levels of PEEP. Several limited studies have suggested that APRV may be beneficial for the treatment of burn patients who develop ARDS. Evidence-based recommendations to use this mode of ventilation await outcome studies.

VOLUMETRIC DIFFUSIVE VENTILATION

The volumetric diffusive ventilator (VDR) is a pneumatically powered, pressure-limited ventilator that stacks oscillatory breaths to a selected peak airway pressure by means of a sliding venturi called a *phasitron*. After inspiration, exhalation is passive and ends at a selected level of oscillatory CPAP.[56] Studies comparing VDR to high-volume strategies have shown VDR improves gas exchange, decreases peak pressures, and lowers mortality. However, there is a need to compare VDR to the low tidal volume ventilation practiced more recently. Usage of the VDR requires special training; the other disadvantages are the inability to monitor tidal and minute volumes and the requirement of humidified air and nebulized saline to prevent airway desiccation.

VENTILATOR SETTINGS

A large multicentered study by the Acute Respiratory Distress Syndrome Network evaluated the use of volume ventilation with low versus high tidal volume on ARDS. This study documented a decreased incidence of mortality in patients with ARDS who were ventilated with small tidal volumes.[29] Based on this study in 2000, it has become clinically accepted practice to use low tidal volumes when initially setting up mechanical ventilation (Table 18.2).

Table 18.1 High-Frequency Percussive Ventilation Set-Up Guidelines

Variable	Settings
Pulsatile Flow Rate (PIP)	20 cm H_2O
Pulse Frequency (high rate)	500–600
Low Respiratory Rate	15–20
I:E Ratio	1:1 or 2:1
Oscillatory PEEP	3 cm H_2O
Demand PEEP	2 cm H_2O

Table 18.2 Targeted Mechanical Ventilation Guidelines in Children

Variable	Settings
Tidal Volumes	6–8 mL/kg
Respiratory Rate	12–45 breaths/min
Plateau Pressures	<30 cm H_2O
I:E Ratio	1:1–1:3
Flow Rate	40–100 L/min
PEEP	7.5 cm H_2O

Tidal Volumes

In volume-cycled ventilation, a machine-delivered tidal volume is set to be consistent with adequate gas exchange and patient comfort. The tidal volume selected for burned patients normally varies between 6 and 8 mL/kg of predicted body weight. Numerous factors, such as lung/thorax compliance, system resistance, compressible volume loss, oxygenation, ventilation, and barotrauma, are considered when volumes are selected.[53] Sousse et al. have recently shown that the use of higher tidal volumes in pediatric burn patients with inhalation injury may decrease the incidence of ARDS and atelectasis as well as the number of days on a ventilator when compared to lower tidal volumes.[57] Of critical importance is the avoidance of overdistension. This can generally be accomplished by ensuring that peak airway and alveolar pressures do not exceed a maximum target. Many would agree that a peak alveolar pressure greater than 35 cm H_2O in adults raises concern regarding the development of barotrauma, and ventilator-induced lung injury increases.[58,59] Expired tidal volumes should be measured for accuracy at the connection between the patient's wye and the artificial airway.

The range of tidal volumes will vary depending on the disease process, with some diseases requiring maximum tidal volumes and others needing less. Severe interstitial diseases such as pneumonia and ARDS may require a tidal volume of greater than 8 mL/kg to adequately inflate the lungs and improve gas exchange if protective ventilation strategies become inadequate.

Respiratory Rate

Setting of the mandatory respiratory rate is dependent on mode of ventilation selected, delivered tidal volume, dead space-to-tidal volume ratio, metabolic rate, targeted P_{CO_2} levels, and level of spontaneous ventilation. With adults, the set mandatory rate normally varies between 4 and 20 breaths/min, with most clinically stable patients requiring mandatory rates in the 8–12 range.[60] It is important to have targeted arterial blood gas values set to aid the clinical team in proper management (Table 18.3). Along with the P_{CO_2}, pH, and patient comfort, the primary variable controlling the selection of the respiratory rate is the development of air trapping and auto PEEP.[61]

The respiratory rates of children and infants all need to be set substantially higher than those of adults. For pediatrics, the respiratory rate can be set from 12 to 45, depending on the disease state and the level of targeted P_{CO_2} one wishes to achieve. Slower respiratory rates are useful in the patient with obstructed airways because slower rates allow more time for exhalation and emptying of hyperinflated areas. Arterial blood gases should be checked after the patient has been on the ventilator for approximately 20 min and the respiratory rate adjusted accordingly.

Table 18.3 Arterial Blood Gas Goals

Variable	Goal
pH	7.25–7.45
PO_2	55–80 mm Hg or SaO_2 of 88–95%
PCO_2	35–55 mm Hg (permissive hypercapnia can be used as long as pH >7.25)

Flow Rates

The selection of peak inspiratory flow rate during volume ventilation is primarily determined by the level of spontaneous inspiratory effort. In patients triggering volume breaths, patient effort, work of breathing, and patient ventilator synchrony depend on the selection of peak inspiratory flow.[34] Peak inspiratory flows should ideally match patient peak inspiratory demands. This normally requires peak flows to be set at 40–100 L/min, depending on expired volume and the inspiratory demand.[27]

Inspiratory/Expiratory (I:E) Ratio

The time allowed for the inspiratory and expiratory phases of mechanical ventilation is commonly referred to as the inspiratory/expiratory (I:E) ratio. The inspiratory part of the ratio includes the time to deliver the tidal volume before the exhalation valve opens and exhalation begins. The expiratory part of the ratio includes the time necessary for the tidal volume to exit through the exhalation valve before the next inspiration begins. The inspiratory time should be long enough to deliver the tidal volume at flow rates that will not result in turbulence and high peak airway pressures. Typically, the I:E ratio is 1:1 to 1:3.[62]

In severe lung disease, it is acceptable to prolong the inspiratory time to allow for better distribution of gas and to enhance oxygen diffusion. When a longer inspiratory time is required, careful attention should be given to sufficient expiration to avoid stacking of breaths and impeding venous return. Prolonged inspiratory time creates a more laminar flow, which helps to keep the peak pressures lower. Fast inspiratory times are tolerated in patients with severe airway obstruction. The fast inspiratory time allows for a longer expiratory phase, which may help to decrease the amount of overinflation.

Inspired Oxygen Concentration

As a starting point, a patient placed on a ventilator should receive an oxygen concentration of 100%. The concentration should be systematically lowered based on values from arterial blood gases. Generally, as a result of the concerns regarding the effects of high oxygen concentration on lung injury, the lowest acceptable oxygen level should be selected as soon as possible. In patients who are difficult to oxygenate, oxygen concentrations can be minimized by optimizing PEEP and mean airway pressures and selecting minimally acceptable oxygen saturation.[63]

Positive End-Expiratory Pressure

PEEP is applied to recruit lung volumes, elevate mean airway pressure, and improve oxygenation.[64] The level of PEEP used varies with the disease process. PEEP levels should start at 8–10 cm H_2O and should be increased in 2.5-cm increments. Increasing levels of PEEP, in conjunction with a prolonged inspiratory time, aids in oxygenation and allows for the safe percentage of oxygen to be used. The use of pressure–volume curves to determine the best PEEP level has been recommended to aid in overstretching the alveoli. The process of using the curves is difficult to

perform in the clinical setting. However the use of PEEP trials can determine the best PEEP without decreasing cardiac output.

Optimal PEEP is the level of end-expiratory pressure that results in the lowering of intrapulmonary shunting, significant improvement in arterial oxygenation, and only a small change in cardiac output, arteriovenous oxygen content differences, or mixed venous oxygen tension. To determine the optimal PEEP for patients with ARDS, the ARDS Network performed a multicenter, randomized, prospective clinical trial.[64] ARDS patients were treated with 6 mL/kg predicted body weight tidal volumes and randomized to either low (5 cm H_2O up to 24) or high (12 cm H_2O up to 24) PEEP. The trial showed no effect of higher levels of PEEP on duration of mechanical ventilation, duration of nonpulmonary organ failure, and in-hospital mortality.

EXTUBATION CRITERIA

Standard extubation criteria include a wide variety of physiologic indices that have been proposed to guide the process of discontinuing ventilation support. Traditional indices include:

- $Pa_{O_2}/F_{I_{O_2}}$ ratio of greater than 250,
- Maximum inspiratory pressure of greater than 60 cm H_2O,
- Vital capacity of at least 15–20 mL/kg,
- Spontaneous tidal volume of at least 5–7 mL/kg,
- Maximum voluntary ventilation of at least twice the minute volume,[66–69] and
- Audible leak around the endotracheal tube must be present.

In general, these indices evaluate a patient's ability to sustain spontaneous ventilation. They do not assess a patient's ability to protect the upper airway. For this reason, traditional indices often fail to reflect the true clinical picture of a patient with an inhalation injury. For a complete evaluation prior to extubation, bronchoscopic examination will aid in determining if the airway edema has decreased enough to attempt extubation. Prior to a scheduled extubation, it is recommended that reintubation equipment be set up and that the person doing the extubation be experienced in emergency intubations. If the patient demonstrates signs of inspiratory stridor, the use of racemic epinephrine by aerosol has been shown to be effective in reducing mucosal edema and may prevent the patient from being reintubated.[18]

Infection Control of Respiratory Equipment

Pneumonia has become one of the most frequent, life-threatening infections, and its incidence has become an important determinant of mortality in burned patients.[68] The majority of pneumonias are nosocomial, occur in burned patients after 72 h of hospitalization, and are often associated with either an inhalation injury or endotracheal intubation with exposure to respiratory care equipment, or both.[70–75] One of the most important risk factors predisposing to pneumonia in burned patients is endotracheal intubation.[76,77] The incidence of pneumonia developing is estimated to be five times higher for intubated than non-intubated patients, and tracheostomy increases this risk even higher.[78] Exposure to respiratory care equipment adds an increased risk of pneumonia above and beyond the risk associated with endotracheal intubation.[79,80] After the use of nebulization equipment in respiratory care became popular, several epidemics of nosocomial pneumonia were reported.[81] The risk of pneumonia from mechanical ventilators was significant, but it decreased with better understanding of the necessity to decontaminate respiratory equipment.[82,83] Respiratory care equipment, if not properly cared for, may provide a source of extraneous organisms that can contaminate the patient's respiratory tract.

The potential role of respiratory care equipment in providing reservoirs for organisms that are capable of infecting the lungs is well established. This problem, particularly pertaining to reservoir devices and medications, has been recognized for a number of years, and effective control strategies have been developed. Most hospitals maintain a bacteriological monitoring system, and significant contamination by this route is not likely.[84] Nebulization equipment delivers a fine-particle aerosol, and, if contaminated, the aerosol droplets may contain bacteria.

Bag-mask units have been shown to allow the persistence of infectious organisms and the subsequent infection of other patients on whom the equipment has been later used.[85] Also, ventilator circuits are inevitably contaminated by the patient's own respiratory tract flora during exhalation and coughing, and the fluid that collects in this tubing is thereby contaminated. However, the American Association for Respiratory Care evidence-based clinical practice guidelines suggest that ventilator circuits should not be changed routinely for infection control purposes.[86]

HANDWASHING

Handwashing is generally considered the single most important procedure for preventing nosocomial infections. The recommended handwashing procedures depend on the purpose of washing. In most situations, a vigorous brief washing with soap and water is adequate to remove transient flora. Antimicrobial handwashing procedures are indicated before all invasive procedures, during the care of patients in strict respiratory or enteric isolation, and before entering intensive care units. The most commonly used agents are 70% isopropyl alcohol, iodophors, and chlorhexidine. Scrub regimens such as povidone-iodine surgical scrub are appropriate as well.[87]

CHEMICAL AGENTS FOR STERILIZATION/ DISINFECTION

Disinfectants act to kill microorganisms by several methods:

- oxidating microbial cells,
- hydrolyzing,
- combining with microbial proteins to form salts,
- coagulating the proteins of microbial cells,
- denaturing enzymes, and/or
- modifying cell wall permeability.[88]

Aldehydes

Aldehydes contain some of the most commonly used antimicrobials in respiratory care practice. These agents achieve their antimicrobial action through the alkylation of enzymes.

The cidal action of glutaraldehyde is accomplished by disruption of the lipoproteins in the cell membrane and cytoplasm of vegetative bacterial forms. This reaction between the chemical glutaraldehyde and cell proteins depends on both time and contact. Items to be disinfected must be free of material that would inhibit contact, and adequate contact time is needed for the chemical reaction to be complete. Alkaline glutaraldehyde, buffered by a 0.3% bicarbonate agent, is used as a 2% solution. This solution is bactericidal, virucidal, and tuberculocidal within 10 min and produces sterilization when applied for 10–20 h. Equipment disinfected or sterilized with glutaraldehyde should be thoroughly rinsed and dried prior to use because any residue would be irritating to mucous membranes.

Glutaraldehyde solutions are commonly used for cold disinfection or sterilization of respiratory care equipment, and they have a large degree of safety. These solutions can be used to disinfect bronchoscopes as well as many of the current respiratory supplies.

Alcohols

Alcohols, especially ethylene and isopropyl alcohol, are perhaps the most commonly used disinfectants. Alcohols as a chemical family have many desirable characteristics needed in disinfectants. They are generally bactericidal and accomplish their bactericidal activity by damaging the cell wall membrane. They also have the ability to denature proteins, particularly enzymes called dehydrogenases. For alcohol to coagulate microbial proteins, water must be present. For this reason, 70% has been considered the critical dilution for alcohol, with a rapid loss of bactericidal activity with dilutions less than 50%. Both ethyl and isopropyl alcohols are rapidly effective against vegetative bacteria and tubercle bacilli but are not sporicidal.

To be sure that the current infection control practice is effective in each institution, random microbiological cultures should be done whenever a problem is suspected or to test the reliability of the disinfection or sterilization techniques.

Late Complications of Inhalation Injury

TRACHEAL STENOSIS

Tracheal complications are commonly seen and consist of tracheitis, tracheal ulcerations, and granuloma formation. The location of the stenosis is almost invariably subglottic and occurs at the site of the cuff of the endotracheal or tracheostomy tube.[89] Several problems arising after extubation represent sequelae of laryngeal or tracheal injury incurred during the period of incubation. While tracheal stenosis or tracheomalacia is usually mild and asymptomatic, each can present as severe fixed or dynamic upper airway obstructions in some patients. These conditions can require surgical correction. In the management of intubated patients, such complications should be mostly preventable by meticulous attention to the tracheostomy or endotracheal tube cuff. Inflation of the cuff should be to the minimal pressure level consistent with preventing a leak in the ventilator at end inspiration.

OBSTRUCTIVE/RESTRICTIVE DISEASE

Chronic airway disease is a relatively rare reported sequel of inhalation injury and its supportive treatment. Spirometry is a useful screening tool for airway obstruction. Reports in the literature for adults indicate that lung function returns to normal after inhalation injury.[90,91] However, Mlcak et al. reported pulmonary function changes following inhalation injury for up to 10 years post-injury in a group of severely burned children.[92] In the great majority of cases, eventual resolution of both symptoms and physiologic abnormalities will occur. During the resolution phase, serial measurement of airflow obstruction should be obtained.[93] Desai et al. demonstrated that physiologic insults that occur as a result of thermal injury may limit exercise endurance in children.[94] Data from exercise stress testing showed evidence of a respiratory limitation to exercise. This was confirmed by a decrease in the maximal heart rate, decrease in the maximal oxygen consumption, and increase in respiratory rate. In the cases of persistent severe respiratory symptoms, the severity of the impairment should be documented and the patient evaluated for a pulmonary rehabilitation program.

Summary

Inhalation injury and associated major burns provide a challenge for healthcare workers who provide direct hands-on care. The technical and physiologic problems that complicate the respiratory management of these patients require a practical knowledge of the possible sources of nosocomial infections. Patients with inhalation injury frequently require the use of respiratory care equipment that, if not properly cared for, can aid in the spread of infections. Important priorities for reducing the risk of infections include an aggressive bronchial hygiene therapy program, adherence to established infection control practices, the use of universal precautions during procedures, and meticulous cleaning of respiratory care equipment, as well as routine epidemiologic surveillance of the established infection control practices within each institution. It is imperative that a well-organized, protocol-driven approach to respiratory care of the burn patient be utilized so that further improvements can be made and the morbidity and mortality associated with inhalation injury be reduced.

Complete references available online at www.expertconsult.inkling.com.

Further Reading

Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342(18):1301-1308.

Cartotto R. Use of high frequency oscillatory ventilation in inhalation injury. *J Burn Care Res*. 2009;30(1):178-181.

Mlcak R, Desai MH, Herndon DN. A prospective randomized study of high frequency percussive ventilation compared to conventional mechanical ventilation in pediatric patients with inhalatiron injury. *J Burn Care Rehabil*. 2000;21(1):S158.

Mlcak R, Desai MH, Robinson E, et al. Inhalation injury and lung function in children – a decade later. *J Burn Care Rehabil*. 2000;21(1):S156.

Peck MD, Koppelman T. Low-tidal-volume ventilation as a strategy to reduce ventilator-associated injury in ALI and ARDS. *J Burn Care Res*. 2009;30(1):172-175.

References

1. Haponik E. Smoke inhalation injury: some priorities for respiratory care professionals. *Resp Care*. 1992;37:609.
2. Frownfelter D. *Chest Physical Therapy and Pulmonary Rehabilitation*. 2nd ed. Chicago: Year Book Medical; 1987.
3. Ivarez SE, Peterson M, Lansford BR. Respiratory treatments of the adult patient with spinal cord injury. *Phys Ther*. 1981;61:1738.
4. Chopra SK, Taplin GV, Simmons DH. Effects of hydration and physical therapy on tracheal transport velocity. *Am Rev Respir Dis*. 1974;115:1009-1014.
5. Marini JJ, Person DJ, Hudson LD. A prospective comparison of fiberoptic bronchoscopy and respiratory therapy. *Am Rev Respir Dis*. 1979;119:971-978.
6. Oldenburg FA, Dolovich MB, Montgomery JM, et al. Effects of postural drainage, exercise and cough on mucus clearance in chronic bronchitis. *Am Rev Respir Dis*. 1979;12:730-747.
7. Remolina C, Khan AV, Santiago TV. Positional hypoxemia in unilateral lung disease. *N Engl J Med*. 1981;304:522-525.
8. Soria C, Walthall W, Price H. *Breathing and Pulmonary Hygiene Techniques: Pulmonary Rehabilitation*. Oxford: Butterworth; 1984:860.
9. Caldwell S, Sullivan K. *Respiratory Care – A Guide to Clinical Practice*. Philadelphia: JB Lippincott; 1977:91.
10. Albanese AJ, Toplitz AD. A hassle free guide to suctioning a tracheostomy. *RN*. 1982;45(4):24-30.
11. Landa JF, Kwoka M, Chapman G, et al. Effects of suctioning on mucociliary transport. *Chest*. 1980;77:202-207.
12. McFadden R. Decreasing respiratory compromise during infant suctioning. *Am J Nurs*. 1981;12:2158-2161.
13. Wanner A. Nasopharyngeal airway: a facilitated access to the trachea. *Ann Intern Med*. 1971;75:592-595.
14. Brandstater B, Maullem M. Atelectasis following trachea suctioning in infants. *Anesthesiology*. 1979;31:294-297.
15. Roper PC, Vonwiller JB, Fisk GL, et al. Lobar atelectasis after nasotracheal intubation in infants. *Aust Paediatr J*. 1982;12:272-275.
16. Yee A, Connors G, Cress D. *Pharmacology and the Respiratory Patient, Pulmonary Rehabilitation*. Oxford: Butterworth; 1984:125.
17. Whitbet TL, Manion CV. Cardiac and pulmonary effects of albuterol and isoproterenol. *Chest*. 1978;74:251-255.
18. Zimet I. *Pharmacology of Drugs Used in Respiratory Therapy. Respiratory Care – A Guide to Clinical Practice*. Philadelphia: JB Lippincott; 1977:473.
19. Lieberman J, Kurnick NB. Influence of deoxyribonucleic acid content on the proteolysis of sputum and pus. *Nature*. 1962;196:988.
20. Porro LJ, Herndon DN, Rodriguez NE, et al. Five-year outcomes after oxandrolone administration in severely burned children: a randomized clinical trial of safety and efficacy. *J Am Coll Surg*. 2012;214:489-502.
21. Sousse LE, Herndon DN, Mlcak RP, et al. Long-term administration of oxandrolone improves lung function in pediatric burned patients. *J Burn Care Res*. 2016.
22. Hirsh SR, Zastrow JE, Kory RC. Sputum liquification agents: a comprehensive in vitro study. *J Lab Clin Med*. 1969;74:346.
23. Brown M, Desai MH, Mlcak R, et al. Dimethylsulfoxide with heparin in the treatment of smoke inhalation injury. *J Burn Care Rehabil*. 1988;9(1):22.
24. Desai MH, Mlcak R, Brown M, et al. Reduction of smoke injury with DMSO and heparin treatment. *Surg Form*. 1985;36:103.
25. Desai MH, Brown M, Mlcak R, et al. Nebulization treatment of smoke inhalation injury in sheep model with DMSO, heparin combinations and acetylcysteine. *Crit Care Med*. 1986;14:321.
26. Desai MH, Mlcak R, Nichols R, et al. Reduction in mortality in pediatric patients with inhalation injury with aerosolized heparin/N-acetylcysteine therapy. *J Burn Care Rehabil*. 1998;19(3):210-212.
27. Slutsky A. American College of Chest Physicians Consensus Conference: mechanical ventilation. *Chest*. 1993;104:1833-1859.
28. Peck MD, Koppelman T. Low-tidal-volume ventilation as a strategy to reduce ventilator-associated injury in ALI and ARDS. *J Burn Care Res*. 2009;30(1):172-175.
29. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-1308.
30. Hickling KG, Walsh J, Henderson S, et al. Low mortality rate in acute respiratory distress syndrome using low volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. *Crit Care Med*. 1994;22:1568-1578.
31. Laffey JG, O'Croinin D, McLoughlin P, et al. Permissive hypercapnia: role in protective lung ventilatory strategies. *Intensive Care Med*. 2004;30:347-356.
32. Petrucci N, Iacovelli W. Lung protective ventilation strategy for the acute respiratory distress syndrome. *Cochrane Database Syst Rev*. 2007;(3):CD003844.
33. Marini JJ, Capps JS, Culver BH. The inspiratory work of breathing during assisted mechanical ventilation. *Chest*. 1985;87:612-618.
34. Marini JJ, Rodriquez RM, Lamb V. The inspiratory workload of patient initiated mechanical ventilation. *Am Rev Respir Dis*. 1986;134:902-904.
35. Ward ME, Corbeil C, Gibbons MW, et al. Optimization of respiratory muscle relaxation during mechanical ventilation. *Anesthesiology*. 1988;69:29-35.
36. Downs JB, Klein EF, Desautels D, et al. Intermittent mandatory ventilation: a new approach to weaning patients. *Chest*. 1973;64:331-335.
37. Weisman IH, Rinaldo JE, Rodgers RM, et al. Intermittent mandatory ventilation. *Am Rev Respir Dis*. 1983;127:641-647.
38. Hirsch C, Kacmarek RM, Stanek K. Work of breathing during CPAP and PSV imposed by the new generation mechanical ventilators. *Respir Care*. 1991;36:815-828.
39. Macintyre NR. Respiratory function during pressure support ventilation. *Chest*. 1986;89:677-683.
40. Brochard L, Harf A, Lorino H. Inspiratory pressure support prevents diaphragmatic fatigue during weaning from mechanical ventilation. *Am Rev Respir Dis*. 1989;139:513-521.
41. Fiastro JF, Habib MP, Quan SF. Pressure support compensates for inspiratory work due to endotracheal tubes. *Chest*. 1988;93:499-505.
42. Brochard L, Rau F, Lorino H, et al. Inspiratory pressure support compensates for the additional work of breathing caused by the endotracheal tube. *Anesthesiology*. 1991;75:739-745.
43. Hickling KG. Ventilatory management of ARDS: can it affect outcome? *Intensive Care Med*. 1990;9:239-250.
44. Gattinoni L, Pesenti A, Avalli L, et al. Pressure–volume curve of total respiratory system in acute respiratory failure. *Am Rev Respir Dis*. 1987;136:730-760.
45. Dreyfuss D, Soler P, Basset G, et al. High inflation pressures, pulmonary edema, respective effects of high airway pressure, high tidal volume and PEEP. *Am Rev Respir Dis*. 1988;137:1159-1164.
46. Kolobow T, Moretti MP, Fumagalli R, et al. Severe impairment of lung function induced by high peak airway pressure during mechanical ventilation. *Am Rev Respir Dis*. 1987;135:312-315.
47. Froese AB, Bryan AC. High frequency ventilation. *Am Rev Respir Dis*. 1987;135:1363-1374.
48. Fusciardi J, Rouby JJ, Barakat T, et al. Hemodynamic effects of high frequency jet ventilation in patients with and without shock. *Anesthesiology*. 1986;65:485-491.
49. Cioffi W, Graves T, McManus W, et al. High-frequency percussive ventilation in patients with inhalation injury. *J Trauma*. 1989;29:350-354.
50. Cioffi W, Rue LW III, Graves T, et al. Prophylactic use of high-frequency percussive ventilation in patients with inhalation injury. *Ann Surg*. 1991;213:575-581.
51. Mlcak R, Cortiella J, Desai MH, et al. Lung compliance, airway resistance, and work of breathing in children after inhalation injury. *J Burn Care Rehabil*. 1997;18(6):531-534.
52. Cortiella J, Mlcak R, Herndon DN. High frequency percussive ventilation in pediatric patients with inhalation injury. *J Burn Care Rehabil*. 1999;20(3):232-235.
53. Mlcak R, Desai MH, Herndon DN. A prospective randomized study of high frequency percussive ventilation compared to conventional mechanical ventilation in pediatric patients with inhalation injury. *J Burn Care Rehabil*. 2000;21(1):S158.
54. Cartotto R. Use of high frequency oscillatory ventilation in inhalation injury. *J Burn Care Res*. 2009;30(1):178-181.
55. Allan PF, Osborn EC, Chung KK, et al. High-frequency percussive ventilation revisited. *J Burn Care Res*. 2010;31:510-520.
56. Harrington D. Volumetric diffusive ventilator. *J Burn Care Res*. 2009;30(1):175-176.
57. Sousse LE, Herndon DN, Anderson CR, et al. High tidal volume decreases adult respiratory distress syndrome, atelectasis, and ventilator days compared to low tidal volumes in pediatric burn patients with inhalation injury. *J Am Coll Surg*. 2015;220:570-580.
58. Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume, pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Med*. 1990;16:372-377.

59. Marini JJ. New approaches to the ventilatory management of the adult respiratory distress syndrome. *J Crit Care*. 1992;87:256-257.
60. Kacmarek RM, Venegas J. Mechanical ventilatory rates and tidal volumes. *Respir Care*. 1987;32:466-478.
61. Pepe PE, Marini JJ. Occult positive pressure in mechanically ventilated patients with airflow obstruction. *Am Rev Respir Dis*. 1982;126:166-170.
62. Kacmareck RM. Management of the patient mechanical ventilator system. In: Pierson DJ, Kacmareck RM, eds. *Foundations of Respiratory Care*. New York: Churchill Livingstone; 1992:973-997.
63. Stroller JK, Kacmareck RM. Ventilatory strategies in the management of the adult respiratory distress syndrome. *Clin Chest Med*. 1990;11:755-772.
64. Suter PM, Fairley HB, Isenberg MD. Optimum end-expiratory airway pressure in patients with acute respiratory failure. *N Engl J Med*. 1975;292:284-289.
65. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2004;351:327-336.
66. Sahn SA, Lakshminarayan S. Bedside criteria for discontinuation of mechanical ventilation. *Chest*. 1973;63:1002-1005.
67. Tahvanainen J, Salmenpera M, Nikki P. Extubation criteria after weaning from IMV and CPAP. *Crit Care Med*. 1983;11:702-707.
68. Herndon DN, Lange F, Thompson P, et al. Pulmonary injury in burned patients. *Surg Clin North Am*. 1987;67:31.
69. Demling RH. Improved survival after major burns. *J Trauma*. 1983;23:179.
70. Luterman A, Dacso CC, Curreri WP. Infections in burned patients. *Am J Med*. 1986;81(A):45.
71. Pruitt BA Jr. The diagnosis and treatment of infection in the burned patient. *Burns*. 1984;11:79.
72. Pruitt BA Jr, Flemma RJ, DiVincenti FC, et al. Pulmonary complications in burned patients. *J Thorac Cardiovasc Surg*. 1970;59:7.
73. Foley DF, Concrief JA, Mason AD. Pathology of the lungs in fatally burned patients. *Ann Surg*. 1968;167:251.
74. Moylan JA, Chan C. Inhalation injury – an increased problem. *Ann Surg*. 1978;188:34.
75. Craven DE, Kunches LM, Kilinsky V, et al. Risk factors for pneumonia and fatalities in patients receiving controlled mechanical ventilation. *Am Rev Respir Dis*. 1986;133:792.
76. Garibaldi RA, Britt MR, Coleman ML, et al. Risk factors for postoperative pneumonias. *Am J Med*. 1984;70:677.
77. Pennington JE. Hospital acquired pneumonias. In: Wenzel RP, ed. *Prevention and Control of Nosocomial Infections*. Baltimore: Williams & Wilkins; 1987:321-324.
78. Centers for Disease Control National Nosocomial Infection Study Report. Annual Summary 1983. *MMWR Morb Mortal Wkly Rep*. 1983;33(259):935.
79. Schwartz SN, Dowling JN, Ben Youic C, et al. Sources of Gram-negative bacilli colonizing the trachea of intubated patients. *J Infect Dis*. 1978;138:227.
80. Pierce AK, Edmonson EB, McGee G, et al. An analysis of factors predisposing to Gram-negative bacillary necrotizing pneumonia. *Am Rev Respir Dis*. 1966;94:309.
81. Ringrose RE, McKown B, Felton FG, et al. A hospital outbreak of *Serratia marcescens* associated with ultrasonic equipment. *Ann Intern Med*. 1968;69:719-729.
82. Simmons BP, Wong ES. CDC guidelines for the prevention and control of nosocomial infections. *Am J Infect Control*. 1983;11:230.
83. Rhame F. The inanimate environment. In: Bennett JV, Bracham PS, eds. *Hospital Infections*. Boston: Little Brown; 1986:223-250.
84. Cross AS, Roupe B. Role of respiratory assistance devices in endemic nosocomial pneumonia. *Am J Med*. 1981;70:681-685.
85. Johanson WG. ••. *Respir Care*. 1982;27:445-452.
86. Hess DR, Kallstrom TJ, Mottram CD, et al. Care of the ventilator circuit and its relation to ventilator-associated pneumonia. *Respir Care*. 2003;48(9):869-878.
87. Garner JS, Faverno MS. CDC guidelines for the prevention and control of nosocomial infections. *Am J Infect Control*. 1986;14:110-129.
88. Edge RS. *Infection Control, Respiratory Care Practice*. Chicago: Year Book Medical; 1988:574.
89. Munster AM, Wong LA. *Miscellaneous Pulmonary Complications in Respiratory Injury*. New York: McGraw-Hill; 1990:326.
90. Demling RH. Smoke inhalation injury. *Postgrad Med*. 1987;82:63.
91. Cahalane M, Demling RH. Early respiratory abnormalities from smoke inhalation. *JAMA*. 1984;251:771.
92. Mlcak R, Desai MH, Robinson E, et al. Inhalation injury and lung function in children – a decade later. *J Burn Care Rehabil*. 2000;21(1):S156.
93. Colic GL. Long term respiratory complications of inhalation injury. In: *Respiratory Injury, Smoke Inhalation and Burns*. New York: McGraw-Hill; 1990:342.
94. Desai MH, Mlcak R, Robinson E. Does inhalation injury limit exercise endurance in children convalescing from thermal injury. *J Burn Care Rehabil*. 1993;14:16-20.

19 The Systemic Inflammatory Response Syndrome

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Introduction

Burn patients, with or without inhalation injuries, commonly exhibit a clinical picture that is largely produced by systemic inflammation. The term *systemic inflammatory response syndrome* (SIRS) was introduced to designate the signs and symptoms of this condition. SIRS has a continuum of severity ranging from physiologic alterations such as tachycardia, tachypnea, fever, and leukocytosis to refractory hypotension and, in its most severe form, shock and multiple organ system dysfunction. In thermally injured patients, the most common cause of SIRS is tissue damage caused by the burn itself. Sepsis, characterized by SIRS in the presence of infection, is also common in burn patients and is a significant cause of morbidity and mortality. Starting from a local infection at the burn wound, an infected catheter tip, or pulmonary infection, the spread of microbes and their toxins can further potentiate systemic inflammation. Pathological alterations of metabolic, cardiovascular, pulmonary, renal, gastrointestinal, and coagulation systems occur as a result of the hyperactive immune system. This chapter will review current understanding of SIRS and the associated immunological, cardiovascular, and pulmonary dysfunction that occurs following trauma and thermal injury.

Definition of SIRS

The term *systemic inflammatory response syndrome* (SIRS) was recommended by the American College of Chest Physicians/Society for Critical Care Medicine (ACCP/SCCM) consensus conference in 1992 to describe a systemic inflammatory process, independent of its cause.[1] The proposal was based on clinical and experimental results indicating that a variety of conditions, both infectious and noninfectious (i.e., burns, ischemia–reperfusion injury, multiple trauma, pancreatitis), induce a similar host response. Two or more of the following conditions must be present for the diagnosis of SIRS to be made:

- Body temperature of greater than 38°C or less than 36°C;
- Heart rate of greater than 90 beats/min;
- Respiratory rate of greater than 20/min or a $Paco_2$ of less than 32 mm Hg;
- Leukocyte count of greater than 12,000/μL, less than 4000/μL, or more than 10% immature (band) forms.

All of these pathophysiologic changes must occur as an acute alteration from baseline in the absence of other known causes. This definition is very sensitive and nonspecific, and most of the SIRS criteria are also addressed in other scoring systems of injury-induced physiologic derangement, such as the Acute Physiology and Chronic Health Evaluation (APACHE), Mortality Probability Model (MPM), and Simplified Acute Physiology Severity (SAPS) systems. Several investigators have criticized the definition of SIRS as being too sensitive and encompassing the majority of ICU patients and certainly the vast majority of patients suffering extensive thermal injury.[2,3] The initial definition of SIRS also did not address the continuum of disease severity defined for sepsis. Criteria for the diagnosis of severe sepsis included the additional derangements of organ dysfunction, hypotension, and hypoperfusion. Evidence of hypoperfusion included, but was not limited to, the presence of lactic acidosis, oliguria, and altered mental status. Septic shock was characterized by hypotension and hypoperfusion in patients who were adequately volume resuscitated or required treatment with catecholamines or other vasoactive drugs to support cardiovascular function. Muckart and Bhagwangee,[2] in an effort to define a continuum of severity for SIRS, later proposed the categories of severe SIRS and SIRS-associated shock. These conditions were defined by the same criteria as severe sepsis and septic shock in the absence of demonstrable infection. In its most severe form, SIRS can induce organ injury and subsequent multiple organ dysfunction syndrome (MODS).

Despite the limitations in the definitions of SIRS and sepsis, most clinicians and investigators generally adopted the SIRS concept. However the initial definition and criteria were not felt to be optimized. To address these issues, a second consensus conference was assembled in 2001.[4] The goal of this conference was to revisit the previously defined criteria for SIRS and sepsis as well as to determine whether revision of these criteria was indicated. The consensus was that the concepts of sepsis and SIRS are useful, but the diagnostic criteria are overly sensitive and nonspecific. The participants added additional criteria that defined metabolic, biochemical, and functional alterations associated with SIRS and sepsis. Among these were hyperglycemia, edema, elevated plasma C-reactive protein (CRP) concentration, coagulation abnormalities, thrombocytopenia, ileus, and hyperbilirubinemia. The group further proposed a staging system for sepsis and SIRS that could be used to stratify patients for prediction of outcome. This staging system, termed PIRO, defined several criteria, including the predisposition of patients to a poor outcome as determined by premorbid conditions and possible genetic factors. Other factors include the severity and type of insult, the host

response to injury, and the presence of organ dysfunction. The participants proposed that this model could be used to generate more specific criteria for defining the SIRS phenomenon. Although the validity of this approach remains to be established, Rubulotta recently reported that the PIRO criteria have predictive value regarding mortality in septic patients.[5] More recent studies have also validated the PIRO model. Macdonald and colleagues reported that the PIRO model performed better than SOFA or MEDS scores in predicting mortality in patients presenting to the emergency room with severe sepsis or septic shock.[6] Some practitioners advocate for the validity and value of the PIRO system, but the system is not widely used in clinical practice.[7]

Although inflammation is certainly present in patients with burn injuries, sepsis, and other severe injuries, the contribution of SIRS to the pathogenesis of those conditions is under question. The most recent consensus conference assembled to define clinical criteria for sepsis dropped SIRS from the defining criteria.[8] The conference participants defined sepsis as "life threatening organ dysfunction due to a dysregulated host response to infection" and noted that SIRS criteria have poor predictive validity among patients who are infected.

Another pitfall in the designation of SIRS is the difficulty of applying the initial criteria to children. Some of the criteria, particularly those for heart and respiratory rates, fall within the normal physiologic range for young children. In 2002, a consensus conference was assembled to define criteria for sepsis and SIRS in children.[9] The participants defined six age groups based on clinical and physiological characteristics (Table 19.1). SIRS was defined as the presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

- temperature of greater than 38.5°C or less than 36°C;
- tachycardia, defined as a mean heart rate of greater than 2 SD above normal for age *or* for children younger than 1 year;
- bradycardia, defined as a heart rate of less than 10% of normal for age;
- mean respiratory rate of greater than 2 SD above normal for age or requirement for mechanical ventilation;
- leukocyte count elevated or depressed for age.

Severe sepsis was defined as sepsis plus one of the following: cardiovascular dysfunction, acute respiratory distress syndrome, or two or more organ dysfunctions (respiratory, renal, neurologic, hematologic, or hepatic).

The definition of septic shock is problematic in children because children can maintain blood pressure until they become severely ill. Therefore hypotension is not a useful criterion for diagnosing shock in children. This group proposed criteria for septic shock that included the presence of tachycardia in conjunction with signs of decreased peripheral perfusion, such as decreased capillary refill, decreased peripheral pulses, decreased urine output, altered mental status, and cold/mottled extremities.[9]

Table 19.1 Pediatric Age Groups for SIRS Criteria

Newborn 0 day to 1 week
Neonate 1 week to 1 month
Infant 1 month to 1 year
Toddler or preschool 2 to 5 years
School age 6 to 12 years
Adolescent 13 to 18 years

Several studies have been conducted with the goal of determining the prognostic value of the SIRS designation. In the acute setting, SIRS has been demonstrated in the majority of critically injured patients, and the intensity of the response correlates directly with the severity of injury.[3,10] The presence of SIRS within the first 24 hours after severe injury has not served as a reliable predictor of mortality in trauma or burn patients.[3,10] However, the presence of shock is an important predictor of poor outcome, particularly when associated with MODS.[2] In addition, the presence of more than two of the SIRS criteria in the setting of acute injury has correlated with increased morbidity and mortality.[11,12] A study by Rangel-Frausto et al.[12] showed that trauma patients who did not meet SIRS criteria had a mortality rate of 3%, compared to 6% in those with two SIRS markers. Patients with three or four SIRS criteria had mortality rates of 10% and 17%, respectively, whereas those with culture-negative shock had a 46% death rate. Haga et al.[13] have shown that the persistence of SIRS for more than 3 days in surgical patients is a harbinger of complications and is associated with increased morbidity. Talmor et al.[10] reported that persistence of SIRS to the second postoperative day in high-risk surgical patients correlated with an increased incidence of MODS. Additional studies have shown that persistence of SIRS criteria for more than 3 days in trauma and burn patients is associated with worse outcome.[13–16] Therefore, three important factors appear to determine the effect of SIRS on the host. The first is the severity of the initial inflammatory response. This response is proportional to the severity of injury, and the presence of shock or MODS within the first 24 hours after injury carries a poor prognosis. The second determinant is the persistence of SIRS beyond the first few days of injury. Specifically prolongation of SIRS beyond the second day after severe trauma or thermal injury is associated with an increased complication rate. Factors that appear to be important in reducing the incidence of a prolonged inflammatory state include adequate fluid resuscitation within the first 24 hours after injury, aggressive excision of necrotic tissue, and enteral feeding.[14–16] A third factor is the adaptive capacity of the host. Results of several studies have shown that extremes of age and the presence of coexisting disease will diminish the adaptive capacity of the host and predict a worse prognosis for any given severity of injury.[17,18] As noted earlier in this chapter, the actual contribution of SIRS to the pathogenesis of sepsis and other forms of systemic injury are in question.[8]

The Initiating Event

The crucial pathophysiologic event that precipitates systemic inflammation is tissue damage. This can occur both as a result of direct injury to tissues from mechanical or thermal trauma and as a result of cellular injury induced by ischemia and reperfusion. Injury results in the acute release of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-6. If injury

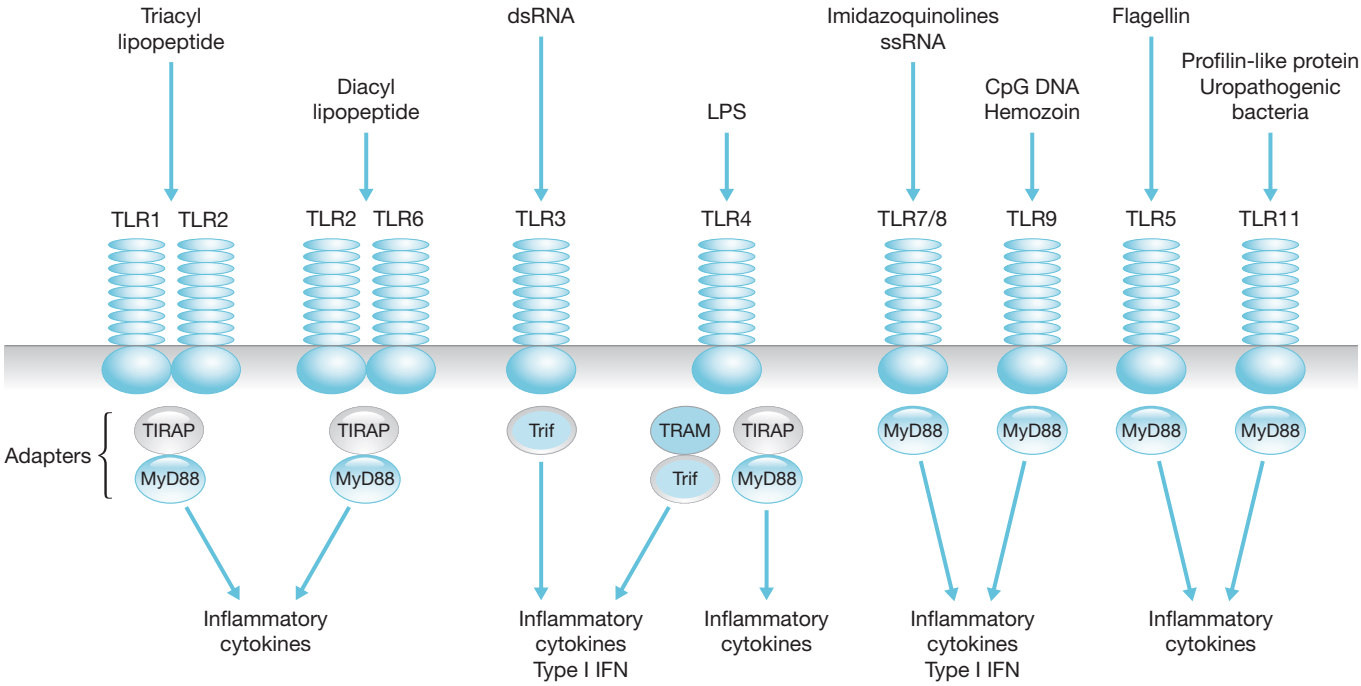


Fig. 19.1 Toll-like receptor signaling. Toll-like receptors (TLR) are membrane-associated receptors that recognize microbial products and endogenous products released during tissue injury, allowing the host to recognize the presence of microbes or tissue injury. TLR activation initiates intracellular signaling pathways that facilitate transcription of pro-inflammatory gene products. (From Kawai T, Akira S. TLR Signaling. Cell Death Differ. 2006; 13:816–825.)

is severe, as in extensive thermal injury, a profound release of cytokines and noncytokine mediators of inflammation occurs, resulting in the induction of a systemic inflammatory reaction. The ability of the host to adapt to this systemic inflammatory response depends on the magnitude and duration of the response as well as the adaptive capacity of the host. If the insult and the host's response to it are beyond the adaptive capacity of the host, or if adequate resuscitation is not promptly initiated, organ injury may ensue during the early post-injury period. Factors that have been implicated in the worsening or prolongation of SIRS include inadequate resuscitation during the acute phase following thermal injury, persistent or intermittent infection, ongoing tissue necrosis, and translocation of bacteria or endotoxin across the bowel.[18,19]

The actual mechanisms that initiate trauma-induced inflammation at the cellular and molecular levels are becoming increasingly understood. Two primary sensing systems have been identified. Toll-like receptors (TLR) respond to endogenous cellular factors that are produced or released following tissue trauma. TLR are expressed by leukocytes and some parenchymal cells. They allow the host to sense the presence of microbes via pathogen-associated molecular patterns (PAMPs) and initiate an innate immune response (Fig. 19.1). TLR also have the ability to respond to endogenous ligands that are leaked from cells upon their destruction by burn injury. These molecules are referred to as damage-associated molecular patterns (DAMPs) and are typically intracellular molecules with normal cellular functions (Fig. 19.2). As cells are damaged by thermal injury, these molecules are released into the extracellular matrix. Due to their normal intracellular localization, these molecules are recognized as danger signals and can bind to the same TLRs that are activated by microbial products. Among the proposed endogenous TLR ligands are heat shock proteins (recognized by TLR4 and TLR2), high-mobility group box 1 (HMGB1; recognized by TLRs 4 and 2), histones (recognized by TLR4), and mitochondrial DNA (recognized by TLR9).[20–22] Activation of TLR signaling pathways results in the transcription of genes associated with inflammatory responses. A second sensing system is comprised of cytoplasmic NOD-like receptors (NLRs) that sense endogenous and exogenous ligands during loss of cellular compartmentalization or membrane integrity and cause activation of inflammasomes (Fig. 19.3).[23] DAMPs that activate NLRs, either directly or via adapter molecules, include uric acid, endogenous DNA, and adenosine triphosphate (ATP).[22] Inflammasome assembly ultimately results in activation of inflammatory caspases such as caspase-1. Activated caspase-1, also known as IL-1-converting enzyme, causes cleavage of pro-IL-1 and pro-IL-18 into active mature proteins. The IL-1 and IL-18 produced by this interaction are released from cells and facilitate the pro-inflammatory response.

SIRS and Immunological Perturbations

Inflammatory responses are important for the early initiation of tissue repair and activation of innate immune cells in response to local infection. Cytokines such as IL-6, TNF-α, and IL-1 recruit and activate macrophages and neutrophils at sites of infection. To prevent tissue damage caused by prolonged or excessive inflammation, local anti-inflammatory responses are initiated to resolve the early

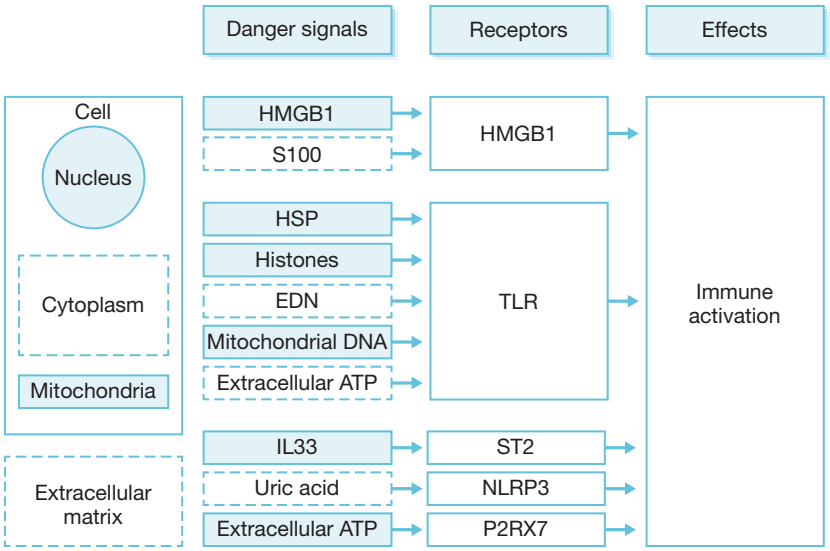


Fig. 19.2 Damage-associated molecular patterns (DAMPs). DAMPS are typically intracellular molecules with normal cellular functions that serve as danger signals when released into the extracellular matrix from damaged cells. DAMPs bind to various Toll-like receptors (TLRs) and other pathogen-associated molecular pattern receptors on leukocytes to activate inflammatory cascades. *HMGB1*, high mobility group box-1 protein; *HSP*, heat shock protein; *EDN*, eosinophil-derived neurotoxin; *IL-33*, interleukin-33; *TLR*, Toll-like receptor; *RAGE*, receptor for advanced glycation end-products; *NLRP3*, NOD-like receptor family, pyrin domain containing 3 (From Fontaine M, Lepape A, Piriou V, Venet F, Friggeri A. Innate danger signals in acute injury: From bench to bedside. *Anaesth Crit Care Pain Med.* 2016;35:283–292.)

inflammatory response. In the case of large burn injuries, the inflammatory response is massive and becomes systemic. A compensatory anti-inflammatory response referred to as the counter anti-inflammatory response syndrome (CARS) may be mounted in an attempt to restore homeostasis and control SIRS. Increased production of anti-inflammatory cytokines such as IL-10 and transforming growth factor-β (TGFβ) and leukocyte apoptosis are part of this response.[24,25] A prolonged or excessive anti-inflammatory response predisposes the patient to infection. The pathogenesis of injury-induced immunosuppression is discussed in detail elsewhere in this book. Nevertheless there is likely great heterogeneity in the host response to injury and infection. A recent report by Davenport and colleagues showed that there is great interindividuality in the peripheral blood transcriptomic response during sepsis but that patients exhibiting a signature reflective of immunosuppression, endotoxin tolerance, and T-cell exhaustion had a worse prognosis.[26] They further noted that the immunosuppressed phenotype can develop early during sepsis and may render the septic host unable to adequately mount an adequate response to clear the primary infection.

Our understanding of these syndromes has evolved to better describe this response that is shared by burn and severe non-burn trauma patients. For decades, the host response to injury-induced systemic inflammation has been described by the SIRS/CARS paradigm. It was initially believed that SIRS was resolved during CARS due to mutual regulatory effects of the mediators associated with the respective syndromes. However, examination of the transcriptome of leukocytes from trauma patients has revealed that SIRS and CARS exist simultaneously. Specifically, genes associated with both inflammatory and anti-inflammatory pathways were simultaneously up-regulated after injury, and this was described as a "genomic storm."[27] Genes associated with adaptive immune responses were down-regulated at the same time, suggesting impaired effector functions. The magnitude and duration of these responses correlated with complications after injury. This is supported by earlier studies examining levels of pro-inflammatory IL-6 and anti-inflammatory IL-10 in the circulation of burn patients.[28] Burn patients who eventually developed sepsis during their acute care had substantially higher levels of circulating IL-6 and IL-10 as early as 1 day post-burn. Later development of lethal sepsis was associated with persistently high levels of these cytokines. More recently, a new model has been proposed to characterize the responses and outcomes of patients following severe traumatic injury (Fig. 19.4). This model proposes that patients who rapidly resolve their SIRS and CARS responses return to immune homeostasis and recover from injury without major complications. However, if SIRS and CARS are not resolved, the patient develops persistent inflammation, immunosuppression, and catabolism syndrome (PICS), in which persistent inflammation and immunosuppression are accompanied by severe muscle protein catabolism (described in other chapters).[29] Secondary nosocomial infections are a risk and can exacerbate the existing inflammation, leading to multiorgan failure and death.

The Two-Hit Hypothesis

Some investigators have described a phenomenon in which the injured host manifests an exaggerated inflammatory response if confronted with a secondary inflammatory stimulus during the post-injury period. This phenomenon has been termed the "two-hit hypothesis." Although the pathobiology of the two-hit hypothesis is not completely understood, monocytes and macrophages appear to play a

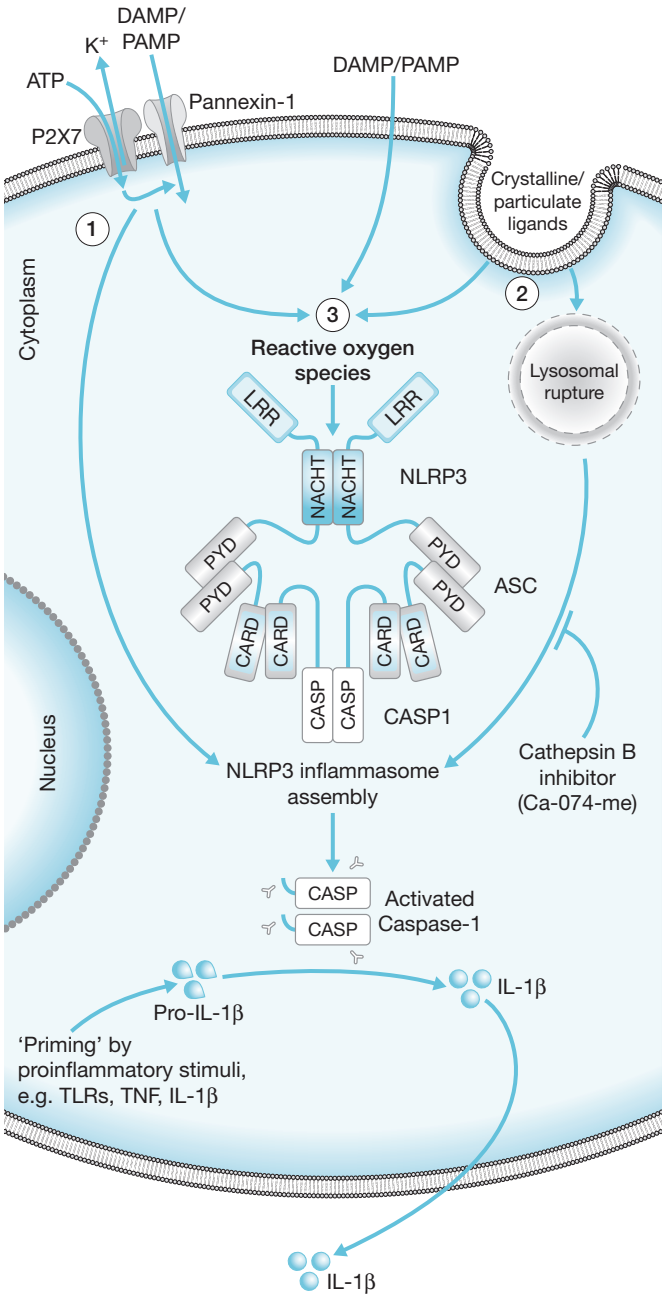


Fig. 19.3 The inflammasome is an intracellular signaling complex that is activated by a variety of endogenous and microbial products and causes activation of inflammatory caspases such as caspase-1. Activation of this system results in release of interleukin-1 (IL-1) and IL-18 during periods of inflammation. (From Schroder K, Tschopp J. The inflammasomes. *Cell* 2010;140:821–832.)

central role in mediating the process. For example, the lymphokine α-interferon (IFN-α), produced during the initial injury, might act as the first signal and prime macrophages for a heightened inflammatory response if a second stimulus is encountered. Several changes in macrophage function, including an increase in the transcription rate of mRNA for TNF-α, can be induced by exposure to IFN-α. However, TNF-α protein is not produced in large amounts in response to the first inflammatory insult. If a second stimulus, such as endotoxin exposure, is provided in even a small dose, macrophages are triggered to become fully activated and to secrete large amounts of TNF-α. Studies by Paterson et al.[30] showed that macrophages have increased responsiveness to ligands for TLR2 and TLR4 following burn injury. TLR2 and TLR4 play an integral role as components of receptor complexes for DAMPs and various microbial products such as peptidoglycans, lipoproteins, and lipopolysaccharide. Enhancement of TLR2 and TLR4 responses during the post-injury period may be one mechanism contributing to the two-hit phenomenon.

The exaggerated response to a secondary stimulus seen in severely injured patients appears to have functional consequences. Several studies that focused on organ injury caused by systemic inflammatory processes indicate that a phenomenon comparable to the cellular events just described can occur in severely injured patients.[31] Dehring et al. found more persistent pulmonary hypertension and an exaggerated hyperdynamic response to bacteremia in sheep when a week-old thermal injury preceded systemic bacterial challenge.[32] In a rat model of intestinal ischemia–reperfusion injury and endotoxemia, lung albumin leak and mortality rate increased only if both injuries occurred sequentially.[33] Combined administration of low doses of endotoxin and TNF-α to rats caused hypotension and metabolic effects that are commonly seen after giving a highly lethal dose of either compound alone.[34] These findings are in keeping with the fact that multiple organ damage usually develops over a prolonged period during which several insults might occur. It also emphasizes why it is so important to minimize inflammatory insults such as tissue ischemia or infection, particularly in patients in whom systemic inflammation is already present.

Cytokine and Noncytokine Mediators of SIRS

Several pro-inflammatory cytokines, chemokines, and noncytokine inflammatory mediators play a role in the pathogenesis of SIRS. Cytokines comprise a broad group of polypeptides with varied functions within the immune response (Table 19.2). The classic mediator of systemic inflammation is TNF-α. TNF-α is released primarily by macrophages within minutes of local or systemic injury and modulates a variety of immunologic and metabolic events.[35] At sites of local infection or inflammation, TNF-α initiates an immune response that activates antimicrobial defense mechanisms and, once the infection is eradicated, tissue repair. It is a potent activator of neutrophils and mononuclear phagocytes and also serves as a growth factor for fibroblasts and as an angiogenesis factor. However, systemic release of TNF-α can precipitate a destructive cascade of events that can result in tissue injury, organ dysfunction, and, potentially, death. Among the systemic effects of TNF-α are the induction of fever, stimulation of acute-phase protein secretion by the liver, activation of the coagulation cascade, myocardial suppression, induction of systemic vasodilators with resultant hypotension, catabolism, and hypoglycemia.[35,36] Numerous studies have shown that administration of TNF-α to experimental animals will mimic the systemic inflammatory response observed in sepsis and after severe injury. Another important effect

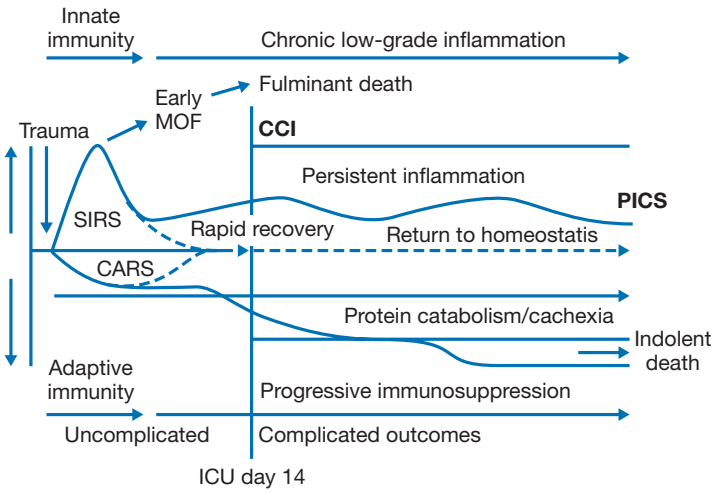


Fig. 19.4 The SIRS–CARS–PICS model of the systemic response to severe injury. Tissue injury induces the production of pro-inflammatory mediators resulting in the systemic inflammatory response syndrome (SIRS). A compensatory anti-inflammatory response may be simultaneously mounted in an attempt to control inflammation, resulting in the counter anti-inflammatory response syndrome (CARS). Patients able to resolve these syndromes recover whereas persistent perturbations in inflammatory balance may lead to persistent inflammation, immunosuppression, and catabolism syndrome (PICS). In this state, patients are susceptible to infection and are at risk for lethal systemic inflammatory responses and severe protein catabolism that leads to cachexia and, if unresolved, death. (From Vanzant EL, Lopez CM, Ozrazgat-Baslanti T, et al. Persistent inflammation, immunosuppression, and catabolism syndrome after severe blunt trauma. *J Trauma Acute Care Surg.* 2014;76:21–30.)

Table 19.2 Cytokine and Chemokine Mediators of Systemic Inflammation

Cytokine	Polypeptide Size	Cell Source	Cell Target	Primary Effects
Tumor necrosis factor- α (TNFα)	17 kDa	Monocytes, macrophages, T lymphocytes	Neutrophil Endothelial cells Hypothalamus Liver Muscle, fat Heart Macrophages T lymphocytes Various tissues	Activation (inflammation) Activation (inflammation/coagulation) Release of vasodilators (NO) Fever Acute-phase response Catabolism Myocardial suppression Release of cytokines, inflammation Inflammation Apoptosis?
Interleukin-1 (IL-1)	17 kDa	Monocytes, macrophages	T cells Endothelial cells Liver Hypothalamus Muscle, fat	Activation (inflammation) Activation (inflammation/coagulation) Release of vasodilators (NO) Acute-phase response Fever Catabolism
Interleukin-6 (IL-6)	26 kDa	Monocytes, macrophages, T cells, endothelial cells	Liver B cells	Acute-phase response Activation
Interleukin-8 (IL-8)	10 kDa	Monocytes, macrophages, endothelial cells	Neutrophils	Chemotaxis, activation
Interferon-γ (IFN-γ)	21–24 kDa	T cells, NK cells	Macrophages	Activation (inflammation)
Interleukin-12 (IL-12)	70 kDa	Macrophages	T cells, B cells, NK cells	Activation, differentiation
Interleukin-18		Macrophages	T cells, NK cells	Activation, differentiation
IL-10		Monocytes/Th2 lymphocytes, mast cells, regulatory T cells	Macrophages Th1 lymphocytes, NK cells	Inhibition, activation regulation

of TNF-α is its ability to induce apoptosis of a variety of cell types.[37] TNF-induced apoptosis may be one mechanism by which it induces tissue injury at high systemic concentrations.

TNF-α is also a potent stimulus for the release of other pro-inflammatory mediators, particularly IL-1 and IL-6. IL-1 is released primarily by mononuclear phagocytes, and its physiologic effects are essentially identical to those of TNF-α.[38] However, important differences exist between the functions of IL-1 and TNF-α. Most notably, IL-1 does not induce tissue injury or apoptotic cell death by itself, but can potentiate the injurious effects of TNF-α. The IL-1 family of

proteins, including IL-18, is the only group of cytokines for which known natural antagonists have been identified. The IL-1 receptor antagonists (IL-1ra) bind to the IL-1 receptor but do not induce receptor activation.[38] These proteins appear to function as competitive inhibitors of IL-1 action. As noted earlier, the systemic release of IL-1 is dependent on the activation of inflammasomes and caspase-1.[23]

IL-6 is another protein that is commonly increased in the circulation of patients with SIRS.[38] Macrophages, endothelial cells, and fibroblasts secrete this protein. IL-6 itself does not induce tissue injury, but its presence in the circulation has been associated with poor outcome in trauma patients, probably because it is a marker of ongoing inflammation. The primary effect of IL-6 is to induce secretion of acute-phase proteins from the liver as well as to serve as a growth and differentiation factor for B lymphocytes.

Interferon-γ (IFN-γ) is a cytokine that facilitates the amplification of the acute inflammatory response, particularly the stimulation of cytokine secretion, phagocytosis, and respiratory burst activity by macrophages. IFN-γ is secreted primarily by T lymphocytes and natural killer (NK) cells in response to antigen presentation, as well as by macrophage-derived cytokines such as IL-12 and IL-18. The primary effect of IFN-γ is to amplify the inflammatory response of macrophages. In response to IFN-γ, the phagocytic and respiratory burst activities of macrophages are increased, secretion of inflammatory mediators such as TNF-α and IL-1 is enhanced, and antigen presentation is potentiated by upregulation of class II major histocompatibility complex. Blockade of IFN-γ production or function has been shown to markedly reduce the deleterious inflammatory effects induced by bacterial endotoxin.[39] Therefore IFN-γ is believed to be an important factor in the amplification of SIRS.

Chemokines are a family of proteins that function primarily as chemotactic factors for leukocytes and, when produced inappropriately or in excess, can contribute to damaging systemic or local inflammation (Table 19.3). IL-8 is the most widely studied chemokine in the setting of sepsis and SIRS; it is a potent chemoattractant for neutrophils and is a major factor in recruiting neutrophils to inflammatory foci. Several studies have shown that IL-8 plays a role in mediating tissue injury in the setting of trauma and burn injury, particularly in the lung.[40,41]

Production of most soluble mediators of inflammation is regulated at the transcriptional level. Some of the key transcription factors that control pro-inflammatory gene expression include nuclear factor-κB (NF-κB), AP-1, and IRF-3 (Fig. 19.5). NF-κB is composed of a family of proteins including p50 (NF-κB1), p65 (RelA), C-Rel, and p52 (NF-κB2) that combine to form homo- or heterodimers and ultimately function to regulate the transcription of a variety of cytokine, chemokine, adhesion molecule, and enzyme genes involved in SIRS.[42] Increased translocation of NF-κB has been associated with a poor outcome in some studies. Activation of NF-κB in peripheral blood monocytes correlates with increased mortality in septic patients, and alveolar macrophages from patients with adult respiratory distress syndrome (ARDS) exhibited higher nuclear NF-κB levels than critically ill patients without ARDS.[43,44] The AP-1 complex is activated through activation of MAP kinases by stimuli that are similar to those required for NF-κB mobilization. IRF-3 is mobilized through activation of the Trif-associated signaling pathway and results primarily in transcription of type I interferon (IFN-α) genes. The STAT1 pathway is induced by activation of type I (IFN-α) and type II (IFN-γ) receptors. Together these transcription factors mediate the transcription of numerous factors involved in inflammation and tissue repair (Fig. 19.6).

Table 19.3 Classification of Chemokines

Chemokine Type	Target Cell
CXC CHEMOKINES	
CXCL8 (IL-8, mouse MIP-2)	Neutrophils
CXCL1 (GROα, mouse KC)	Neutrophils
CXCL2 (GROβ, mouse KC)	Neutrophils
CXCL3 (GROγ, mouse KC)	Neutrophils
CXCL5 (ENA-78)	Neutrophils
CXCL6 (GCP-2)	Neutrophils
CXCL4 (PF4)	Fibroblasts, stem cells
CXCL9 (Mig)	T and NK cells
CXCL10 (IP-10)	T and NK cells
CXCL11 (I-TAC)	T and NK cells
CXCL12 (SDF-1α/β)	T lymphocytes
CC CHEMOKINES	
CCL3 (MIP-1α)	Monocyte/macrophages, T and B cells, NK cells, basophils
CCL4 (MIP-1β)	Same as above
CCL22 (MDC)	Monocyte, T lymphocytes
CCL25 (TECK)	Macrophages, T lymphocytes
CCL17 (TARC)	T lymphocytes
CCL5 (RANTES)	Monocyte/macrophages, T/NK cells
BASOPHILS	
CCL14 (HCC-1)	Monocytes
CCL16 (HCC-4)	Monocytes, lymphocytes
CCL18 (DC-CK-1)	T lymphocytes
CCL20 (MIP-3α)	T lymphocytes
CCL19 (MIP-3β)	T lymphocytes
CCL2 (MCP-1)	T lymphocytes, monocytes,
CCL8 (MCP-2)	Same as above
CCL7 (MCP-3)	Same as above
CCL13 (MCP-4)	Same as above
CCL11 (Eotaxin)	Eosinophils
OTHER CHEMOKINES	
XCL1 (Lymphotactin)	T lymphocytes, NK cells
CX3CL1 (Fractalkine)	T lymphocytes, monocytes

The current conventional names of chemokines are presented and original names are provided in parentheses for reference.

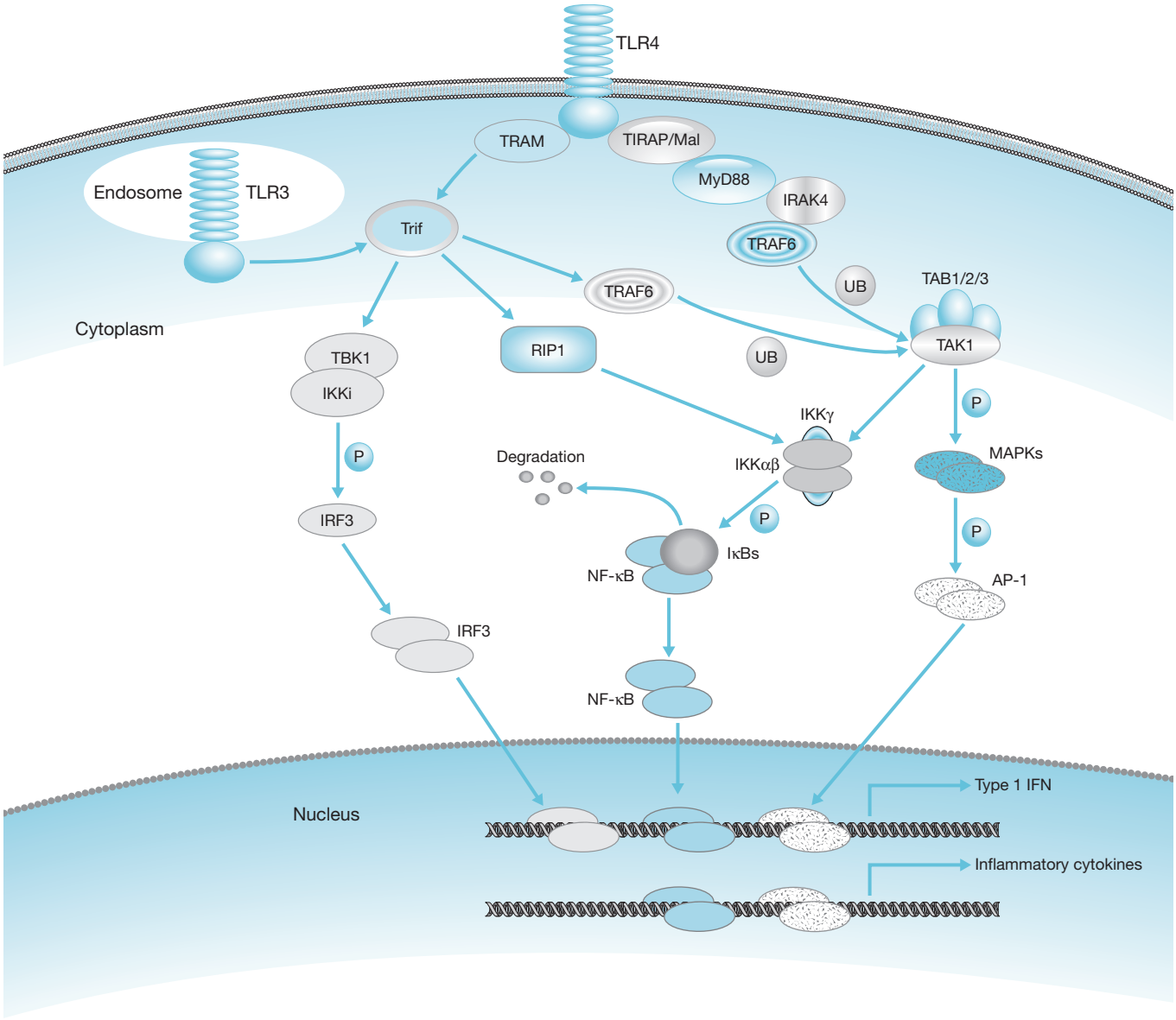


Fig. 19.5 Major inflammation-associated transcription factors include nuclear factor-κB (NF- κB), AP-1, and IRF-3. Activation of these pathways is mediated through MyD88- and Trif-dependent signaling after Toll-like receptor ligation. (From Kawai T, Akira S. TLR Signaling. Cell Death Differ. 2006;13:816–825.)

Several noncytokine factors have been implicated in the pathogenesis of SIRS. Platelet-activating factor (PAF) is a phospholipid autocoid released by endothelial cells that regulates the release of cytokines and amplifies the proinflammatory response. It appears to be an important factor in the adhesion of neutrophils to endothelial cells. The prolonged presence of PAF in the serum of patients with SIRS has correlated with poor outcome.[45] Eicosanoids are arachidonic acid metabolites that regulate many aspects of the immune response. Leukotrienes (LTC4–LTE4) induce contraction of endothelial cells and encourage capillary leakage.[46] Thromboxane A2, a macrophage- and platelet-derived factor, promotes platelet aggregation, vasoconstriction and, potentially, tissue thrombosis.[47]

The complement cascade is composed of more than 30 proteins that interact in a complex fashion to mediate inflammation and direct lysis of microbes and other cells (Fig. 19.7). However, in SIRS, excessive complement activation appears to cause significant cellular injury in the host. Products of the complement cascade, most notably C3a and C5a, are potent activators of inflammation and leukocyte chemotaxis.[48] C3a and C5a also directly activate neutrophils and promote release of reactive oxygen intermediates and proteases. Excessive release of these factors can result in significant tissue injury. The membrane attack complex (MAC) is the terminal component of the complement cascade. MAC results from the aggregation of the complement components C5–C9 on biological membranes. The accumulation of MAC on cell surfaces can result in significant tissue and cellular injury and may be a major factor in the pathogenesis of MODS. Suber and colleagues[49] have reported that complement-mediated responses to self-antigens exacerbate tissue injury after burn injury.

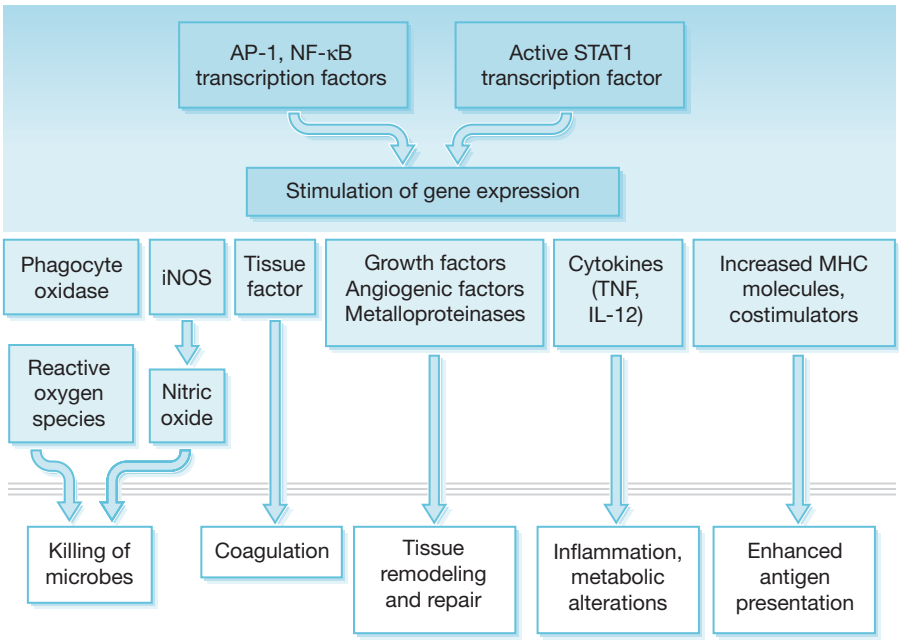
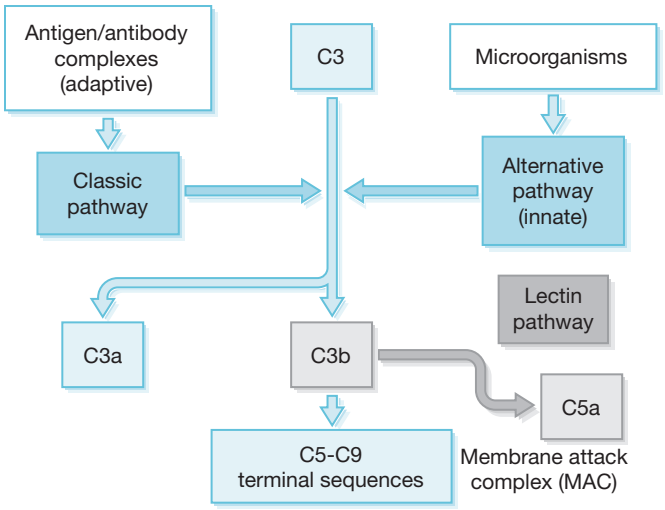


Fig. 19.6 Regulation of pro-inflammatory gene expression. Inflammatory stimuli induce activation of transcriptional pathways mediated by nuclear factor-κB (NF-κB), AP-1, and STAT1 that result in production of pro-inflammatory mediators. (From Cotran R, Kumar V, Collins T, eds., *Robbins pathologic basis of disease*, 6th edn. Philadelphia: WB Saunders; 1999:75.)



C3a and C5a (anaphylactotoxins): increase vascular permeability, chemotactic factors, opsonins

Fig. 19.7 The complement system can be activated by three primary mechanisms and facilitates the amplification of innate and acquired immune responses as well as directly mediating microbial lysis. The primary functions of complement are opsonization, leukocyte chemotaxis, and direct killing of microbes. (From Abbas AK and Lichtman AH, *Cellular and molecular immunology*, 5th edn., Saunders).

Circulating Cytokines as Markers of SIRS and Predictors of Outcome

Numerous studies have been undertaken with the goal of using plasma cytokine levels as diagnostic and prognostic markers in patients with SIRS or sepsis. This approach seems logical based on the observation that circulating cytokines have been observed in several clinical studies of trauma, sepsis, and thermal injury. Given its central role in the activation and regulation of the pro-inflammatory response, TNF-α has been studied extensively as a plasma marker of SIRS. The results have been inconsistent. Martin et al.[50] showed that TNF-α levels were markedly elevated in patients with septic shock and correlated with fatal outcome. However, their results also showed that trauma patients did not exhibit the same marked elevations in circulating TNF-α, nor did circulating TNF-α concentrations correlate with increased mortality in trauma patients. In some published studies, measurement of circulating TNF-α levels in burn patients has not provided a useful marker of outcome.[51,52] Overall, plasma TNF-α levels have been variable and inconsistent and have not correlated with mortality or the development of MODS. However a study by Zhang et al.[53] in 25 patients with greater than 30% total body surface area (TBSA) burns demonstrated marked increases in plasma TNF-α levels and a significant correlation between TNF-α concentration and shock, MODS, and death. These findings support the results of Marano et al.,[54] who showed a significant correlation between circulating TNF-α concentration and mortality in burned patients. Therefore, taken together, these results show that TNF-α could serve as a useful marker of ongoing inflammation as well as an indicator of morbidity and mortality in the setting of burn injury, but controversy remains.

TNF-α interacts with two known cell surface receptors designated tumor necrosis factor receptor (TNFR)-I and TNFR-II. TNFR-I, also known as TNF-R55 or p55, is expressed on a variety of cells and its activation mediates most of the activities of TNF-α, including induction of apoptosis. Activation of TNFR-II (TNF-R75 or p75) results

in cellular proliferation and activation. During inflammatory states, TNFR are released from cells and may serve as antagonists of TNF-α. Several investigators have characterized surface-bound and soluble TNFR (sTNFR) in sepsis and trauma.[53,55,56] Hubl et al.[55] showed that surface TNFR-I was up-regulated, whereas TNFR-II was down-regulated in patients with SIRS. Increased TNFR-I correlated with increased body temperature but not with survival. SIRS patients with decreased surface TNFR-II had a trend toward increased mortality. A study by Zhang et al.[53] showed a higher incidence of shock, MODS, and mortality in burn patients with increased plasma sTNFR-I and sTNFR-II levels. Presterl et al.[56] showed a correlation between sTNFR and APACHE III scores, as well as the incidence of shock and mortality in septic patients. Sikora and colleagues[57] have reported increased concentrations of sTNFR-I and sTNFR-II in the plasma of burned children. sTNFR concentrations correlated with burn surface area and decreased with adequate treatment. Children with hypovolemic shock had higher plasma concentrations of sTNFR. Overall, in the studies published to date, the presence of high levels of circulating sTNFR correlates with ongoing inflammation and may serve as an indicator of poor prognosis.

Another family of proteins that has been extensively analyzed as markers of SIRS is IL-1 and IL-1ra. In burn patients, low IL-1ra levels correlated with mortality in two independent studies.[58,59] Plasma IL-1ra levels have been shown to correlate with body surface area burned, extent of third-degree burn, and the presence of inhalational injury, both in adults and children.[52,57,58]

Recently, IL-8 has been reported as a predictor of poor outcome in burn patients.[60] In burn patients with lower levels of IL-8 (<234 pg/mL), IL-8 levels were predictive for multiorgan failure and correlated with the size of the burn injury. In burn patients with high levels (>234 pg/mL), IL-8 was predictive for the development of sepsis and mortality.

Of the cytokine markers studied to date, elevated levels of IL-6 appear to be one of the more consistent markers of poor outcome in burn, trauma, and septic patients. One of the known functions of IL-6 is induction of acute-phase proteins such as CRP by the liver. In some studies, CRP has been shown to parallel IL-6 as a marker of increased mortality.[59] Although IL-6 itself does not appear to have any known direct injurious effects, it apparently serves as a consistent marker of ongoing inflammation. Elevated plasma IL-6 levels have correlated with increased mortality in experimental and clinical studies of thermal injury, sepsis, trauma, and hemorrhagic shock.[51,61] A study by Taniguchi et al.[61] showed that an increased ratio of IL-6 to the anti-inflammatory cytokine IL-10 was a predictor of poor outcome in patients with SIRS.

In trauma and burn patients it is often difficult to differentiate whether SIRS is a result of the injury itself or due to superimposed infection. Most of the clinical signs of systemic infection, such as fever and leukocytosis, are by definition present in SIRS. Therefore considerable attention has been placed on identifying indirect markers of systemic infection that could serve to differentiate SIRS caused by infection from that caused by trauma. It is important clinically to identify patients with systemic infection in order to initiate antibiotic therapy in a timely fashion. Additionally positive blood cultures are the gold standard for diagnosis of systemic infections. Although blood cultures provide important information regarding the presence of infection and the identity of the infecting organism, it can often take several days to obtain reliable results, and the presence of negative cultures does not assure the absence of infection. Therefore efforts have been made to identify other markers of systemic infection. The two markers that have been most consistently elevated in patients with infection are procalcitonin and CRP. Studies have shown that increased plasma levels of procalcitonin or CRP are sensitive markers of systemic infection.[62] Both of these markers have been shown to be more reliable than clinical signs in the diagnosis of infection in high-risk surgical and trauma patients. Recent studies show that procalcitonin and CRP can be used to distinguish patients with systemic infection from those with noninfectious systemic inflammatory processes.[63–65]

Overall several markers of inflammation and infection have been identified in burn and trauma patients. Some of these have been shown to be consistent indicators of injury severity. However, cytokine and noncytokine markers of inflammation are not used routinely in the laboratory evaluation of burned patients. With further research and demonstration of the reliability of these markers, they may become an accepted part of clinical practice. In addition, technology is evolving to measure these markers in a rapid and cost-effective manner, which may allow blood cytokine markers to become a component of patient management in the future.

Anti-Inflammatory Therapy for SIRS

Despite our increased understanding of the role of inflammatory mediators in the pathogenesis of SIRS and sepsis, most anti-inflammatory drug regimens have had little success in the treatment of this problem. Neutralizing approaches to several inflammatory mediators have been studied. All of these studies have demonstrated, at best, marginal improvement in septic morbidity and mortality. None of the direct anti-inflammatory strategies has been successfully employed to minimize burn-associated inflammation. One of the most widely studied approaches for the treatment of SIRS is the use of monoclonal antibodies to TNF-α. Several multicenter, prospective clinical trials were undertaken in septic patients using several different antibodies to TNF-α.[66,67] Those studies did not demonstrate improved outcome in patients receiving anti-TNF-α compared to placebo. One study evaluated the efficacy of a chimeric antibody to TNF in patients with severe sepsis.[67] Circulating levels of TNF-α as well as a variety of other inflammatory mediators were assessed. Although circulating levels of TNF-α were transiently decreased, anti-TNF-α therapy did not result in reduction of circulating levels of other inflammatory mediators such as IL-1β, IL-1ra, sTNFR, or IL-6. In addition, evidence of systemic inflammation was not reduced and overall mortality was not improved in anti-TNF-α-treated patients. Similarly, the use of sTNFR as a strategy to neutralize the systemic effects of TNF-α and reduce sepsis-associated morbidity and mortality was unsuccessful.[68] Other anti-inflammatory approaches that have been studied and found to be largely ineffective include

the use of IL-1ra,[69,70] anti-bradykinin,[71] PAFra,[72,73] and ibuprofen.[74,75]

Because of the relative ineffectiveness of anti-inflammatory therapy aimed at neutralizing single mediators, more broad-based strategies were developed with the goal of simultaneously neutralizing, removing, or inhibiting the production of numerous inflammatory mediators. Hemofiltration was one approach that received considerable attention. Several studies have shown that hemofiltration will increase the clearance of inflammatory mediators, particularly IL-6, from blood in patients with sepsis.[76,77] However none of these studies has demonstrated a significant reduction in IL-6 plasma levels. A study by Kellum et al.[77] showed that continuous venovenous hemofiltration (CVVH) reduced plasma TNF-α concentrations by 13%, and the use of continuous venovenous hemodialysis (CVVHD) resulted in a 32% increase in circulating TNF-α levels. Overall the use of hemofiltration has been largely ineffective in removing significant amounts of inflammatory mediators from the blood of patients with sepsis, and there is currently no evidence that this approach will reduce morbidity and mortality.

The use of glucocorticoids in the treatment of sepsis has been proposed for more than 30 years. A meta-analysis[78] of studies using high-dose glucocorticoids in the treatment of sepsis was published in 1995 and later summarized by Zeni and colleagues.[79] Overall the use of high-dose glucocorticoids to treat sepsis and septic shock has not been beneficial. In many studies, the use of glucocorticoids in septic patients was associated with increased mortality. In burned patients there is no evidence that administration of glucocorticoids provides effective treatment for systemic inflammation. More recent studies show that replacement dose steroids will improve survival in septic patients who have adrenal insufficiency.[80] Recent guidelines from the Surviving Sepsis Campaign advocate the use of replacement dose glucocorticoids in septic patients refractory to conventional management.[81]

The failure of anti-inflammatory approaches to improve outcome in patients with severe sepsis or septic shock is likely to be multifactorial. First, the inflammatory response to injury and sepsis is induced by a complex array of mediators that are largely interrelated and have significant redundancy. Therefore, blocking or neutralizing a single mediator is not likely to have a marked effect on the overall response. Second, the same mediators that are important in inducing tissue injury also play an important role in antimicrobial immunity, and blockade of these mediators may leave the host more susceptible to subsequent infection. Third, many of the mediators, particularly TNF-α and IL-1β, are released within minutes of injury and mobilize the inflammatory cascade shortly thereafter. Therefore, by the time that signs of SIRS or sepsis are apparent, many of the injurious effects of the inflammatory response have already been set in motion, making therapy ineffective. A recent emphasis has been placed on the identification of late mediators of inflammatory injury. This search has been prompted by the observation that SIRS- and sepsis-associated death occur days after the peak effect of inflammatory cytokines. One potential late mediator that has recently been identified is HMGB-1.[82] HMGB-1 is released by macrophages up to 8 h after lipopolysaccharide (LPS) challenge and persists in the circulation for days. Administration of anti-HMGB-1 to septic mice has been shown to improve survival. Conversely systemic administration of HMGB-1 to mice is lethal. Whether HMGB-1 plays an important role in inflammatory injury in humans remains to be determined. However the concept of late mediators of inflammatory tissue injury may improve our understanding of the pathophysiology of SIRS.

As discussed earlier, factors that appear to be important in limiting the extent of SIRS and, in many cases, reducing the incidence of shock and MODS are appropriate fluid resuscitation, hemodynamic support, treatment of infection with antibiotics, excision of necrotic tissue, and adequate nutritional support.[83] There is controversy regarding the ideal fluid for volume resuscitation in trauma and burn patients. However, recent studies show that hypertonic saline has beneficial effects in modulating the SIRS-associated immunological cascade as well as in restoring hemodynamic parameters and microcirculatory flow. The effect of hypertonic saline on immune function has largely centered on attenuation of post-injury immunosuppression. Recent studies have shown that resuscitation with hypertonic saline will improve macrophage and T-cell function as well as increase resistance to infection in experimental models of trauma and hemorrhage.[84,85] However, the use of hypertonic fluids has not gained widespread support in burn resuscitation because of the risk of hypernatremia and associated complications. Proper nutritional support is also an important factor in the treatment of severely injured patients. Enteral feeding formulas supplemented with glutamine, arginine, omega-3 fatty acids, and nucleotides have been shown to improve outcome in trauma patients.[86] Overall, trauma patients receiving immune-enhancing diets have been shown to have fewer infectious complications. In general, enteral feeding has been shown to maintain gut integrity and improve outcome in burn patients.

Tracey and colleagues have described a cholinergic anti-inflammatory pathway that may be important in the regulation of inflammation and could be exploited for therapeutic benefit.[87,88] As described, local inflammation activates afferent fibers of the vagus nerve that signal the brain to elicit an anti-inflammatory response through efferent vagal fibers (Fig. 19.8). Acetylcholine released by the vagus interacts with α7 nicotinic acetylcholine receptors (α7 nAChR) on macrophages and suppresses the production of pro-inflammatory mediators. Those investigators have shown that electrical stimulation of the vagus nerve will attenuate the pro-inflammatory response induced by cecal ligation and puncture or endotoxin challenge. Acetylcholine has also been shown to inhibit the release of pro-inflammatory cytokines by cultured macrophages following endotoxin challenge.[87,88] More specific α7 nAChR agonists are under investigation for the treatment of hyperinflammatory states, and the possibility of exploiting the cholinergic anti-inflammatory pathway for therapeutic benefit remains to be established.

ACTIVATION OF THE COAGULATION CASCADE DURING INFLAMMATION

Inflammation and coagulation are intimately intertwined. The coagulation cascade is activated during both tissue

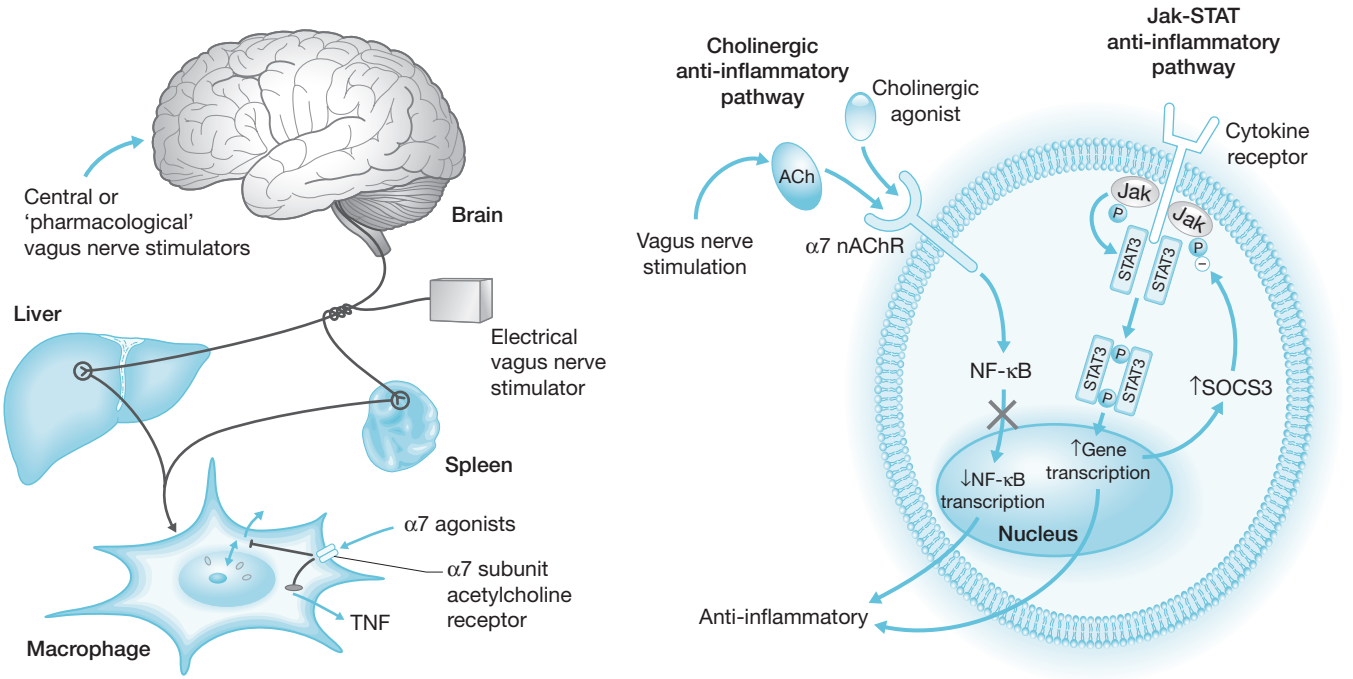


Fig. 19.8 The cholinergic anti-inflammatory pathway. Tissue inflammation sends afferent signals to the central nervous system, resulting in activation of the cholinergic anti-inflammatory pathway. Release of acetylcholine by the vagus nerve induces anti-inflammatory effects by binding to nicotinic receptors on the surface of leukocytes. (Adapted from Czura CJ and Tracey KJ. Automatic neural regulation of immunity. *J Int Med.* 2005;257:156–166; Metz CN, Tracey KJ. It takes nerve to dampen inflammation. *Nat Immunol.* 2005;6(8):756–757; Pavlov et al. *Crit Care Med.* 2007;35:1139.)

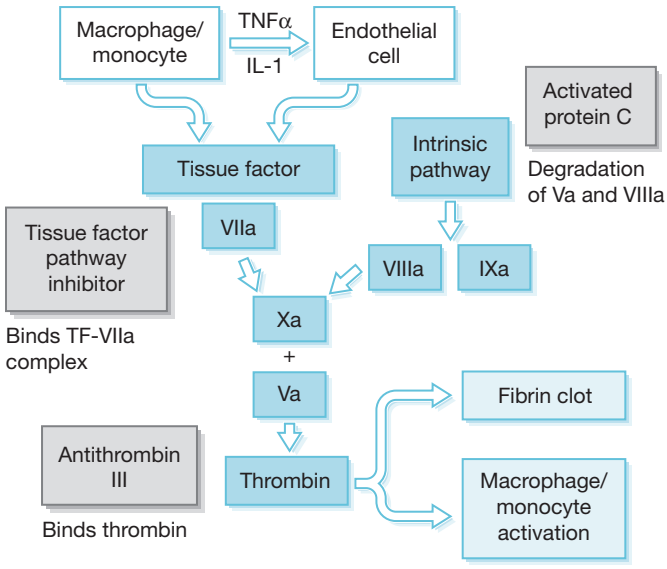


Fig. 19.9 Regulation of the coagulation cascade during inflammation. Inflammation primarily causes activation of the extrinsic coagulation pathway.

injury and infection. It is divided into two pathways that converge and ultimately cause the activation of thrombin, with subsequent cleavage of fibrinogen into fibrin (Fig. 19.9). The intrinsic pathway is a series of plasma proteins that are activated by Hageman factor (factor XII), a protein synthesized in the liver that is activated by binding to collagen, basement membrane, or activated platelets. Activated Hageman factor triggers a cascade of proteins to become activated, resulting in the formation of thrombin. The intrinsic pathway is most commonly activated by direct tissue trauma. In contrast, the extrinsic pathway is initiated by the production of tissue factor. Recent studies indicate that the extrinsic pathway is the primary coagulation pathway activated during infection and systemic inflammation, particularly during sepsis and SIRS.[89] Tissue factor is expressed on tissue surfaces that are not normally exposed to the vascular compartment, such as subcutaneous tissues and the adventitial layer of blood vessels. In addition, endothelial cells and activated monocytes produce tissue factor during periods of inflammation in response to TNF-α, IL-1, IL-6, and CRP.[90] The presence of tissue factor causes activation of factor VII, which then forms a complex with tissue factor and ultimately causes the formation of thrombin by the activation of a series of coagulation factors (Fig. 19.9). Activation of the coagulation cascade is not only important in the formation of fibrin clots but also has important effects on the pro-inflammatory response. Factor Xa, thrombin, and the tissue factor-VIIa complex have been shown to elicit pro-inflammatory activity. Specifically, thrombin and the tissue factor-VIIa complex can induce production of pro-inflammatory cytokines such as TNF-α by mononuclear and endothelial cells.[89] That effect appears to be mediated by the binding of these factors to protease-activated receptors on the surface of target cells. Therefore acute inflammation causes activation of the coagulation cascade, which can then further potentiate the inflammatory response.

Activation of the clotting cascade during inflammation is limited by several factors. This is important because it prevents uncontrolled induction of procoagulant mechanisms.

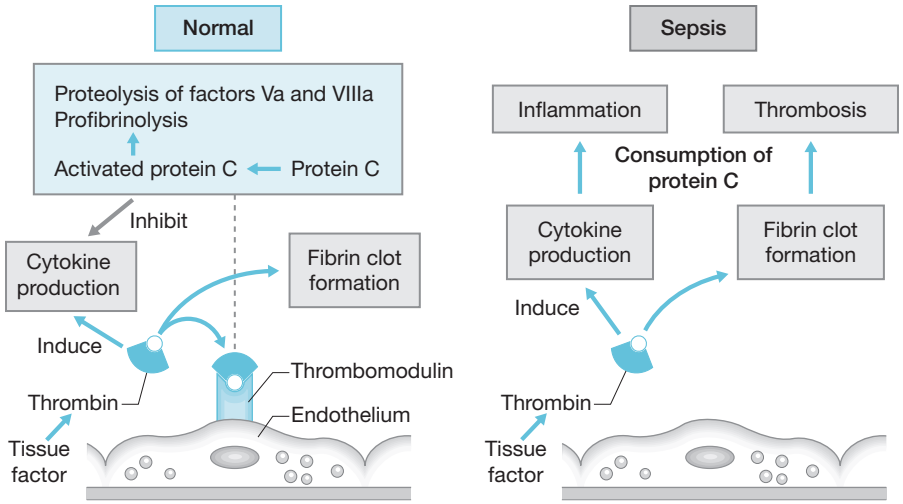


Fig. 19.10 Protein C is a circulating protein that is activated by the thrombin–thrombomodulin complex on the surface of endothelial cells. Activation of protein C decelerates the clotting cascade by inactivating factors Va and VIIIa. Activated protein C also inhibits thrombin-induced production of tumor necrosis factor-α (TNFα) by monocytes by inhibiting the activation of transcription factors nuclear factor-κB (NF-κB) and AP-1.

The best-defined factors are antithrombin, the protein C system, and the tissue factor pathway inhibitor. Antithrombin is produced in the liver and directly binds to and inactivates thrombin.[91] The binding of antithrombin to thrombin is greatly potentiated by heparin and by glycosaminoglycans present on the endothelial cell surface. In rodents interaction of antithrombin with the endothelial cell surface promotes the release of PGI_2, which inhibits TNF-α production by monocytes through the inhibition of transcription factor NF-κB activation.[92] Thus antithrombin may have anti-inflammatory properties in addition to its function in regulating coagulation.

Protein C is a circulating protein that is activated by the thrombin–thrombomodulin complex on the surface of endothelial cells (Fig. 19.10). Activation of protein C decelerates the clotting cascade by inactivating factors Va and VIIIa. Activated protein C (APC) also inhibits thrombin-induced production of TNF-α by monocytes by inhibiting the activation of transcription factors NF-κB and AP-1.[93] Therefore APC has both anticoagulant and anti-inflammatory properties. During sepsis, APC levels can become depleted due to consumption and inflammation-induced down-regulation of thrombomodulin. This results in unchecked formation of thrombin, causing accelerated coagulation and increased pro-inflammatory activity. The importance of protein C in regulating thrombin formation during sepsis is demonstrated by increased mortality in septic patients with low APC levels.[94] Those findings led to the investigation of APC as an intervention in patients with sepsis. Early trials showed that APC therapy was effective in improving survival in patients with severe sepsis.[95] However, further investigation did not demonstrate significant benefit.[96,97]

A third important factor in the regulation of thrombin formation is the tissue factor pathway inhibitor (TFPI). TFPI is present on the surface of endothelial cells and bound to lipoproteins in plasma. TFPI inactivates tissue factor by forming a quaternary complex with tissue factor and factor VIIa. Factor Xa is the fourth component of the complex.[98] Inhibition of tissue factor function inhibits activation of the extrinsic clotting pathway during inflammation. Infusion of TFPI has also been shown to reduce pro-inflammatory cytokine production during endotoxin infusion in baboons but not in humans.

THE HEMODYNAMIC RESPONSE

The full clinical picture of systemic inflammation after thermal injury is characterized by two primary phases. After the initial injury, inflammation leads to increased vascular permeability and the exudation of protein-rich fluid from the vascular compartment to the interstitium. This early fluid leak results in intravascular hypovolemia and interstitial edema formation. If the patient is adequately resuscitated, a hyperdynamic phase will ensue that is characterized by a low systemic vascular resistance and high cardiac output. Patients who are not well resuscitated or whose cardiac function is compromised may not be able to increase their cardiac output to the extent needed to maintain arterial blood pressure during states of extensive vasodilatation and so might exhibit tissue hypoperfusion and shock. A reduced vascular responsiveness to vasoconstrictors may inhibit successful pharmacologic intervention, and patients could develop irreversible shock. An intravenous bolus injection of 4 ng/kg endotoxin into healthy volunteers mimics some aspects of the hemodynamic response seen in septic patients and adequately resuscitated burn victims.[99,100] The low systemic vascular resistance and the elevated cardiac output can also be induced in animal models by continuous infusion of low-dose endotoxin[101] or bacteria.[102,103]

Changes in Endothelial Permeability

Burn injury, trauma, and sepsis increase microvascular permeability in both the systemic[104] and the pulmonary

circulations.[105] Increased vascular permeability and cutaneous edema are hallmarks of burn shock. The increase in systemic vascular permeability results in the exudation of protein-rich fluid from the vascular compartment into the interstitium. This results in intravascular volume loss and the concomitant development of interstitial edema. If resuscitation is not prompt and adequate, this loss in intravascular volume will lead to intravascular hypovolemia, hypotension, and inadequate tissue perfusion. Severe interstitial edema formation can lead to the development of compartment syndrome, with compromise of neurovascular integrity. The lungs may also be affected. Edema formation due to an increase in microvascular permeability is a hallmark of the acute lung injury. The factors that determine the transvascular fluid flux are summarized in the Starling-Landis equation:[106,107]

$$J_v = K_f[(P_{mv} - P_i) - \alpha(\pi_{mv} - \pi_i)]$$

where J_v is the transvascular fluid flux, K_f is the filtration coefficient (measure of the endothelial permeability to small solutes and water as well as of the permeability surface area), P_{mv} is the microvascular hydrostatic pressure, P_i is the interstitial hydrostatic pressure, α is the osmotic reflection coefficient to protein, π_{mv} is the microvascular oncotic pressure, and π_i is the interstitial oncotic pressure.

Several investigators have studied lymph flow and lymph protein flux after administration of bacteria or short-time infusion of 1–2 μg/kg of endotoxin in sheep. Two phases of permeability change could be distinguished in these models.[108] During phase 1 there was a high microvascular hydrostatic pressure, as defined by the Gaar equation.[109] This was associated with an increase in lung lymph flow, but the lymph protein concentration was low. It was concluded that the high microvascular hydrostatic pressure was responsible for the early increase in transvascular fluid flux. Thromboxane A2 (TXA2) has been found to be responsible for the vasoconstriction that causes local increases in hydrostatic pressure. Therefore it is not surprising that administration of the thromboxane synthetase inhibitor OKY046 prevented the rise in lymph flow during phase 1.[110] That effect was also noted after blockage of cyclooxygenase by ibuprofen.[111] Early edema formation at the site of burn injury might be due to a different mechanism. Data suggest that a marked fall in interstitial hydrostatic pressure might occur in the injured tissue, which could explain the immediate onset of edema formation after thermal injury.[112,113] These changes might be the result of an inhibition of the fibroblast β1-integrin attachment to collagen.

During phase 2, lymph flow continues to be high. However, the lymph protein concentration rises considerably and the pulmonary artery pressure is only mildly elevated.[108] The oncotic pressure gradient between microvasculature and interstitial space is reduced during that period.[114] Together these data suggest that the permeability of the pulmonary endothelium to protein increases in phase 2. In fact, the reflection coefficient for total protein fell from 0.73 to 0.58, with respective changes in the reflection coefficients for albumin (0.66 to 0.5), IgG (0.76 to 0.64), and IgM (0.91 to 0.83) after 4 hours of *Escherichia coli* sepsis in sheep.[115] Confirmation of this hypothesis is still pending in models of endotoxemia, but it has been generally accepted that the changes in pulmonary transvascular fluid flux in phase 2 represent changes in microvascular permeability. The mechanisms of the increased microvascular permeability are still under discussion.

Endothelial cells play an important role in the regulation of vascular permeability. It has been hypothesized that endothelial cells can contract upon stimulation.[116] As a result, the intercellular gaps might increase in number and/or size, establishing the so-called capillary leak syndrome. The development of the protein-rich high-permeability edema can be ameliorated if substances are administered that raise the endothelial cell content of cyclic adenosine or guanosine monophosphate.[117,118] However, endothelial cells do not merely serve as targets during systemic inflammation: they actively contribute to the ongoing inflammatory process. The endothelial cell can be stimulated by endotoxin, TNF-α, or IL-1 to express E-selectin, an adhesion molecule.[119] E-selectin on the surface of endothelial cells interacts with the corresponding L-selectin complex on polymorphonuclear neutrophils (PMNs) to facilitate rolling of these cells along the endothelium.[120] Moreover endothelial cells secrete the pro-inflammatory cytokines TNF-α and IL-1, which activate PMNs. Conflicting data exist regarding the role of PMNs in SIRS. PMNs are usually found at the site of tissue injury, to which they migrate following a concentration gradient of chemotactic stimuli. Upon stimulation, PMNs roll along endothelial cells, and, in a further step mediated by PMN CD18/CD11b interactions with endothelial ICAM-1, emigrate from the vessel into the interstitial space. Antibodies against the common CD18β chain showed beneficial effects in an animal model of sepsis-induced lung injury, suggesting that integrin-mediated PMN emigration is a functionally important process in the development of acute lung injury.[121] On the other hand, patients who are deficient in CD18 have abundant PMNs in their alveolar spaces, and the monoclonal antibody 60.3 was ineffective in completely blocking the migration of PMNs into the lung in a number of conditions.[122] We have found that in chronic endotoxemia there are few PMNs in the lung but numerous macrophages. Activated PMNs and macrophages release oxygen free radicals and proteases at sites of inflammation. Those processes appear to be functionally important in the development of vascular permeability because administration of oxygen free radical scavengers and antiproteases proved to be useful in diminishing edema accumulation after endotoxin challenge.[123] However, proteases and oxygen radicals are also released by macrophages, which are already present in the tissue, and by monocytes that migrate to sites of inflammation. Depletion of granulocytes by anti-PMN antiserum or by treatment with nitrogen mustard did not prevent the changes in microvascular permeability following the administration of endotoxin.[124,125] Moreover patients deficient in PMNs still develop acute respiratory distress syndrome (ARDS) associated with sepsis.[126,127] On the other hand, treatment of sheep or goats with hydroxyurea, which is another compound used to deplete granulocytes, was effective and diminished fluid accumulation in the lung after endotoxin challenge.[128] However, urea scavenges free radicals, which might explain its efficacy.[129] As the inflammatory response becomes chronic, many

mediators have been released and more than one mechanism may be responsible for capillary leak.

The role of arachidonic acid metabolites in facilitating increased vascular permeability has been extensively investigated. Administration of the thromboxane synthetase inhibitor OKY046 not only reduced transvascular fluid flux in phase 1, but was also effective in phase 2 after endotoxin challenge.[110] This finding suggests that thromboxanes participate in permeability alterations during systemic inflammation. Oxygen free radicals can also increase microvascular permeability, both by activation of endothelial cell contraction and by damaging the endothelial cell membrane. OKY046 has been shown to reverse oxygen free radical-induced lung injury.[130,131] On the other hand, inhibition of cyclooxygenase did not affect transvascular fluid flux during phase 2, even though thromboxane A2 is a cyclooxygenase metabolite.[111] This discrepancy is still unexplained; however, prostacyclin is elevated after endotoxin administration, and this material has many actions that counter the actions of thromboxane. Administration of a cyclooxygenase inhibitor will prevent the release of this salutary eicosanoid.

TNF-α is one of the early mediators in systemic inflammation. It has been reported to be elevated during sepsis and endotoxemia after hemorrhagic shock or thermal injury. It is considered to be one of the most important mediators in the cascade because it has the potential to stimulate or enhance most of the steps in the inflammatory response. Moreover administration of human recombinant TNF-α in the chronic sheep model reproduced most of the effects of endotoxemia, including alterations in pulmonary microvascular permeability.[132,133] TNF-α also induces the secretion of PAF, which is a further early mediator of systemic inflammation. PAF causes an increase in lung lymph flow and permeability to protein when it is infused into conscious sheep.[134] Administration of a PAF antagonist abolished the cardiopulmonary response that occurs during phase 1 and attenuated it during phase 2. However, PAF had no direct effect on endothelial cells. This suggests that it probably increases microvascular permeability through other mechanisms, such as its priming effect on PMNs.[135,136]

If burn patients are adequately resuscitated, they most commonly enter into a phase characterized by hyperdynamic cardiovascular function. The hyperdynamic cardiovascular response is associated with profound changes in pulmonary transvascular fluid flux in the ovine model of continuous endotoxemia.[104,137] The lymph protein concentration gradually decreased after phase 2, and after 24 hours of endotoxemia, the reflection coefficient to protein was at baseline level, whereas the lymph flow was still high. Microvascular hydrostatic pressure, evaluated by Holloway's technique, was not significantly different from baseline.[138] The elevated transvascular fluid flux was attributed to a high filtration coefficient. An increase in both perfused surface area and pore numbers might have contributed to the change in filtration. Repeated injections of endotoxin also reduced subsequent lung lymph production in response to endotoxin.[132] These changes in lung lymph flow were associated with elevations in endothelin and atrial natriuretic peptide.[138,139] However, further studies must determine whether these factors affect pulmonary microvascular changes during the late phases of sepsis and multiple organ failure.

INCREASED EPITHELIAL PERMEABILITY

Permeability changes during systemic inflammation are not restricted to the endothelium. Loss of epithelial barrier function has been noted both in the lung and in the intestine. Administration of 2–4 ng/kg endotoxin to healthy human volunteers increased their alveolar epithelial permeability to the inhaled 492 Da molecule [^{99m}Tc] diethylenetriamine pentaacetate (DTPA) 3 hours after endotoxin had been given.[100] Human volunteers demonstrated a higher intestinal epithelial permeability to mannitol/lactulose.[140] Bacterial translocation occurred during endotoxemia,[141] thermal injury,[142] and multiple trauma with hemorrhagic shock.[143] This might well be interpreted as a loss of intestinal barrier function. Nevertheless one must bear in mind that epithelial permeability to molecules such as lactulose/mannitol and bacterial translocation do not necessarily relate to each other. The epithelium could also be injured by ischemia–reperfusion.[144] In addition to changes in vascular permeability, burn injury also causes marked alterations in vascular tone and myocardial function that are characterized by a variety of temporal alterations.

The Hyperdynamic State

Continuous infusion of endotoxin into sheep and pigs results in a hyperdynamic circulation.[145,146] In addition to a low systemic vascular resistance and a high cardiac output with a slightly decreased mean arterial pressure, the hyperdynamic response is further characterized by hyporesponsiveness of isolated vessels to vasoconstrictors and an increased pulmonary shunt fraction in the presence of a reduced pulmonary hypoxic vasoconstriction.[145,147–149] The high cardiac output is due to low systemic vascular resistance and increased heart rate.[150,151] Paradoxically myocardial function is depressed during sepsis and in severely burned patients.[152,153] The underlying cause of impaired myocardial function is not fully understood. However, reports indicate that pro-inflammatory mediators such as TNF-α, IL-1, IL-6, and nitric oxide (NO) contribute to this alteration.[153,154] The treatment of myocardial function during sepsis and after burn trauma is an important consideration in overall hemodynamic management. The combination of myocardial dysfunction and increased pulmonary vascular resistance is a likely cause of right heart failure in pediatric burn patients. Treatment options include dobutamine and phosphodiesterase inhibitors such as milrinone. The Surviving Sepsis Campaign recommends dobutamine as a first-line agent for treatment of hypotension and hypoperfusion in pediatric patients with sepsis, especially when myocardial dysfunction is present.[81]

NO has been implicated as a mediator of systemic vasodilation and myocardial depression during sepsis and after major burn injury. NO can be synthesized from its precursor L-arginine by three different enzymes (Fig. 19.11). The calcium-dependent constitutive nitric oxide synthases (NOS) such as endothelial NOS (eNOS) and neuronal NOS (nNOS) are responsible for the basal release of NO, which seems to play an important role in the regulation of vascular tone under physiologic conditions. In vitro data suggest that these enzymes might become inactivated early after

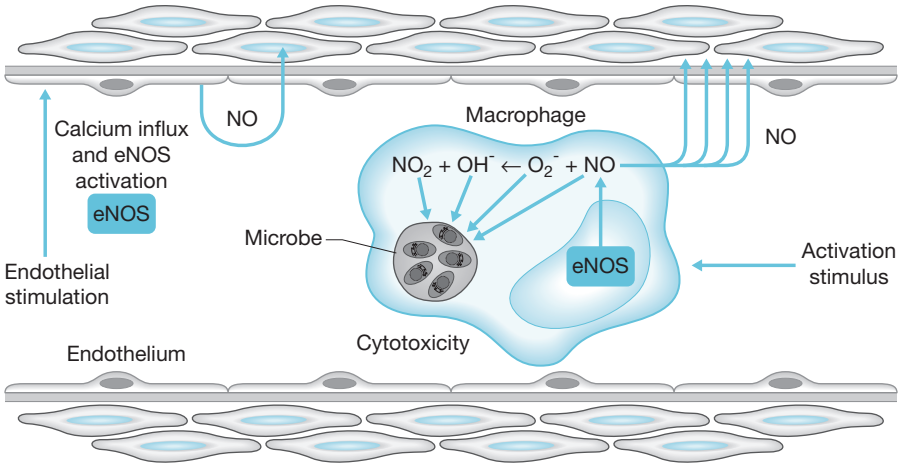


Fig. 19.11 Nitric oxide is an important mediator of inflammation-induced vasodilation, myocardial depression, and organ injury. The synthesis of nitric oxide is mediated by three major nitric oxide synthase (NOS) isoforms.

administration of endotoxin, thereby accounting for some of the vasoconstrictive phenomena seen in phases 1 and 2.[155] Inducible NOS (iNOS) is the major NOS isoform induced during acute inflammation. Depending on the species, cells producing the inducible NOS upon stimulation by endotoxin, TNF-α, IL-1, or IFN-α include macrophages, vascular smooth muscle cells, and vascular endothelium.[156] NO is a lipophilic gas that can easily enter vascular smooth muscle cells where it stimulates the soluble guanylate cyclase to synthesize cyclic guanosine monophosphate (cGMP).[157,158] High levels of cGMP stimulate cells to lower their intracellular Ca^{2+} concentration. This leads to vascular dilatation and hyporesponsiveness to vasoconstrictors. Administration of an NOS inhibitor to septic humans and to endotoxemic sheep increases their vascular resistance and restores their responsiveness to vasoconstrictors.[159–161] Overall it appears that NO is an important mediator of SIRS-induced vascular alterations. However, administration of NOS inhibitors in humans has not improved overall outcome during sepsis or SIRS. Therefore, the mechanisms by which NO alters vascular function during SIRS in humans require further investigation.

Peroxynitrite is an additional NO-associated factor that appears to contribute to SIRS-induced pathology. Peroxynitrite is a free radical that is generated through interactions of NO and oxygen free radicals during periods of severe inflammation and is known to cause cellular injury and organ dysfunction in experimental burn models.[162,163] Treatment of burned sheep with a peroxynitrite degradation catalyst has been shown to reduce lung injury in an ovine model of burn and smoke inhalation injuries.[164] Therefore peroxynitrite appears to be an important mediator of organ injury during periods of systemic inflammation. However, further research is needed to determine the efficacy of treatment approaches aimed at promoting peroxynitrite degradation and neutralization in the clinical setting.

Conclusion

Burn injuries, associated ischemia–reperfusion injury, the presence of necrotic tissue, and sepsis are all events that contribute to SIRS after severe burn injury. Widespread increases in microvascular permeability lead to intravascular hypovolemia and interstitial edema, thereby impairing oxygen diffusion to the tissue. Blood flow may become maldistributed owing to a loss of vasoregulatory function and as a result of widespread microthrombosis. Oxygen utilization also appears to be impaired. The resultant hypoxic cell damage further promotes organ dysfunction. Oxygen free radicals, peroxynitrite, and cytokines also appear to contribute to tissue damage and organ dysfunction. Despite improved understanding of the cellular and molecular mechanisms underlying SIRS, targeting the inflammatory response is not currently an effective treatment option for patients with burn-induced SIRS. Treatment is supportive and includes adequate fluid resuscitation, appropriate use of vasoactive drugs, support of failing organ systems, excision of necrotic tissue, and treatment of infection with antibiotics.

Complete references available online at http://www.expertconsult.inkling.com

Further Reading

dos Santos CC, Gattas DJ, Tsoporis JN, et al. Sepsis-induced myocardial depression is associated with transcriptional changes in energy metabolism and contractile related genes: a physiological and gene expression-based approach. *Crit Care Med.* 2010;38:894-902.

Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med.* 2005;6(1):2-8.

Muckart DJ, Bhagwanjee S. American College of Chest Physicians/Society of Crit Care Med Consensus Conference definitions of the systemic inflammatory response syndrome and allied disorders in relation to critically injured patients. *Crit Care Med.* 1997;25(11):1789-1795.

Szabó C, Módis K. Pathophysiological roles of peroxynitrite in circulatory shock. *Shock.* 2010;34(suppl 1):4-14.

Westphal M, Enkhbaatar P, Schmalstieg FC, et al. Neuronal nitric oxide synthase inhibition attenuates cardiopulmonary dysfunctions after combined burn and smoke inhalation injury in sheep. *Crit Care Med.* 2008;36:1196-1204.

References

1. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM consensus conference committee. American college of chest physicians/society of critical care medicine. *Chest*. 1992;101:1644-1655.
2. Muckart DJ, Bhagwanjee S. American College of Chest Physicians/Society of Critical Care Medicine consensus conference definitions of the systemic inflammatory response syndrome and allied disorders in relation to critically injured patients. *Crit Care Med*. 1997;25(11):1789-1795.
3. Pittet D, Rangel-Frausto S, Li N, et al. Systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock: incidence, morbidities and outcomes in surgical ICU patients. *Intensive Care Med*. 1995;21(4):302-309.
4. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31(4):1250-1256.
5. Rubulotta F, Marshall JC, Ramsay G, et al. Predisposition, insult/infection, response, and organ dysfunction: a new model for staging severe sepsis. *Crit Care Med*. 2009;37(4):1329-1335.
6. Macdonald SP, Arendts G, Fatovich DM, Brown SG. Comparison of PIRO, SOFA, and MEDS scores for predicting mortality in emergency department patients with severe sepsis and septic shock. *Acad Emerg Med*. 2014;21:1257-1263.
7. Marshall JC. The PIRO (predisposition, insult, response, organ dysfunction) model: toward a staging system for acute illness. *Virulence*. 2014;5:27-35.
8. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*. 2016;315:762-774.
9. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med*. 2005;6(1):2-8.
10. Talmor M, Hydo L, Barie PS. Relationship of systemic inflammatory response syndrome to organ dysfunction, length of stay, and mortality in critical surgical illness: effect of intensive care unit resuscitation. *Arch Surg*. 1999;134(1):81-87.
11. Asayama K, Aikawa N. Evaluation of systemic inflammatory response syndrome criteria as a predictor of mortality in emergency patients transported by ambulance. *Keio J Med*. 1998;47(1):19-27.
12. Rangel-Frausto MS, Pittet D, Costigan M, et al. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study [see comments]. *JAMA*. 1995;273:117-123.
13. Haga Y, Beppu T, Doi K, et al. Systemic inflammatory response syndrome and organ dysfunction following gastrointestinal surgery. *Crit Care Med*. 1997;25(12):1994-2000.
14. Sheridan RL, Ryan CM, Yin LM, et al. Death in the burn unit: sterile multiple organ failure. *Burns*. 1998;24(4):307-311.
15. Ryan CM, Schoenfeld DA, Thorpe WP, et al. Objective estimates of the probability of death from burn injuries. *N Engl J Med*. 1998;338(6):362-366.
16. Gando S, Nanzaki S, Kemmotsu O. Disseminated intravascular coagulation and sustained systemic inflammatory response syndrome predict organ dysfunctions after trauma: application of clinical decision analysis. *Ann Surg*. 1999;229(1):121-127.
17. Still JM, Law EJ, Belcher K, et al. A regional medical center's experience with burns of the elderly. *J Burn Care Rehabil*. 1999;20(3):218-223.
18. Wolf SE, Rose JK, Desai MH, et al. Mortality determinants in massive pediatric burns. An analysis of 103 children with > or = 80% TBSA burns (> or = 70% full-thickness). *Ann Surg*. 1997;225:554-565.
19. Kelly JL, O'Sullivan C, O'Riordain M, et al. Is circulating endotoxin the trigger for the systemic inflammatory response syndrome seen after injury? *Ann Surg*. 1997;225(5):530-541, discussion 541-543.
20. Osterloh A, Breloer M. Heat shock proteins: linking danger and pathogen recognition. *Med Microbiol Immunol*. 2008;197:1-8.
21. Zhang Q, Raoof M, Chen Y, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature*. 2010;464(7285):104-107.
22. Fontaine M, Lepape A, Piriou V, Venet F, Friggeri A. Innate danger signals in acute injury: From bench to bedside. *Anaesth Crit Care Pain Med*. 2016;35:283-292.
23. Schroder K, Tschopp J. The inflammasomes. *Cell*. 2010;140(6):821-832.
24. Yeh FL, Shen HD, Fang RH. Deficient transforming growth factor beta and interleukin-10 responses contribute to the septic death of burned patients. *Burns*. 2002;28(7):631-637.
25. Schwacha MG, Chaudry IH. The cellular basis of post-burn immunosuppression: macrophages and mediators. *Int J Mol Med*. 2002;10(3):239-243.
26. Davenport EE, Burnham KL, Radhakrishnan J, et al. Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. *Lancet Respir Med*. 2016;4:259-271.
27. Xiao W, Mindrinos MN, Seok J, et al; the Inflammation and Host Response to Injury Large-Scale Collaborative Research Program. A genomic storm in critically injured humans. *JEM*. 2011;208(13):2581-2590.
28. Pileri D, Accardo Palombo A, D'Amelio L, et al. Concentrations of cytokines IL-6 and IL-10 in plasma of burn patients: their relationship to sepsis and outcome. *Ann Burns Fire Disasters*. 2008;21(4):182-185.
29. Vanzant EL, Lopez CM, Ozrazgat-Baslanti T, et al. Persistent inflammation, immunosuppression, and catabolism syndrome after severe blunt trauma. *J Trauma Acute Care Surg*. 2014;76:21-30.
30. Paterson HM, Murphy TJ, Purcell EJ, et al. Injury primes the innate immune system for enhanced Toll-like receptor reactivity. *J Immunol*. 2003;171(3):1473-1483.
31. Anderson BO, Harken AH. Multiple organ failure: inflammatory priming and activation sequences promote autologous tissue injury. *J Trauma*. 1990;30:S44-S49.
32. Dehring DJ, Lübbesmeyer HJ, Fader RC, et al. Exaggerated cardiopulmonary response after bacteremia in sheep with week-old thermal injury. *Crit Care Med*. 1993;21:888-893.
33. Koike K, Moore FA, Moore EE, et al. Endotoxin after gut ischemia/reperfusion causes irreversible lung injury. *J Surg Res*. 1992;52:656-662.
34. Ciancio MJ, Hunt J, Jones SB, et al. Comparative and interactive in vivo effects of tumor necrosis factor alpha and endotoxin. *Circ Shock*. 1991;33:108-120.
35. Spooner CE, Markowitz NP, Saravolatz LD. The role of tumor necrosis factor in sepsis. *Clin Immunol Immunopathol*. 1992;62:S11-S17.
36. Torre-Amione G, Bozkurt B, Deswal A, et al. An overview of tumor necrosis factor alpha and the failing human heart. *Curr Opin Cardiol*. 1999;14(3):206-210.
37. Voss M, Cotton MF. Mechanisms and clinical implications of apoptosis. *Hosp Med*. 1998;59(12):924-930.
38. van der Poll T, van Deventer SJ. Cytokines and anticytokines in the pathogenesis of sepsis. *Infect Dis Clin North Am*. 1999;13(2):413-426, ix.
39. Doherty GM, Lange JR, Langstein HN, et al. Evidence for IFN-gamma as a mediator of the lethality of endotoxin and tumor necrosis factor-alpha. *J Immunol*. 1992;149(5):1666-1670.
40. Laffon M, Pittet JF, Modelska K, et al. Interleukin-8 mediates injury from smoke inhalation to both the lung endothelial and the alveolar epithelial barriers in rabbits. *Am J Respir Crit Care Med*. 1999;160:1443-1449.
41. Sakurai H, Soejima K, Schmalstieg FC, et al. Inhibition of lung permeability changes after burn and smoke inhalation by an anti-interleukin-8 antibody in sheep. *Surg Today*. 2009;39(5):399-406.
42. Christman JW, Lancaster LH, Blackwell TS. Nuclear factor kappa B: a pivotal role in the systemic inflammatory response syndrome and new target for therapy. *Intensive Care Med*. 1998;24(11):1131-1138.
43. Bohrer H, Qiu F, Zimmermann T, et al. Role of NFkappaB in the mortality of sepsis. *J Clin Invest*. 1997;100(5):972-985.
44. Schwartz MD, Moore EE, Moore FA, et al. Nuclear factor-kappa B is activated in alveolar macrophages from patients with acute respiratory distress syndrome. *Crit Care Med*. 1996;24(8):1285-1292.
45. Graham RM, Stephens CJ, Silvester W, et al. Plasma degradation of platelet-activating factor in severely ill patients with clinical sepsis. *Crit Care Med*. 1994;22(2):204-212.
46. Quinn D, Tager A, Joseph PM, et al. Stretch-induced mitogen-activated protein kinase activation and interleukin-8 production in type II alveolar cells. *Chest*. 1999;116(1 suppl):89S-90S.
47. Heller A, Koch T, Schmeck J, et al. Lipid mediators in inflammatory disorders. *Drugs*. 1998;55(4):487-496.
48. Czermak BJ, Sarma V, Pierson CL, et al. Protective effects of C5a blockade in sepsis. *Nat Med*. 1999;5(7):788-792.
49. Suber F, Carroll MC, Moore FD Jr. Innate response to self-antigen significantly exacerbates burn wound depth. *Proc Natl Acad Sci USA*. 2007;104(10):3973-3977.

50. Martin C, Boisson C, Haccoun M, et al. Patterns of cytokine evolution (tumor necrosis factor-alpha and interleukin-6) after septic shock, hemorrhagic shock, and severe trauma. *Crit Care Med*. 1997;25:1813-1819.
51. Cannon JG, Friedberg JS, Gelfand JA, et al. Circulating interleukin-1 beta and tumor necrosis factor-alpha concentrations after burn injury in humans. *Crit Care Med*. 1992;20(10):1414-1419.
52. Drost AC, Burleson DG, Cioffi WG, et al. Plasma cytokines following thermal injury and their relationship with patient mortality, burn size, and time postburn. *J Trauma*. 1993;35:335-339.
53. Zhang B, Huang YH, Chen Y, et al. Plasma tumor necrosis factor-alpha, its soluble receptors and interleukin-1beta levels in critically burned patients. *Burns*. 1998;24(7):599-603.
54. Marano MA, Fong Y, Moldawer LL, et al. Serum cachectin/tumor necrosis factor in critically ill patients with burns correlates with infection and mortality. *Surg Gynecol Obstet*. 1990;170:32-38.
55. Hubl W, Wolfbauer G, Streicher J, et al. Differential expression of tumor necrosis factor receptor subtypes on leukocytes in systemic inflammatory response syndrome. *Crit Care Med*. 1999;27(2):319-324.
56. Presterl E, Staudinger T, Pettermann M, et al. Cytokine profile and correlation to the APACHE III and MPM II scores in patients with sepsis. *Am J Respir Crit Care Med*. 1997;156(3 Pt 1):825-832.
57. Sikora JP, Chlebna-Sokol D, Andrzejewska E, et al. Clinical evaluation of proinflammatory cytokine inhibitors (sTNFR I, sTNFR II, IL-1ra), anti-inflammatory cytokines (IL-10, IL-13) and activation of neutrophils after burn-induced inflammation. *Scand J Immunol*. 2008;68:145-152.
58. Mandrup-Poulsen T, Wogensen LD, Jensen M, et al. Circulating interleukin-1 receptor antagonist concentrations are increased in adult patients with thermal injury. *Crit Care Med*. 1995;23(1):26-33.
59. Neely AN, Hoover DL, Holder IA, et al. Circulating levels of tumour necrosis factor, interleukin 6 and proteolytic activity in a murine model of burn and infection. *Burns*. 1996;22(7):524-530.
60. Kraft R, Herndon DN, Finnerty CC, et al. Predictive value of IL-8 for sepsis and severe infections after burn injury: a clinical study. *Shock*. 2015;43(3):222-227.
61. Taniguchi T, Koido Y, Aiboshi J, et al. Change in the ratio of interleukin-6 to interleukin-10 predicts a poor outcome in patients with systemic inflammatory response syndrome. *Crit Care Med*. 1999;27(7):1262-1264.
62. Miller PR, Munn DD, Meredith JW, et al. Systemic inflammatory response syndrome in the trauma intensive care unit: who is infected? *J Trauma*. 1999;47(6):1004-1008.
63. Bafadhel M, Clark TW, Reid C, et al. Procalcitonin and C reactive protein in hospitalized adult patients with community acquired pneumonia, exacerbation of asthma and chronic obstructive pulmonary disease. *Chest*. 2011;139:1410-1418.
64. Gilbert DN. Use of plasma procalcitonin levels as an adjunct to clinical microbiology. *J Clin Microbiol*. 2010;48:2325-2329.
65. Becker KL, Snider R, Nylen ES. Procalcitonin in sepsis and systemic inflammation: a harmful biomarker and therapeutic target. *Br J Pharmacol*. 2010;159:253-264.
66. Abraham E, Anzueto A, Gutierrez G, et al. Double-blind randomised controlled trial of monoclonal antibody to human tumour necrosis factor in treatment of septic shock. NORASEPT II Study Group. *Lancet*. 1998;351(9107):929-933.
67. Clark MA, Plank LD, Connolly AB, et al. Effect of a chimeric antibody to tumor necrosis factor-alpha on cytokine and physiologic responses in patients with severe sepsis – a randomized, clinical trial. *Crit Care Med*. 1998;26(10):1650-1659.
68. Fisher CJ Jr, Agosti JM, Opal SM, et al. Treatment of septic shock with the tumor necrosis factor receptor: Fc fusion protein. The Soluble TNF Receptor Sepsis Study Group. *N Engl J Med*. 1996;334(26):1697-1702.
69. Fisher CJ Jr, Dhainaut JF, Opal SM, et al. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra Sepsis Syndrome Study Group. *JAMA*. 1994;271(23):1836-1843.
70. Opal SM, Fisher CJ, Dhainaut JFA, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis – a phase III, randomized, double-blind, placebo-controlled, multicenter trial. *Crit Care Med*. 1997;25:1115-1124.
71. Fein AM, Bernard GR, Criner GJ, et al. Treatment of severe systemic inflammatory response syndrome and sepsis with a novel bradykinin antagonist, deltibant (CP-0127). Results of a randomized, double-blind, placebo-controlled trial. CP-0127 SIRS and Sepsis Study Group. *JAMA*. 1997;277(6):482-487.
72. Dhainaut JF, Tenaillon A, Hemmer M, et al. Confirmatory platelet-activating factor receptor antagonist trial in patients with severe gram-negative bacterial sepsis: a phase III, randomized, double-blind, placebo-controlled, multicenter trial. BN 52021 Sepsis Investigator Group. *Crit Care Med*. 1998;26(12):1963-1971.
73. Dhainaut JF, Tenaillon A, Le Tulzo Y, et al. Platelet-activating factor receptor antagonist BN 52021 in the treatment of severe sepsis: a randomized, double-blind, placebo-controlled, multicenter clinical trial. BN 52021 Sepsis Study Group. *Crit Care Med*. 1994;22(11):1720-1728.
74. Bernard GR, Wheeler AP, Russell JA, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. *N Engl J Med*. 1997;336(13):912-918.
75. Haupt MT, Jastremski MS, Clemmer TP, et al. Effect of ibuprofen in patients with severe sepsis: a randomized, double-blind, multicenter study. The Ibuprofen Study Group. *Crit Care Med*. 1991;19:1339-1347.
76. Sander A, Armbruster W, Sander B, et al. Hemofiltration increases IL-6 clearance in early systemic inflammatory response syndrome but does not alter IL-6 and TNF alpha plasma concentrations. *Intensive Care Med*. 1997;23(8):878-884.
77. Kellum JA, Johnson JP, Kramer D, et al. Diffusive vs. convective therapy: effects on mediators of inflammation in patient with severe systemic inflammatory response syndrome. *Crit Care Med*. 1998;26(12):1995-2000.
78. Cronin L, Cook DJ, Carlet J, et al. Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. *Crit Care Med*. 1995;23(8):1430-1439.
79. Zeni F, Freeman B, Natanson C. Anti-inflammatory therapies to treat sepsis and septic shock: a reassessment. *Crit Care Med*. 1997;25(7):1095-1100.
80. Annane D, Briegel J, Sprung CL. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med*. 2003;348(21):2157-2159.
81. Dellinger RP, Carlet JM, Masur H, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med*. 2004;32(3):858-873.
82. Wang H, Bloom O, Zhang M, et al. HMG-1 as a late mediator of endotoxin lethality in mice. *Science*. 1999;285(5425):248-251.
83. Wolf SE, Rose JK, Desai MH, et al. Mortality determinants in massive pediatric burns. An analysis > or = 80% TBSA burns (> or = 70% full-thickness). *Ann Surg*. 1997;225:554-565.
84. Junger WG, Coimbra R, Liu FC, et al. Hypertonic saline resuscitation: a tool to modulate immune function in trauma patients? *Shock*. 1997;8(4):235-241.
85. Woehrle T, Yip L, Manohar M, et al. Hypertonic stress regulates T cell function via pannexin-1 hemichannels and P2X receptors. *J Leukocyt Biol*. 2010;88:1181-1189.
86. Beale RJ, Bryg DJ, Bihari DJ. Immunonutrition in the critically ill: a systematic review of clinical outcome. *Crit Care Med*. 1999;27(12):2799-2805.
87. Metz CN, Tracey KJ. It takes nerve to dampen inflammation. *Nat Immunol*. 2005;6(8):756-757.
88. Pavlov VA, Tracey KJ. The cholinergic anti-inflammatory pathway. *Brain Behav Immun*. 2005;19(6):493-499.
89. Pawlinski R, Pedersen B, Kehrle B, et al. Regulation of tissue factor and inflammatory mediators by Egr-1 in a mouse endotoxemia model. *Blood*. 2003;101(10):3940-3947.
90. Lippi G, Ippolito L, Cervellin G. Disseminated intravascular coagulation in burn injury. *Semin Thromb Hemost*. 2010;36(4):429-436.
91. Messori A, Vacca F, Vaiani M, et al. Antithrombin III in patients admitted to intensive care units: a multicenter observational study. *Crit Care*. 2002;6(5):447-451.
92. Okajima K. Regulation of inflammatory responses by natural anticoagulants. *Immunol Rev*. 2001;184:258-274.
93. Yuksel M, Okajima K, Uchiba M, et al. Activated protein C inhibits lipopolysaccharide-induced tumor necrosis factor-alpha production by inhibiting activation of both nuclear factor-kappa B and activator protein-1 in human monocytes. *Thromb Haemost*. 2002;88(2):267-273.
94. Shorr AF, Bernard GR, Dhainaut JF, et al. Protein C concentrations in severe sepsis: an early directional change in plasma levels predicts outcome. *Crit Care*. 2006;10(3):R92.

95. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. 2001;344:699-709.
96. Angus DC, Laterre PF, Helterbrand J, et al. The effect of drotrecogin alfa (activated) on long-term survival after severe sepsis. *Crit Care Med*. 2004;32:2199-2206.
97. Angus DC. Drotrecogin alfa (activated)...a sad final fizzle to a roller-coaster party. *Crit Care*. 2012;16:107.
98. Broze GJ Jr. The rediscovery and isolation of TFPI. *J Thromb Haemost*. 2003;1(8):1671-1675.
99. Suffredini AF, Fromm RE, Parker MM, et al. The cardiovascular response of normal humans to the administration of endotoxin. *N Engl J Med*. 1989;321:280-287.
100. Suffredini AF, Shelhamer JH, Neumann RD, et al. Pulmonary and oxygen transport effects of intravenously administered endotoxin in normal humans. *Am Rev Respir Dis*. 1992;145:1398-1403.
101. Traber DL, Redl H, Schlag G, et al. Cardiopulmonary responses to continuous administration of endotoxin. *Am J Physiol*. 1988;254:H833-H839.
102. Dehring D, Lingnau W, McGuire R, et al. L-NAME transiently reverses hyperdynamic status during continuous infusion of Pseudomonas aeruginosa. *Circ Shock*. 1993;39:49.
103. Traber DL. Models of endotoxemia in sheep. In: Schlag G, Redl H, Traber DL, eds. *Pathophysiology of Shock Sepsis and Organ Failure*. New York: Springer Verlag; 1993:194-199.
104. Demling RH. The burn edema process: current concepts. *J Burn Care Rehabil*. 2005;26:207-227.
105. Nakazawa H, Noda H, Noshima S, et al. Pulmonary transvascular fluid flux and cardiovascular function in sheep with chronic sepsis. *J Appl Physiol*. 1993;75:2521-2528.
106. Landis EM, Pappenheimer JR. Exchange of substances through the capillary walls. In: Hamilton WF, Dow P, eds. *Handbook of Physiology*. 2(2). Baltimore, MD: Williams & Wilkins; 1963:961-1034.
107. Starling EH. On the absorption of fluids from the connective tissue spaces. *J Physiol*. 1896;19:312-326.
108. Brigham KL, Bowers R, Haynes J. Increased sheep lung vascular permeability caused by Escherichia coli endotoxin. *Circ Res*. 1979;45:292-297.
109. Gaar KA, Taylor AE, Owens LJ, et al. Effect of capillary pressure and plasma protein on development of pulmonary edema. *Am J Physiol*. 1967;213:79-82.
110. Fujioka K, Sugi K, Isago T, et al. Thromboxane synthase inhibition and cardiopulmonary function during endotoxemia in sheep. *J Appl Physiol*. 1991;71:1376-1381.
111. Adams T Jr, Traber DL. The effects of a prostaglandin synthetase inhibitor, ibuprofen, on the cardiopulmonary response to endotoxin in sheep. *Circ Shock*. 1982;9:481-489.
112. Lund T, Wiig H, Reed RK, et al. A 'new' mechanism for oedema generation: strongly negative interstitial fluid pressure causes rapid fluid flow into thermally injured skin. *Acta Physiol Scand*. 1987;129:433-435.
113. Lund T, Wiig H, Reed RK. Acute postburn edema: role of strongly negative interstitial fluid pressure. *Am J Physiol*. 1988;255:H1069-H1074.
114. Traber DL, Herndon DN, Fujioka K, et al. Permeability changes during experimental endotoxemia and sepsis. In: Schlag G, Redl H, Siegel JH, et al, eds. *Shock, Sepsis, and Organ Failure: Second Wiggers Bernard Conference*. New York: Springer-Verlag; 1991:425-447.
115. Smith L, Andreasson S, Thoren Tolling K, et al. Sepsis in sheep reduces pulmonary microvascular sieving capacity. *J Appl Physiol*. 1987;62:1422-1429.
116. Oliver JA. Endothelium-derived relaxing factor contributes to the regulation of endothelial permeability. *J Cell Physiol*. 1992;151:506-511.
117. Farrukh IS, Gurtner GH, Michael JR. Pharmacological modification of pulmonary vascular injury: possible role of cAMP. *J Appl Physiol*. 1987;62:47-54.
118. Kurose I, Kubes P, Wolf R, et al. Inhibition of nitric oxide production. Mechanisms of vascular albumin leakage. *Circ Res*. 1993;73:164-171.
119. Leeuwenberg FM, Jeunhomme TMA, Buurman WA. Induction of an activation antigen on human endothelial cells in vitro. *Eur J Immunol*. 1989;19:715-720.
120. Lasky LA. Selectins: interpreters of cell-specific carbohydrate information during inflammation. *Science*. 1992;258:964-969.
121. Walsh CJ, Carey D, Cook DJ, et al. Anti-CD18 antibody attenuates neutropenia and alveolar capillary-membrane injury during gram-negative sepsis. *Surgery*. 1991;110:205-212.
122. Doerschuk CM, Winn RK, Coxson HO, et al. CD18-dependent and -independent mechanisms of neutrophil emigration in the pulmonary and systemic microcirculation of rabbits. *J Immunol*. 1990;144:2327-2333.
123. Traber DL. Anti-proteases in endotoxemia. *Prog Clin Biol Res*. 1987;236:149-157.
124. Basadre JO, Singh H, Herndon DN, et al. Effect of antibody-mediated neutropenia on the cardiopulmonary response to endotoxemia. *J Surg Res*. 1988;45:266-275.
125. Winn R, Maunder R, Chi E, et al. Neutrophil depletion does not prevent lung edema after endotoxin infusion in goats. *J Appl Physiol*. 1987;62:116-121.
126. Maunder RJ, Hackman RC, Riff E, et al. Occurrence of the adult respiratory distress syndrome in neutropenic patients. *Am Rev Respir Dis*. 1986;133:313-316.
127. Laufe MD, Simon RH, Flint A, et al. Adult respiratory distress syndrome in neutropenic patients. *Am J Med*. 1986;80:1022-1026.
128. Heflin AC Jr, Brigham KL. Prevention by granulocyte depletion of increased vascular permeability of sheep lung following endotoxemia. *J Clin Invest*. 1981;68:1253-1260.
129. Klausner JM, Paterson IS, Goldman G, et al. Interleukin-2-induced lung injury is mediated by oxygen free radicals. *Surgery*. 1991;109:169-175.
130. Paterson IS, Klausner JM, Goldman G, et al. Thromboxane mediates the ischemia-induced neutrophil oxidative burst. *Surgery*. 1989;106:224-229.
131. Turker RK, Aksulu HE, Ercan ZS, et al. Thromboxane A2 inhibitors and iloprost prevent angiotensin II-induced oedema in the isolated perfused rat lung. *Arch Int Pharmacodyn Ther*. 1987;287:323-329.
132. Redl H, Schlag G, Lamche H. TNF-and LPS-induced changes of lung vascular permeability: studies in unanesthetised sheep. *Circ Shock*. 1990;31:183-192.
133. Johnson J, Meyrick B, Jesmok G, et al. Human recombinant tumor necrosis factor alpha infusion mimics endotoxemia in awake sheep. *J Appl Physiol*. 1989;66:1448-1454.
134. Burhop KE, Garcia JG, Selig WM, et al. Platelet-activating factor increases lung vascular permeability to protein. *J Appl Physiol*. 1986;61:2210-2217.
135. Vercellotti GM, Yin HQ, Gustavson KS, et al. Platelet activating factor primes neutrophil responses to agonists: role in promoting neutrophil-mediated endothelial damage. *Blood*. 1988;71:1100-1107.
136. Sessler CN, Glauser FL, Davis D, et al. Effects of platelet-activating factor antagonist SRI 63–441 on endotoxemia in sheep. *J Appl Physiol*. 1988;65:2624-2631.
137. Gregoretti S, Gelman S, Dimick A, et al. Hemodynamic changes and oxygen consumption in burned patients during enflurane or isoflurane anesthesia. *Anesth Analg*. 1989;69:431-436.
138. Holloway H, Perry M, Downey J, et al. Estimation of effective pulmonary capillary pressure in intact lungs. *J Appl Physiol*. 1983;54(3):846-851.
139. Morel DR, Pittet JF, Gunning K, et al. Time course of plasma and pulmonary lymph endothelin-like immunoreactivity during sustained endotoxaemia in chronically instrumented sheep. *Clin Sci*. 1991;81:357-365.
140. O'Dwyer ST, Michie HR, Ziegler TR, et al. A single dose of endotoxin increases intestinal permeability in healthy humans. *Arch Surg*. 1988;123:1459-1464.
141. Navaratnam RL, Morris SE, Traber DL, et al. Endotoxin (LPS) increases mesenteric vascular resistance (MVR) and bacterial translocation (BT). *J Trauma*. 1990;30:1104-1113.
142. Tokyay R, Loick HM, Traber DL, et al. Effects of thromboxane synthetase inhibition on postburn mesenteric vascular resistance and the rate of bacterial translocation in a chronic porcine model. *Surg Gynecol Obstet*. 1992;174:125-132.
143. Roumen RM, Hendriks T, Wevers RA, et al. Intestinal permeability after severe trauma and hemorrhagic shock is increased without relation to septic complications. *Arch Surg*. 1993;128:453-457.
144. Zeigler ST, Traber DL, Herndon DN. Bacterial translocation in burns. In: Schlag G, Redl H, eds. *Pathophysiology of Shock, Sepsis, and Organ Failure*. New York: Springer-Verlag; 1993:300-313.
145. Meyer J, Traber LD, Nelson S, et al. Reversal of hyperdynamic response to continuous endotoxin administration by inhibition of NO synthesis. *J Appl Physiol*. 1992;73:324-328.
146. Sloane PJ, Elsasser TH, Spath JA, et al. Plasma tumor necrosis factor-alpha during long-term endotoxemia in awake sheep. *J Appl Physiol*. 1992;73:1831-1837.

147. Nelson S, Steward RH, Traber L, et al. Endotoxin-induced alterations in contractility of isolated blood vessels from sheep. *Am J Physiol*. 1991;260:H1790-H1794.
148. Theissen JL, Loick HM, Curry BB, et al. Time course of hypoxic pulmonary vasoconstriction after endotoxin infusion in unanesthetized sheep. *J Appl Physiol*. 1991;70:2120-2125.
149. Meyer J, Lentz CW, Stothert JC, et al. Effects of nitric oxide synthesis inhibition in hyperdynamic endotoxemia. *Crit Care Med*. 1994;22:306-312.
150. Sugi K, Newald J, Traber LD, et al. Cardiac dysfunction after acute endotoxin administration in conscious sheep. *Am J Physiol*. 1991;260:H1474-H1481.
151. Noshima S, Noda H, Herndon DN, et al. Left ventricular performance during continuous endotoxin-induced hyperdynamic endotoxemia in sheep. *J Appl Physiol*. 1993;74:1528-1533.
152. dos Santos CC, Gattas DJ, Tsoporis JN, et al. Sepsis-induced myocardial depression is associated with transcriptional changes in energy metabolism and contractile related genes: a physiological and gene expression-based approach. *Crit Care Med*. 2010;38:894-902.
153. Westphal M, Enkhbaatar P, Schmalstieg FC, et al. Neuronal nitric oxide synthase inhibition attenuates cardiopulmonary dysfunctions after combined burn and smoke inhalation injury in sheep. *Crit Care Med*. 2008;36:1196-1204.
154. Barber RC, Maass DL, White DJ, Horton JW. Increasing percent burn is correlated with increasing inflammation in an adult rodent model. *Shock*. 2008;30(4):388-393.
155. Myers PR, Wright TF, Tanner MA, et al. EDRF and nitric oxide production in cultured endothelial cells: direct inhibition by E. coli endotoxin. *Am J Physiol*. 1992;262:H710-H718.
156. Vallance P, Moncada S. Role of endogenous nitric oxide in septic shock. *New Horizons*. 1993;1:77-86.
157. Furchgott RF. Endothelium-derived relaxing factor: discovery, early studies, and identification as nitric oxide. *Biosci Rep*. 1999;19:235-251.
158. Bryan NS, Bian K, Murad F. Discovery of the nitric oxide signaling pathway and targets for drug development. *Front Biosci*. 2009;14:1-18.
159. Petros A, Lamb G, Leone A, et al. Effects of a nitric oxide synthase inhibitor in humans with septic shock. *Cardiovasc Res*. 1994;28:34-39.
160. Geroulanos S, Schilling J, Cakmakci M, et al. Inhibition of NO synthesis in septic shock. *Lancet*. 1992;339:435-440.
161. Kiehl MG, Ostermann H, Meyer J, et al. Nitric oxide synthase inhibition by L-NAME in leukocytopenic patients with severe septic shock. *Intensive Care Med*. 1997;23(5):561-566.
162. Traber DL, Hawkins HK, Enkhbaatar P, et al. The role of the bronchial circulation in the acute lung injury resulting from burn and smoke inhalation. *Pulm Pharmacol Ther*. 2007;20(2):163-166.
163. Szabó C, Módis K. Pathophysiological roles of peroxynitrite in circulatory shock. *Shock*. 2010;34(suppl 1):4-14.
164. Lorigados CB, Soriano FG, Szabo C. Pathomechanisms of myocardial dysfunction in sepsis. *Endocr Metab Immune Disord Drug Targets*. 2010;10(3):274-284.

20 Host Defense Antibacterial Effector Cells Influenced by Massive Burns

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Introduction

Infectious complications are one of the leading causes of death in patients with severe burn injuries.[1–5] Increases in the total body surface area and depth of burn injuries correlate with the excessive risk of infectious complications.[6] Burn patients are commonly treated with many components such as fluid resuscitation, wound excision, grafting and coverage, infection control, and nutritional support. Progress in each treatment has contributed significantly to reduce mortality in severely burned patients. However mortality rates associated with infectious complications still remain high, and bacterial infections are a major cause of morbidity in burned patients.[7–9]

Infections in severely burned patients frequently occur as opportunistic infections. In these patients, a majority of the causative infectious pathogens come from their own microbiota distributed in and on the skin, respiratory tract, and intestines.[5] For example, staphylococci are found in 40% of wound isolates, and 14%–17% of burned patients become infected once they are colonized.[10–12] Although antibiotics are useful to control infections, excessive antibiotic usage is directly related to the development of methicillin-resistant *Staphylococcus aureus* (MRSA).[13] Vancomycin is utilized clinically to treat MRSA; however, the management of invasive MRSA infection will become a serious problem if VISA/GISA strains spread widely.[14–16] Currently, newer antibiotics such as linezolid (oxazolidinones) and quinupristin/dalfopristin (macrolides) are available to treat MRSA infection.[17] In general, however, these agents are of limited usefulness because of their propensity to create antibiotic-resistant bacteria.[13] These facts strongly indicate that a new strategy, apart from antibiotic therapy, is required to treat infections.[18,19]

Sepsis stemming from wound infections is usually found in patients with severe thermal injuries. Topical antibacterials (silver sulfadiazine, silver nitrate, mafenide acetate, etc.) are very useful for controlling the colonization and multiplication of microorganisms on the surface of burn wounds. However, due to the burn-induced defects of the host's antibacterial defenses, very small amounts of *Pseudomonas aeruginosa* that escape from this treatment are enough to spread throughout the whole body.[20] In fact, only 50 colony-forming units (CFU) of *P. aeruginosa* applied to burn wounds are sufficient to kill severely burned mice, whereas more than 1×10^8 CFU applied intradermally are required to kill noninjured mice. Similarly, burn-associated defects in host antibacterial defenses have been demonstrated against enteric bacteria in severely burned mice (Fig. 20.1). In addition, polymicrobial sepsis frequently occurs in severely burned patients. Because such infections do not usually develop in healthy individuals, immune dysfunctions associated with burn injuries are a major reason for the increased susceptibility of severely burned patients to these infections.

The innate immune system is the first line of host defense against microbial invasion.[21] The cells and molecules of innate immunity are rapidly activated by microbes or some signals induced by damaged tissues.[22–25] The innate immune system consists of (1) soluble recognition molecules, (2) physical barriers, and (3) cellular components (myeloid cells and lymphoid cells). Soluble recognition molecules include natural antibodies (IgM and IgA), acute phase proteins, and the complement system. In heathy individuals, natural IgM is constitutively produced. However, reduced levels of antibodies are evident in severely burned patients.[26] Burn-associated hypermetabolic responses stimulate the synthesis of acute phase proteins located in the liver and intestinal mucosa.[27–29] Burn injury to tissues leads to complement activation with subsequent depletion of complement components, mainly C3, C4, and C5.[30–32] As physical barriers, epithelial cells produce antimicrobial peptides (β-defensins and LL-37/hCAP-18), which are small molecular weight proteins with broad-spectrum antimicrobial activity.[33,34] After injury or infection, epithelial cells produce alarmins such as thymic stromal lymphopoietin (TSLP), interleukin (IL)-25 and IL-33. This causes the initiation of type 2 immune responses.[35–37] Although β-defensins are normally produced by epidermal keratinocytes,[33] mRNA expression of these peptides is greatly decreased in the tissue around the burn wound when compared with normal skin in thermally injured patients.[38,39] Decreased local production of antimicrobial peptides around burn wounds allows the local growth of bacteria, putting the patient at risk for wound-derived systemic infections. Studies in animal models of burn injury suggest that decreased antimicrobial peptide production by epidermal keratinocytes around burn wounds is due to the infiltration of suppressive myeloid and lymphoid cells that appear in response to burn injuries.

It is well established that burn injury initiates an early proinflammatory innate immune response followed by an adaptive counter-inflammatory response.[40–42] The innate immune system is activated in response to either pathogen-associated or damage-associated molecular patterns.[22–25] Both patterns are recognized by pattern recognition

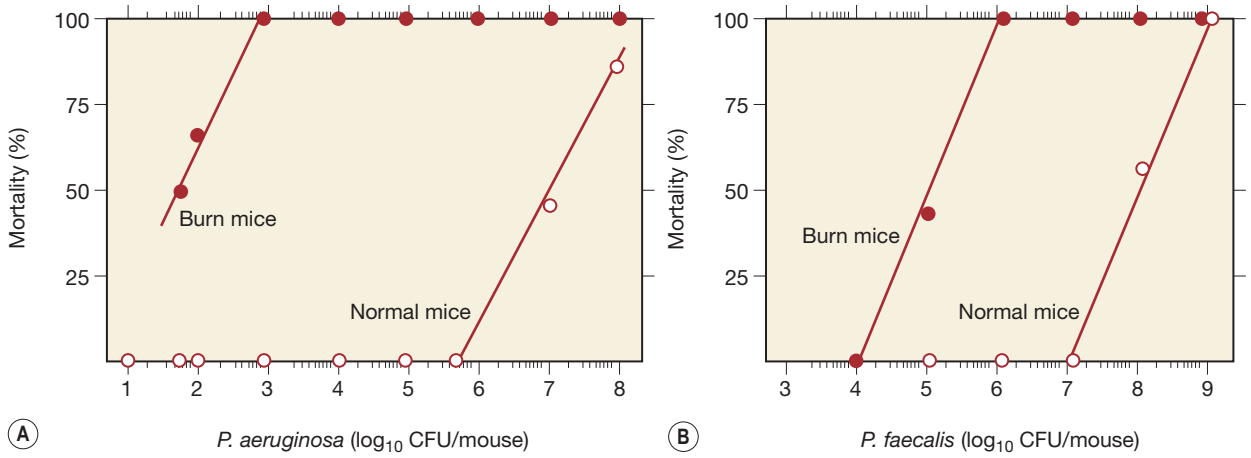


Fig. 20.1 Susceptibility of burn mice to *Pseudomonas aeruginosa* and *Enterococcus faecalis* infections. Severely burned mice are 10^4-times or more susceptible to *P. aeruginosa* (**A**) or *E. faecalis* (**B**) infection when compared to normal mice.

receptors (PRRs) on innate immune cells. Depending on the molecular patterns recognized, pro- or antiinflammatory soluble factors are rapidly released from these cells. Thus the development of burn-associated immunosuppression is initiated early after burn injury. Antiinflammatory responses are helpful for wound healing[43–45] and the resolution of liver and intestinal inflammation[21,46,47] in burn patients. However, dysregulated immunosuppression and persistent inflammation cause immunoparalysis,[48] and patients with immunoparalysis become extremely susceptible to infections.[49] This chapter will discuss cell populations and their functions involved in innate immunity as influenced by severe burn injuries.

Neutrophils

Neutrophils are the most abundant white blood cells in the innate immune system. They are rapidly recruited to the injury or infection site, where they phagocytose and kill invading microorganisms.[50] The maturation of neutrophils is under the control of transcription factors PU.1 and C/EBP.[51] During maturation, the neutrophil goes through several stages, namely myeloblast, promyelocyte, myelocyte, metamyelocyte, band cell, and, finally, polymorphonuclear (segmented) cell.[52] In the absence of infection or inflammation, mature neutrophils die within 15 hours by caspase 3-mediated spontaneous apoptosis.[53,54] Inflammatory signals are capable of prolonging the life span of neutrophils by several days.[53] However, even during inflammation, mature neutrophils die by apoptosis or NETosis (death during formation of neutrophil extracellular traps [NETs] for extracellular killing) while performing their antimicrobial function.[55,56] These dead neutrophils are engulfed by macrophages.[57]

IMPAIRED NEUTROPHIL RECRUITMENT

Mature neutrophils leave the bone marrow and enter to the circulation.[58] Getting neutrophils to the site of infection is of prime importance, and an elaborate series of adhesion events between neutrophils and the endothelium ensures that neutrophils leave the bloodstream only at the inflammatory site.[59] This process includes tethering (capturing), rolling, adhesion, crawling, and transmigration. IL-8 production by activated neutrophils plays a central role in the recruitment of additional neutrophils to the infection site.[60] After severe burn injuries, levels of IL-8 in plasma are approximately 60 times higher than those in plasma of healthy controls.[61] An increase in peripheral blood neutrophils is seen in patients 2–5 days after burn injury. However, the chemotactic function and efficient migration of neutrophils are impaired in severely burned patients due to the decreased expression of CXCR2 (a receptor for IL-8).[62] Migration speed of neutrophils toward the chemoattractant source is also impaired in severely burned patients.[63] Such impairment of neutrophils starts as early as 24 hours after burn injury, reaches a maximum at 3 to 5 days after burn injury, and correlates to the size of the burn injury.

IMPAIRED NEUTROPHIL KILLING

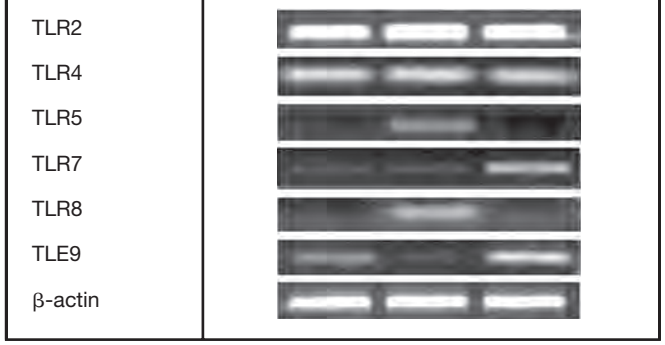
Neutrophils are efficient phagocytes that engulf microbes into phagosomes. The phagosome fuses with granules to produce a phagolysosome, in which microbes are exposed to many destructive enzymes, antimicrobial peptides, and reactive oxygen species.[55] These components synergize and effectively kill microbes. Highly activated neutrophils kill extracellular microbes by releasing NETs, which consist of fibrils formed by active expulsion of DNA, chromatin, antimicrobial protein, and enzymes.[64] The sticky DNA fibers of the NETs bind and immobilize pathogens and thus inhibit their further spread. NETs kill pathogens directly by means of antimicrobial histones and proteases. IL-8 is well-known to enhance NET formations of neutrophils.[56,64] As described earlier, increased levels of IL-8 in the circulation of severely burned patients have been demonstrated.[61] Increased levels of KC and MIP-2 have also been demonstrated in the sera and lungs of mice 2–8 hours after burn injury.[65,66] KC and MIP-2 are functionally homologous to human IL-8. However, phagocytosis, oxidative metabolism, granular enzyme contents, and intracellular killing of neutrophils are greatly reduced in severely burned patients compared with those of neutrophils from healthy individuals.[67] The

attenuating CXCR2 expression on neutrophils is,[62] at least in part, responsible for neutrophil dysfunction following burn injury.

PRO- AND ANTIINFLAMMATORY NEUTROPHILS

Experimental studies in rodents have identified distinctive types of neutrophils that affect resistance to MRSA infections in burned mice (Fig. 20.2).[68] Neutrophils isolated from slightly burned (5% TBSA burn, MRSA-resistant hosts) or severely burned mice (25% TBSA burn, MRSA-susceptible hosts) are biologically and histologically different from the neutrophils isolated from naïve mice. These three neutrophil populations have unique cytokine/chemokine-producing patterns. Also, these three neutrophils express Toll-like receptors (TLRs) and surface CD49d/CD11b integrins differently. Neutrophils isolated from MRSA-resistant mice are proinflammatory IL-12^{+} CCL3^{+}

Properties	PMN-N	PMN 1	PMN 2
CCL2	trace	trace	17.1 ng/ml
CCL3	trace	11.6 ng/ml	trace
IL-12	trace	0.5 ng/ml	trace
IL-10	trace	trace	1.3 ng/ml
IL-4	trace	trace	0.05 ng/ml
TNF-α	0.8 ng/ml	0.6 ng/ml	0.6 ng/ml
IL-1β	3.9 ng/ml	3.6 ng/ml	3.5 ng/ml
CXCL1	1.7 ng/ml	10.7 ng/ml	11.1 ng/ml
M1Mϕ induction	no	yes	no
M2Mϕ induction	no	no	yes
H_2O_2	<0.2 nmol	7.8 nmol	5.8 nmol
Killing	0%	58%	47%



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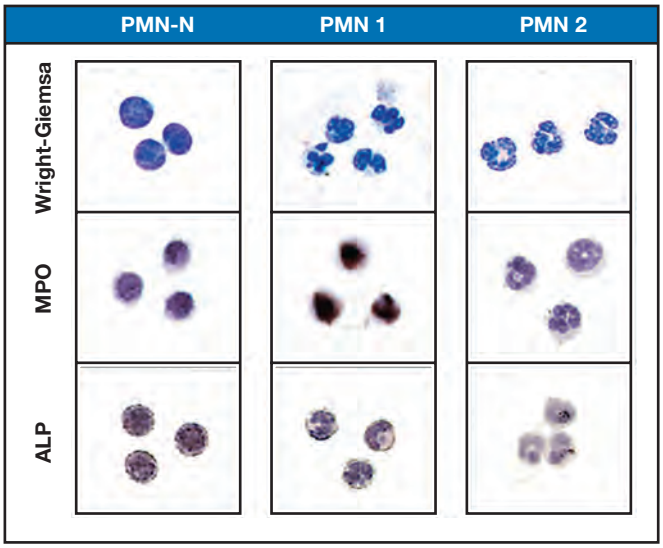

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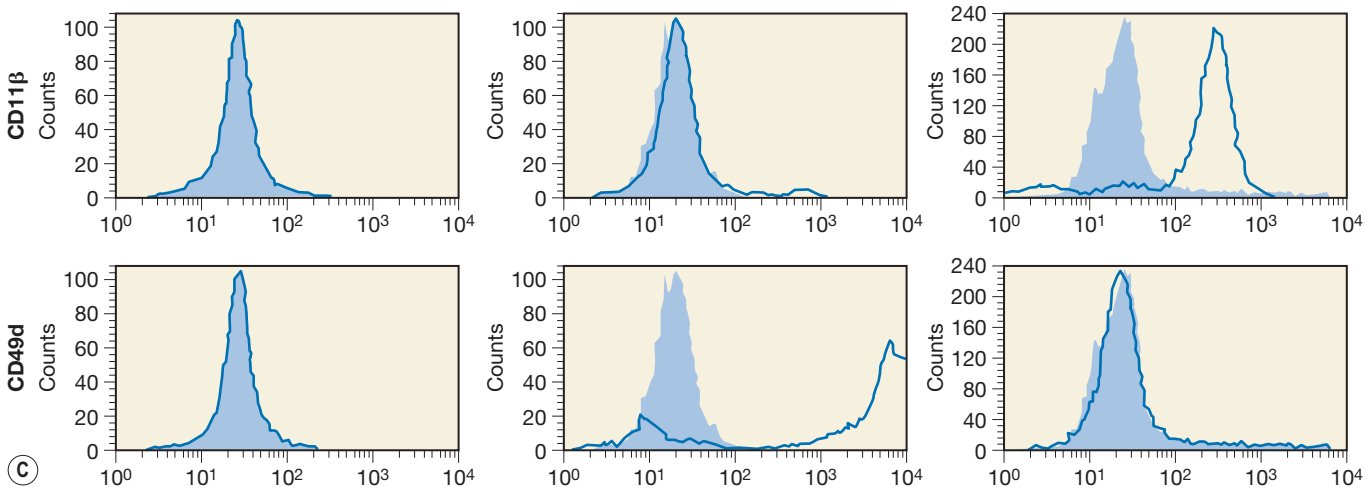

C

Fig. 20.2 Properties of PMN-N, PMN 1, and PMN 2. Peripheral blood neutrophils (PMNs), isolated from slightly burned mice (5% TBSA burn, PMN 1) or severely burned mice (25% TBSA burn, PMN 2), were biologically and histologically different from naive mouse neutrophils (PMN-N). (Modified from Tsuda Y, Takahashi H, Kobayashi M, et al. Three different neutrophil subsets exhibited in mice with different susceptibilities to infection by methicillin-resistant *Staphylococcus aureus*. *Immunity*. 2004;21:215–226.)

cells (PMN 1 or N1), whereas neutrophils from MRSA-susceptible mice are an antiinflammatory IL-10$^+$ CCL2$^+$ cells (PMN 2 or N2). Neutrophils isolated from naïve mice are IL-12$^-$ and IL-10$^-$ cells. These neutrophils also differ in their promotion of macrophage differentiation. Quiescent macrophages from the lamina propria of normal mice convert to the M1 phenotype after cultivation with polymorphonuclear leukocyte (PMN) 1 in dual-chamber transwells supplemented with a mixture of TLR3/TLR9 agonists. In contrast, quiescent macrophages convert to the M2 phenotype after cultivation with PMN 2 in the same transwells. Neither M1 nor M2 macrophages appear even when quiescent macrophages are transwell-cultured with naïve PMN. Also, PMN 2 are shown to be inhibitory for macrophage conversion to the M1 phenotype under stimulation with TLR3/TLR9 agonists. Subsequently, IL-10 and CCL2 produced by PMN 2 are identified as inhibitors of TLR3/TLR9-induced macrophage polarization toward the M1 phenotype. Another distinguishing feature is their morphology. Although IL-12$^-$and IL-10$^-$ neutrophils have a round nucleus, PMN 1 has a multilobular nucleus (indicative of mature neutrophils), and the nucleus of PMN 2 is ring-shaped. PMN 2 is predominantly demonstrated in severely burned mice.[68]

Furthermore the role of PMN 1 and PMN 2 on host anti-MRSA resistance has been examined in γ-irradiated NSG mice (lacking the functional immunocompetent cells) reconstituted with normal mouse macrophages (Mϕ-reconstituted γNSG mice).[68] Mϕ-reconstituted γNSG mice become more resistant after inoculation with PMN 1, whereas the same mice become susceptible after inoculation with PMN 2. Additionally, γNSG mice are shown to be resistant against MRSA infection when they are inoculated with normal mouse macrophages previously cultured with PMN 1. Macrophages previously cultured with PMN 2 do not protect Mϕ-reconstituted γNSG mice infected with a lethal dose of MRSA. Similar results are obtained when Mϕ-reconstituted γNSG mice are orally infected with a lethal dose of *Enterococcus faecalis*.[69] These results indicate that MRSA infection and *E. faecalis* translocation are not controlled in hosts predominantly bearing PMN 2. IL-10 and CCL2 released from PMN 2 are characterized as active cytokines that induce M2 macrophages from quiescent macrophages.[68,70,71] Therefore these cytokines are targets for the macrophage polarization influenced by PMN 2. Infectious complications due to MRSA infection and enteric bacterial translocation have been successfully controlled in severely burned mice depleted of CCL2 or IL-10 by their antisense oligodeoxynucleotide (ODN).[72,73] Thus antiinflammatory neutrophils appearing in hosts after severe burn injury suppress effective immune responses and increase susceptibility to infections.

ROLE OF DAMAGE-ASSOCIATED MOLECULAR PATTERNS IN INDUCING ANTIINFLAMMATORY NEUTROPHILS POSTBURN INJURY

In microbial infection, pathogen-associated molecular patterns (PAMPs) present in diverse organisms but, when absent in the host, provide exogenous signals that alert the immune system to the presence of pathogens, thereby promoting immunity.[74] For instance, bacterial lipopolysaccharide (LPS) is a PAMP and is recognized by TLR4 on the immune cell surface. Bacterial DNA that contains unmethylated CpG motifs is also a PAMP and is recognized by TLR9, which is located in the endosomal compartment of neutrophils. Both TLR4 and TLR9 are PRRs. In contrast, a variety of stressed, injured, or dying cells (including epithelial cells following burn injury) release damage-associated molecular patterns (DAMPs) as the endogenous danger signals that alert the innate immune system to unscheduled cell death and microbial invasion and in response to stress (Fig. 20.3).[22–25] HMGB1, hyaluronic acid, formyl peptides, heat-shock protein 70, S100A8, S100A9, and serum amyloid A are well-known DAMPs. These DAMPs are specifically recognized by several receptors (Table 20.1).[75] These ligand-specific interactions are able to induce either pro- or antiinflammatory effects. In severely burned patients, circulating mitochondrial DAMP levels are notably elevated (>10-fold) within 72 hours of burn injury. These mitochondrial DAMPs cause systemic inflammation, which is commonly characterized by fever, leukocytosis, increased

Table 20.1 Receptors of Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs)

Receptor	PAMPs	DAMPs
TLR1/TLR2	Lipopeptide	Serum amyloid A
TLR4	LPS	Fatty acid
		Hyaluronic acid
		S100A8/A9
NLRP3	Uric acid	Uric acid
		ATP
RIG-1, MDA5, TLR7/8	Viral RNA	Immune complex of snRNPs
TLR9	Bacterial DNA	Self-DNA-containing immune complex
		Histone
RAGE		HMGB1
DAI, IFI16, AIM2, H2B, RNA polymerase III	Bacterial DNA, viral DNA	Self-DNA

AIM2, Absent in melanoma 2; *ATP,* adenosine 5′-triphosphate; *DAI,* DNA-dependent activator of IFN-regulatory factors; *DAMPs,* damage-associated molecular patterns; *HMGB1,* high mobility group box-1; *H2B,* histone H2B; *IFI16,* interferon-inducible protein 16; *LPS,* lipopolysaccharide; *MDA5,* melanoma differentiation-associated protein 5; *NLRP3,* the NOD-like receptor family, pyrin domain-containing protein 3; *PAMPs,* pathogen-associated molecular patterns; *RAGE,* receptor for advanced glycation end products; *RIG-1,* retinoic acid-inducible gene 1; *TLR,* Toll-like receptor.

Modified from Jounai N, Kobiyama K, Takeshita F, et al. Recognition of damage-associated molecular patterns related to nucleic acids during inflammation and vaccination. *Front Cell Infect Microbiol.* 2013;2:168.

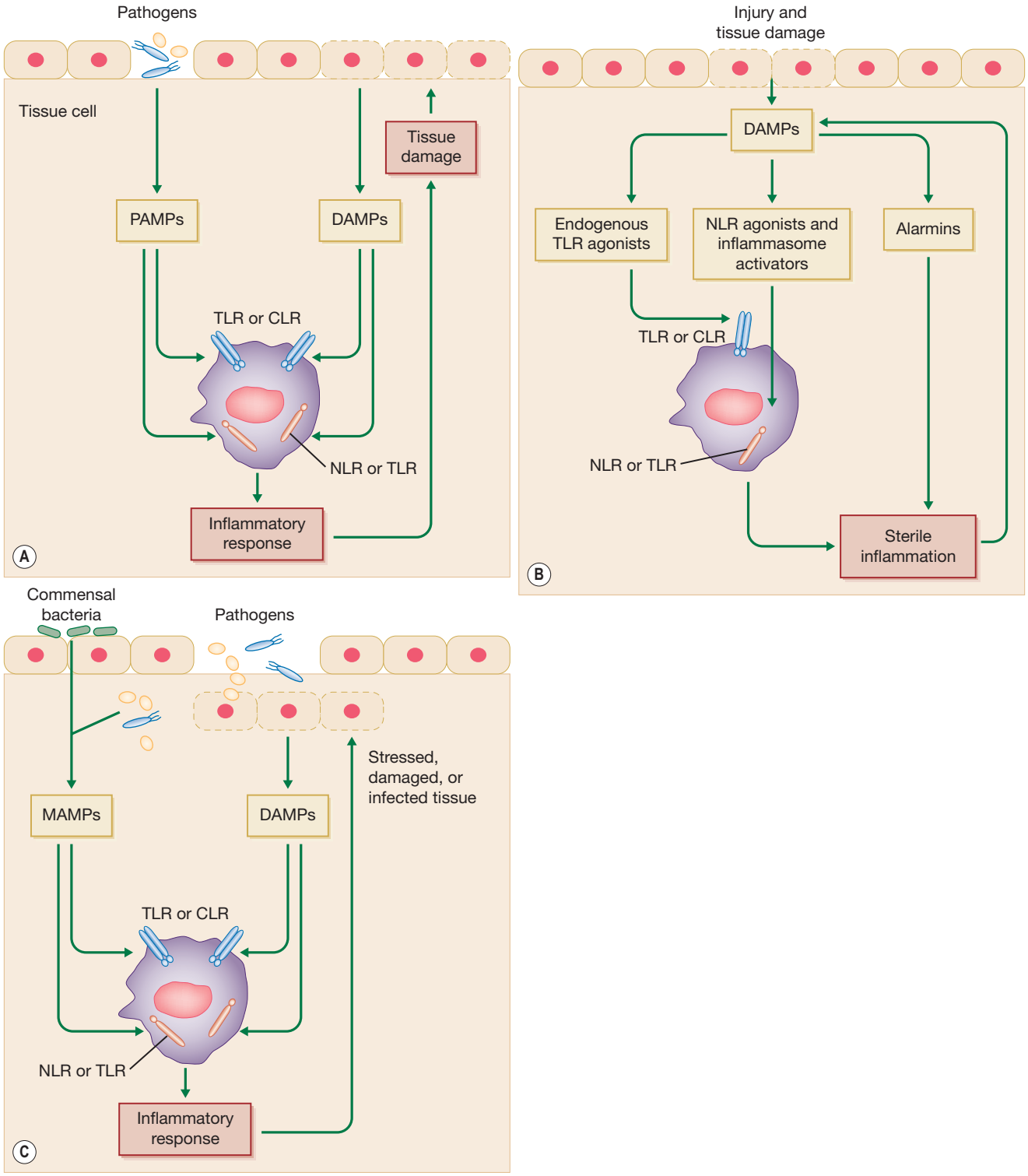

Fig. 20.3 Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). (**A**) PAMPs (including TLR, NLR, and CLR ligands) mediate the induction of proinflammatory cytokines in response to infection. (**B**) DAMPs or alarmins released from dead or dying cells mediate the induction of proinflammatory cytokine production from tissues in response to injury or stress. (**C**) In combination with DAMPs released from pathogen-infected or damaged host cells, microorganism-associated molecular patterns (MAMPs) mediate the induction of proinflammatory cytokines in response to pathogens. *ATP,* Adenosine 5′-triphosphate; *CLR,* C-type lectin receptor; *NLR,* NOD-like receptor; *TLR,* Toll-like receptor. (Modified from Mills KH. TLR-dependent T cell activation in autoimmunity. *Nat Rev Immunol.* 2011;11:807–822.)

secretion of adrenocorticotropic hormone and glucocorticoids, and alterations in plasma protein concentrations.[76–78] Simultaneously, these DAMPs cause desensitization of chemokine receptors and formyl-peptide receptors on neutrophils. Neutrophils influenced by DAMPs lose their antimicrobial functions. Also, Clec12a (binding to uric acid crystals) mediates the antiinflammatory response of neutrophils influenced by DAMPs.[79] Antiinflammatory neutrophils secrete high amounts of IL-10 and CCL2,[68,69] potent antiinflammatory cytokines, and have been implicated in impaired host antibacterial immunity in severely burned patients.[80]

SUPPRESSING ADAPTIVE IMMUNITY

Neutrophils have long been recognized as professional killer cells. They also participate in adaptive immunity. PMN 1 stimulates naïve T cells to polarize to T helper (Th1) cells through the production of interferon (IFN)-γ and IL-12, whereas PMN 2 promotes Th2 responses through the production of CCL2 and IL-10.[68] Because PMN 2 (but not PMN 1) appears in severely burned patients[80] and Th2 responses develop in these patients,[81–83] the blockage of PMN 2 is a potential effective strategy to control Th2 responses in severely burned patients.

Macrophages

Macrophages play a pivotal role in recognizing and eliminating various microbes. Macrophages, together with dendritic cells (DCs), function as antigen-presenting cells. Together with natural killer (NK) cells and lymphocytes, macrophages eliminate microbes. Macrophages are characterized by plasticity and flexibility.[84–86] Depending on the environmental stimuli, macrophages have a wide array of functions, especially in the modulation of innate immune responses through the release of several factors. Macrophages have been primarily classified into two major phenotypes: M1 and M2.[87–89]

TISSUE MACROPHAGES AND INFILTRATING MONOCYTE-DERIVED MACROPHAGES

In various tissues, macrophages acquire long-term, respective populations (e.g., peritoneal macrophages in the peritoneal cavity, Kupffer cells in the liver, alveolar macrophages in the lungs, microglia in the brain, etc.). Kupffer cells, microglia, and cardiac tissue macrophages are primarily yolk sac-derived cells.[90] Recent growing evidence clearly shows that yolk sac-derived tissue macrophages are self-maintained throughout adulthood.[91–93] The development and maintenance of tissue macrophages require specific growth factors and are regulated by tissue-selective transcriptional factors.[94] For example, macrophage colony-stimulating factor (M-CSF) is essential for Kupffer cells;[95] transforming growth factor (TGF)-β1 and IL-34 are essential for microglia and Langerhans cells;[96,97] and granulocyte macrophage colony-stimulating factor (GM-CSF) is essential for alveolar macrophages.[98] The transcription factor GATA6 is responsible for the transcriptome profile of resident peritoneal macrophages as well as for their proliferation under homeostatic conditions and in response to inflammation.[99,100] Peripheral blood monocytes are classified into three different populations. In humans, these populations correspond to $CD14^{++}CD16^{-}$ (classical monocytes), $CD14^{+}CD16^{+}$ (intermediate monocytes), and $CD14^{+}CD16^{++}$ (nonclassical monocytes); and in mice the equivalent populations are $Ly6C^{+}CD62L^{+}CD43^{-}CCR2^{+}$ (classical monocytes), $Ly6C^{int}CD62L^{-}CD43^{+}CCR2^{-}$ (intermediate monocytes), and $Ly6C^{-}CD62L^{-}CD43^{+}CCR2^{-}$ (nonclassical monocytes).[101] Classical monocytes can transport antigens to lymph nodes with minimal differentiation changes from their state in blood, although a proportion can convert to nonclassical monocytes. However, in the context of inflammation, recruited monocytes differentiate to macrophages. These monocyte-derived macrophages are distinct from resident macrophages.[102] Severe burn injuries induce inflammation in various organs including liver, intestine, and lung due to burn-induced hypermetabolic responses.[103] In these tissues, yolk sac-derived tissue macrophages coexist with monocyte-derived macrophages. Studies to determine the functional differences of these macrophage subsets in the organs of severely burned hosts are needed to develop therapeutic approaches for proper resolution of inflammation.

M1 MACROPHAGES AS AN ANTIBACTERIAL EFFECTOR CELL

In steady-state conditions, macrophages are immunologically quiescent. In the event of infection, quiescent macrophages are activated through the engagement of TLRs or the binding of IFN receptors.[104] IFN-γ induces downstream phosphorylation of Signal transducer and activator of transcription 1 (STAT1). In particular, LPS activates TLR4, which affects mitogen-activated protein kinases (MAPK), interferon regulatory factors (IRF), and nuclear factor kappa B (NF-κB) pathways. Thus, the activation of transcription factors NF-κB, activator protein 1 (AP-1), CCAAT/enhancer-binding protein α (C/EBPα), Krüppel-like factor 6 (KLF6), IRF5, and STAT1 promote macrophage polarization toward the M1 phenotype.[85,104,105] M1 macrophages exhibit (1) high oxygen consumption, (2) the ability to kill cells infected with intracellular pathogens, (3) the ability to express inducible nitric oxide synthase (iNOS), and (4) the ability to secrete nitric oxide, some proinflammatory cytokines, Th1 response-associated cytokines, and various chemokines.[87–89] Thus the dissemination of bacteria following local infection is prevented by M1 macrophages. M1 macrophages have been demonstrated in bacterial translocation site tissues such as lamina propria (LP) and mesenteric lymph nodes (MLNs)[106,107] and are the major effector cells in host antibacterial resistance against enterococcal translocation.

M2 MACROPHAGES AS INHIBITORS FOR MACROPHAGE POLARIZATION FROM QUIESCENCE TO THE M1 PHENOTYPE

Even though M1 macrophages play a role in host antibacterial responses, sustained inflammation can be very detrimental to the host. For controlling inflammation-associated damage, a large number of M2 macrophages

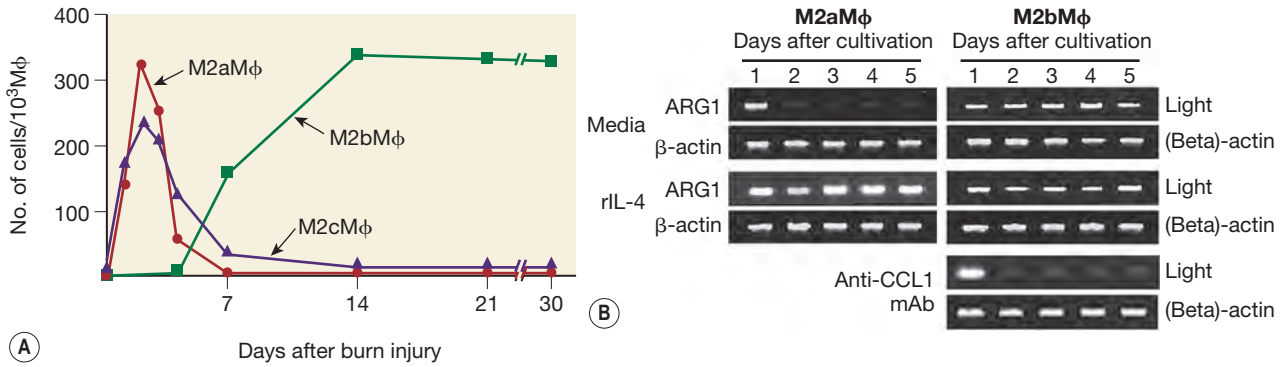

Fig. 20.4 M2a, M2b, and M2c macrophages in severely burned mice. **(A)** M2b macrophages were detected in the mesenteric lymph nodes (MLNs) of mice 1–3 weeks after burn injury. M2a macrophages lost their properties within 2 days of cultivation in IL-4-depleted media, whereas M2b macrophages lived longer once they appeared (**B**).

are generated.[108] M2 macrophages suppress the development of protective type 1 immune responses to pathogens[84] and thereby facilitate uncontrolled or persistent infections. IL-4 and IL-13, produced by a wide variety of cells (e.g., PMN 2, group 2 innate lymphoid cells, NKT cells, Th2 cells, etc.),[68,109] are typical cytokines to induce M2 macrophages. CCL2, produced by PMN 2, also stimulates M2 macrophage generation.[70–72] The macrophage polarization to the M2 phenotype is mediated via the activation of transcription factors, such as STAT3/6, KLF4, IRF4, PPARγ, and C/EBPβ.[85,104] Although the activation of NF-κB, STAT1, and MAPK signaling pathways is required for the macrophage polarization to the M1 phenotype, IL-10 inhibits these transcription factors and promotes STAT3 activation.[110,111] Therefore M1 macrophages are not generated from quiescent macrophages when M2 macrophages are present.

M2 macrophages are composed of three different subtypes: M2a (which expresses CD163, CD206, FIZZ1/Retna, Ym1/Chu3l3, and ARG1 and produces IL-10 and CCL17), M2b (which expresses CD163 and LIGHT, and produces IL-10, CCL1, TNF-α, IL-1, and IL-6), and M2c (which expresses CD163, CD206, ARG1, and FIZZ1, and produces IL-10, TGF-β, and CXCL13).[112] IL-4 and IL-13 are inducers for M2a macrophages. IL-10 and TGF-β in combination with cortisol (which increases 10- to 50-fold in the plasma of severely burned hosts within 24 h of burn injury)[113] are inducers for M2c macrophages. Although M2b macrophages are generally known to be induced by immune complexes and TLR or IL-1 receptor agonists,[112] the mechanism involved in the appearance of M2b macrophages after burn injuries remains unclear. Although all three M2 macrophages appear in severely burned hosts, the kinetics of the appearance of each M2 subtype are different. In LP and MLNs, M2a and M2c macrophages appear 1–4 days after burn injury in mice, and M2b macrophages appear 1–4 weeks after burn injury (Fig. 20.4A).[71,114] In humans, M2b monocytes are predominantly distributed in the circulation of patients 7–10 days after burn injury and persist for 1–2 months. M2a and M2c monocytes are present minimally in the circulation of patients after burn injury.[80] Experimental studies have shown that elimination of M2b macrophages from severely burned mice improves resistance against opportunistic infections.[114–116] Thus M2b macrophages may be an effective therapeutic target for controlling opportunistic infections in severely burned patients.

PLASTICITY OF VARIOUS PHENOTYPES OF MACROPHAGES

Macrophages easily switch from one functional phenotype to another in response to new microenvironmental signals.[84–86] Shortly after severe burn injury, quiescent macrophages switch to the M1 phenotype in response to invading pathogens. Subsequently, certain microRNAs (miRNAs) are produced in M1 macrophages through this stimulation or after efferocytosis of apoptotic phagocytic cells, which skews these macrophages toward the M2 phenotype.[117–119] miRNAs are short noncoding RNAs of approximately 21–23 nucleotides that function in RNA silencing and post-transcriptional regulation of gene expression.[120] Furthermore M2a macrophages can switch to quiescent macrophages depending on the presence of IL-4[121] or be reprogramed to switch to M1 macrophages in response to TLR agonists. Therefore the M2a phenotype is transient and relatively short. In vitro, M2a macrophages lose their properties within 2 days of cultivation in IL-4-depleted media (Fig. 20.4B). In contrast, M2b macrophages live longer once they appear and do not require exogenous growth factors (e.g., IL-4), due to the self-sustaining production of CCL1, which is an essential chemokine for the maintenance of M2b properties.[114] These results indicate that M2b macrophages have poor plasticity and may explain why M2b macrophages are persistent in severely burned hosts.

Innate Lymphoid Cells

Innate lymphoid cells (ILCs) are a population of lymphocyte-like lineage-negative (Lin^-; i.e., lacking surface markers for T, B, NK, and monocytes/macrophages lineages) cells. These cells are present in a wide variety of epithelial compartments and have important effector functions in the innate immune response.[122,123] ILCs develop from common lymphoid progenitors that express IL-7Rα (CD127). Mature ILCs rapidly respond to alarmins emanating from epithelial cells or from myeloid cells and are potent innate cellular

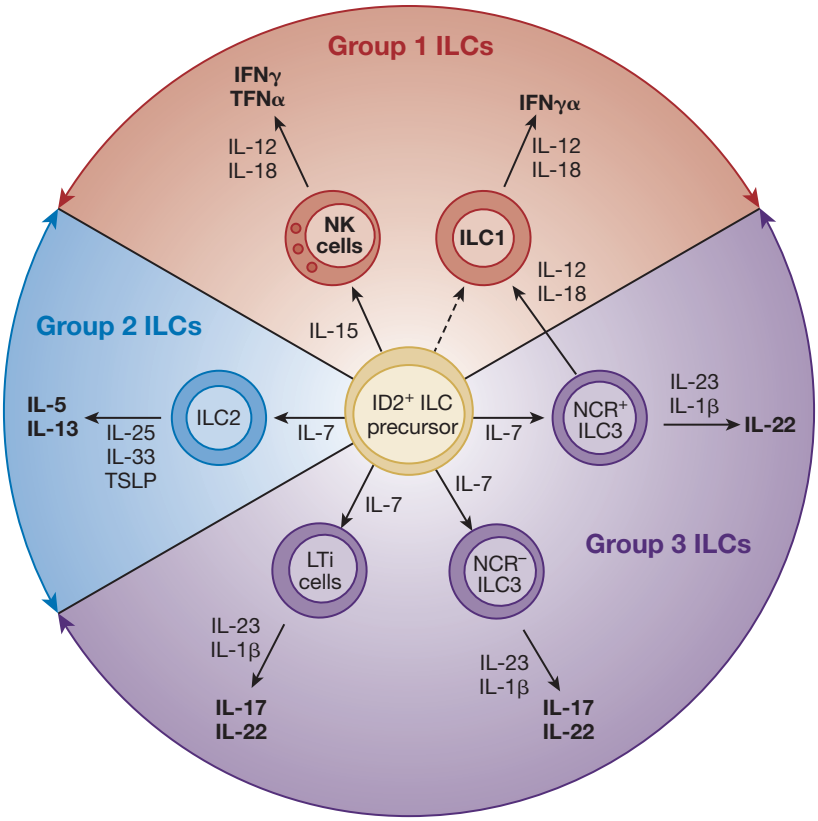

Fig. 20.5 Classification of innate lymphoid cells (ILCs) into three groups. ILCs are immune cells that belong to the lymphoid lineage, but do not express antigen-specific receptors. *LTi,* Lymphoid tissue inducer; *NCR,* natural cytotoxic receptor; *TSLP,* thymic stromal lymphopoietin. (Modified from Spits H, Artis D, Colonna M, et al. Innate lymphoid cells–a proposal for uniform nomenclature. *Nat Rev Immunol.* 2013;13:145–149.)

sources of multiple proinflammatory and immunoregulatory cytokines. ILCs are now classified into three groups, group 1 ILCs (ILC1s), group 2 ILCs (ILC2s), and group 3 ILCs (ILC3s), based on their abilities to produce cytokines and to express transcription factors typically associated with Th1-, Th2-, and Th17-type immune responses, respectively (Fig. 20.5).[124] ILC1s and ILC3s have a crucial role in promoting type 1 immune responses that provide protection against many microorganisms. By contrast, ILC2s have a role in promoting type 2 immune responses.[125] Cell transfer experiments and in vivo fate-mapping approaches have estimated the half-life for ILC subsets to be 2–3 weeks.[126]

IMPAIRED ILC1 GENERATION DUE TO IMPAIRED IL-12 PRODUCTION AFTER BURN INJURY

ILC1s respond to IL-12.[123] These cells are the dominant innate source of IFN-γ (and TNF-α) after infection and have a role in recruiting inflammatory cells that control infection. ILC1s, constitutively expressing T-bet, can be divided into at least three subsets: conventional NK (cNK) cells, $CD103^+$ $CD127^{low}$ intraepithelial ILC1s, and $CD127^+$ ILC1s.[123] cNK cells are $CD56^+$ $NKp44^+$ $CD161^+$ $CD127^-$ cells, and they require eomes and IL-15 for the development from NK-cell progenitors.[127] cNK cells exhibit cytotoxic activity by degranulating granzyme and perforin, both of which induce apoptosis of target cells, such as infected epithelial cells. $CD103^+$ $CD127^{low}$ intraepithelial ILC1s bear resemblance to cNK cells because they are $CD56^+$ $NKp44^+$ $CD161^+$ cells and express perforin/granzyme, whereas $CD127^+$ ILC1s are noncytotoxic cells. Both subsets of ILC1s lack eomes. $CD127^+$ ILC1s express TNF-α and TNF-related apoptosis-inducing ligand (TRAIL), which can induce apoptosis after binding to TRAIL-R1 (DR4) and/or TRAIL-R2 (DR5) on virus-infected cells.[126]

Many studies have demonstrated that the numbers and activities of cNK cells decrease due to severe burn injuries.[128–130] In severely burned patients, the expression of NKG2D (a natural cytotoxicity receptor) by peripheral blood cNK cells is significantly reduced.[131] NKG2D is constitutively expressed on the surface of circulating and tissue-resident cNK cells. Activated NKG2D stimulates cytotoxic effects of cNK cells against infected, transformed, or stressed cells in vitro and in vivo via interactions with NKG2D ligands (such as MICB and ULBP1) expressed on the surface of target cells. However, serum concentration levels of NKG2D ligands (shed from damaged tissues or from other tissues responding to stress) increase 3- to 20-fold within 24 hours after severe burn injury and are maintained for several weeks.[131] As an active immune-evasion mechanism, high concentrations of soluble NKG2D ligands may be involved in suppressed cNK cell activity in severely burned patients. Little is known about the influence of severe burn injuries on the numbers and activities of $CD103^+$ $CD127^{low}$ ILC1s or $CD127^+$ ILC1s. Because impaired IL-12 production by various antigen-presenting cells has been demonstrated

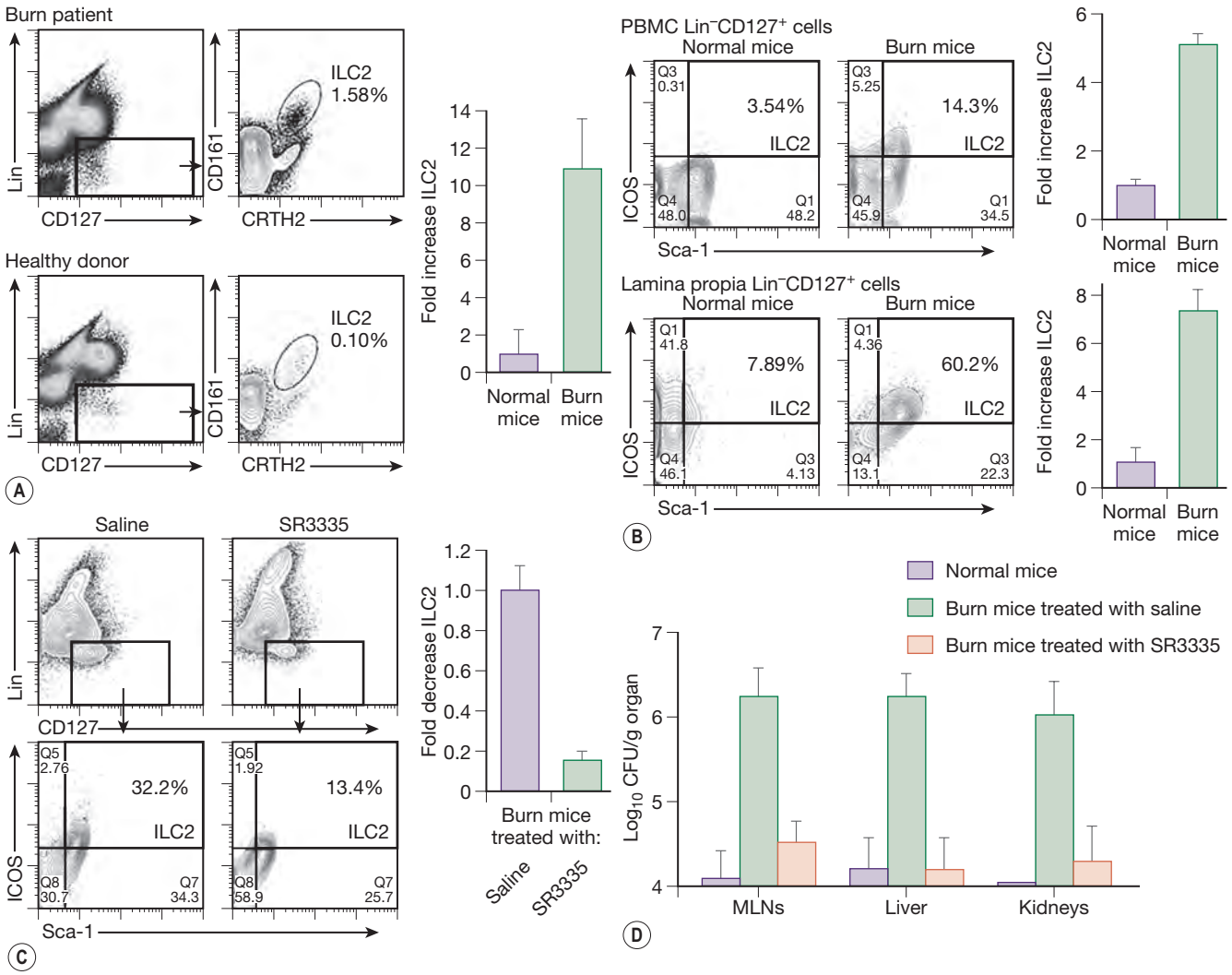

Fig. 20.6 Innate lymphoid cells-2 (ILC2s) appearing in severely burned patients and mice are responsible for the increased susceptibility to gut bacteria-associated sepsis. ILC2 increased in PBMCs of severely burned patients (**A**) and PBMCs and lamina propria (LP) of mice 1 day after burn injury (**B**). ILC2 decreased in LP of burned mice treated with SR3335 (**C**). The resistance of severely burned mice to gut bacteria-associated sepsis was improved by treatment with SR3335 (**D**).

in severely burned patients and mice,[80,81] burn-associated defects in IL-12 production cause insufficient activities of $CD103^+$ $CD127^{low}$ ILC1s or $CD127^+$ ILC1s for the production of IFN-γ.

TYPE 2 IMMUNE RESPONSES INDUCED BY ACTIVATED ILC2S

ILC2s respond rapidly to IL-25, IL-33, and TSLP, which are produced by epithelial cells and macrophages during inflammation and infection.[123] ILC2s have a crucial role in boosting type 2 immune responses by producing IL-4, IL-5, IL-9, and IL-13.[125] Although the type 2 immune responses have important host protective functions to maintain mucosal homeostasis, hyperreactive type 2 immune responses suppress the development of protective type 1 immune responses to pathogens and thereby facilitate uncontrolled or persistent infection. ILC2s constitutively express high levels of GATA3, which is required for their development from ILC progenitors. GATA3 is also required for the maintenance and function of mature ILC2s, and RAR-related orphan receptor (ROR)-α is an essential transcription factor of ILC2 maturation.[123,126] In fact, ILC2s are not detected in any tissues of RORα KO mice.[132] In mice, two distinct ILC2s are isolated: natural ILC2s ($ST2^+$, nILC2s) and inflammatory ILC2s ($ST2^-$, iILC2s).[133] nILC2s are present in steady-state conditions and support the maintenance of IgA secretion from B cells in the intestine, whereas iILC2s are induced in inflammatory circumstances.

Increased numbers of ILC2s have been detected in the peripheral blood of severely burned patients (Fig. 20.6A), as well as in the peripheral blood and lamina propria of severely burned mice (Fig. 20.6B). After depletion of ILC2 by treatment with a specific inhibitor against the RORα-dependent transcription factor (SR3335, a synthetic ligand for RORα[133]) (Fig. 20.6C), sepsis stemming from enteric bacterial infections was controlled in severely burned mice (Fig. 20.6D). Thus ILC2s play an important role in the

impaired host antibacterial defenses influenced by severe burn injuries.

INTESTINAL ILC3S

Similar to ILC1s, ILC3s have a crucial role in promoting type 1 immune responses.[123] ILC3s are predominantly present in gut-associated lymphoid tissues. These ILC3s respond to IL-1β, IL-6, and IL-23, which are produced by DCs or myeloid cells. They are IL-22 (and IL-17) producer cells and constitutively express RORγt. ILC3s are classified into three subsets including lymphoid tissue-inducer (LTi) cells and two RORγt$^+$ subsets distinguished by their expression or lack of expression of NK cell receptors (NCR$^+$ ILC3s and NCR$^-$ ILC3s).[123,126] LTi cells produce lymphotoxin and TNF-α and stimulate the mesenchymal cell production of chemokines and adhesion molecules essential for lymphoid organogenesis. NCR$^+$ ILC3s express NK-specific molecules (NKp46 in mice and NKp44 in human); however, these cells lack cytotoxicity and do not produce IFN-γ. In contrast, NCR$^-$ ILC3s are IFN-γ producers. Through the production of IL-17, NCR$^-$ILC3s stimulate neutrophil migration and the secretion of antimicrobial peptides by epithelial cells.[134] In the intestine, ILC3s have an important role in regulating tissue repair.[123,135] ILC3s rapidly respond to extracellular bacterial or fungal infections and produce IL-22 for the maintenance of the epithelial barrier, production of antimicrobial peptides, and suppression of the reactivity of commensal bacteria-specific T cells by presenting a peptide derived from commensal bacteria. ILC3 crosstalk with macrophages and DCs promotes intestinal homeostasis by enhancing the levels of regulatory T cells.[136] In response to IL-1β, which is produced by macrophages stimulated with extracellular bacteria, LTi cells and NCR$^+$ILC3s produce GM-CSF to promote oral tolerance. ILC3s differentiate into ILC1s on stimulation with IL-2 and IL-12.[137]

In severely burned patients, bacteria-elicited IL-12 production by macrophages and neutrophils is greatly impaired.[80,81] Also, mitogen-stimulated T-cell production of IL-2 is decreased in these patients.[83,138] The deficiency of IL-2 and IL-12 production results in minimal differentiation of ILC3s into ILC1s. The decrease of ILC1s in severely burned patients leads to reduced antibacterial effector cell generation and subsequent impaired adaptive immune responses. Since ILC3s resolve intestinal inflammation and enhance intestinal barrier function through the stimulation of antimicrobial peptide production by epithelial cells,[123] ILC3s play an important role in reducing bacterial translocation following severe burn injuries.

Dendritic Cells

DCs are phagocytic cells that play an important role in initiating both innate and adaptive immune responses to infection. DCs reside in areas of high antigen exposure, such as the skin, airway, and intestine. As phagocytes, DCs detect invading microbes and produce cytokines and antimicrobial peptides that can attract and activate other innate immune cells to limit microbial growth and spread. As antigen-presenting cells, DCs present antigens to T cells to initiate adaptive immune responses. Both of these DC roles are important for controlling and eliminating infections. Circulating DCs are significantly depleted in burn patients. As early as 1 day after injury, burn patients have significantly lower numbers of both conventional and plasmacytoid classes of DCs. In burn patients who do not develop sepsis, circulating DCs are restored within a week. However, in burn patients who develop sepsis during the acute post-burn recovery phase (within 20 days of injury), DCs are not restored to normal levels and remain significantly lower than DC levels in burn patients who do not develop sepsis.[139] This suggests that a burn-associated deficit in DCs decreases the ability of burn patients to fight infection. The inability to replenish DCs after burn injury is associated with a decrease in differentiation from their myeloid precursor cells. Monocytes from burned patients show decreased DC differentiation potential in vitro and are associated with high monocyte expression of MafB, a transcription factor that promotes the differentiation of myeloid progenitor cells into monocytes instead of DCs. In vitro silencing of MafB in burn patient monocytes restored their differentiation potential into DCs.[140] This is also observed in mouse models of burn injury, where the differentiation potential of myeloid precursors favors the production of monocytes and not DCs. Severely burned mice show a significant decrease in DC numbers for up to 2 weeks postinjury, and this is associated with increased expression of MafB, and a decrease in the expression of GATA-1, a DC differentiation transcription factor.[141,142]

In addition to depletion of DCs, burn injury also impairs some DC functions that are critical for effective responses to infection. Locally, skin DCs are not only depleted near the burn wound, but their expression of human leukocyte antigen-D related (HLA-DR; a MHC-II antigen presentation molecule) and TLR4 (important for DC activation) and their ability to stimulate T lymphocytes, are impaired after burn injury.[143,144] Local impairment of DC functions can increase susceptibility to wound infections. Rodent models of burn injury demonstrate similar impairments in DC functions. DC expression of TLR4 and production of Th1-associated cytokines such as IL-12 are decreased, while production of Th2-associated cytokines such as IL-10 is increased after burn injury. T-cell activation by DCs is impaired by burn injury.[145,146] Additionally, the ability of DCs to produce antimicrobial β-defensins is decreased following burn injury, and this is associated with decreased in vitro killing of bacteria.[147] Collectively, the burn-induced depletion and impairment of DCs can reduce both innate and adaptive immune responses to infection.

Experimental studies have investigated pharmacological stimulation of DC production in mice after burn injury as a mechanism to restore DC numbers and functions after burn injury. Treatment of burned mice with the DC growth factor *fms*-like tyrosine kinase-3 ligand (Flt3L) after severe burn injury restores and increases DC numbers, increases DC production of Th1-associated cytokines, and increases DC stimulation of neutrophil and lymphocyte activation.[148,149] This results in improved bacterial clearance, decreased systemic inflammation, and increased survival in response to burn wound infection. This suggests that DC impairment plays a critical role in susceptibility to infections after burn injury and that DC-targeted therapies may help to restore immune function in severely burned patients.

Summary

The immunological perturbations induced by burn injury are heterogeneous and may differ in each burn patient. Therefore, targeting a sole cell type or implementing a single-agent therapy may not be sufficient to significantly decrease the morbidity and mortality of severely burned patients. Defining patient-specific immune deficits and then targeting these defects with a cocktail of immunotherapies without inducing exaggerated inflammatory activities will be the best approach for boosting the immune system and reducing infection-associated mortality of severely burned patients. Therefore identification of predictive biomarkers is necessary for the future development of personalized immunotherapy for severely burned patients.

Complete references available online at
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References

1. Sheridan RL. Sepsis in pediatric burn patients. *Pediatr Crit Care Med*. 2005;6:S112-S119.
2. Weber J, McManus A. Infection control in burn patients. *Burns*. 2004;30:A16-A24.
3. Vostrugina K, Gudaviciene D, Vitkauskiene A. Bacteremias in patients with severe burn trauma. *Medicina*. 2006;42:576-579.
4. Bang RL, Gang RK, Sanyal SC, et al. Burn septicaemia: an analysis of 79 patients. *Burns*. 1998;24:354-361.
5. Sharma BR. Infection in patients with severe burns: causes and prevention thereof. *Infect Dis Clin North Am*. 2007;21:745-759.
6. Rodgers GL, Mortensen J, Fisher MC, et al. Predictors of infectious complications after burn injuries in children. *Pediatr Infect Dis J*. 2000;19:990-995.
7. Wolf SE, Rose JK, Desai MH, et al. Mortality determinants in massive pediatric burns. An analysis of 103 children with > or = 80% TBSA burns (> or = 70% full-thickness). *Ann Surg*. 1997;225:554-565.
8. Geyik MF, Aldemir M, Hosoglu S, et al. Epidemiology of burn unit infections in children. *Am J Infect Control*. 2003;31:342-346.
9. Murray CK, Loo FL, Hospenthal DR, et al. Incidence of systemic fungal infection and related mortality following severe burns. *Burns*. 2008;34:1108-1112.
10. Heggers JP, Phillips LG, Boertman JA, et al. The epidemiology of methicillin-resistant *Staphylococcus aureus* in a burn center. *J Burn Care Rehabil*. 1988;9:610-612.
11. Hunt JL, Purdue GF, Tuggle DW. Morbidity and mortality of an endemic pathogen: methicillin-resistant *Staphylococcus aureus*. *Am J Surg*. 1988;156:524-528.
12. Ransjö U, Malm M, Hambraeus A, et al. Methicillin-resistant *Staphylococcus aureus* in two burn units: clinical significance and epidemiological control. *J Hosp Infect*. 1989;13:355-365.
13. Haddadin AS, Fappiano SA, Lipsett PA. Methicillin resistant *Staphylococcus aureus* (MRSA) in the intensive care unit. *Postgrad Med J*. 2002;78:385-392.
14. Smith TL, Pearson ML, Wilcox KR, et al. Emergence of vancomycin resistance in *Staphylococcus aureus*. Glycopeptide-Intermediate *Staphylococcus aureus* Working Group. *N Engl J Med*. 1999;340:493-501.
15. Sieradzki K, Roberts RB, Haber SW, et al. The development of vancomycin resistance in a patient with methicillin-resistant *Staphylococcus aureus* infection. *N Engl J Med*. 1999;340:517-523.
16. Liñares J. The VISA/GISA problem: therapeutic implications. *Clin Microbiol Infect*. 2001;Suppl 4:8-15.
17. Stevens DL, Herr D, Lampiris H, et al. Linezolid versus vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infections. *Clin Infect Dis*. 2002;34:1481-1490.
18. Tredget EE, Shankowsky HA, Rennie R, et al. *Pseudomonas* infections in the thermally injured patient. *Burns*. 2004;30:3-26.
19. Stryjewski ME, Sexton DJ. Hauser AR, Rello J, eds. *Severe Infections Caused by Pseudomonas Aeruginosa*. Boston: Kluwer Academic Publishers; 2003:1-15.
20. Stieritz DD, Holder IA. Experimental studies of the pathogenesis of infections due to *Pseudomonas aeruginosa*: description of a burned mouse model. *J Infect Dis*. 1975;131:688-691.
21. Medzhitov R, Janeway C Jr. Innate immunity. *N Engl J Med*. 2000;343:338-344.
22. Zhang Q, Raoof M, Chen Y, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature*. 2010;464:104-107.
23. Mills KH. TLR-dependent T cell activation in autoimmunity. *Nat Rev Immunol*. 2011;11:807-822.
24. Maslanik T, Tannura K, Mahaffey L, et al. Commensal bacteria and MAMPs are necessary for stress-induced increases in IL-1β and IL-18 but not IL-6, IL-10 or MCP-1. *PLoS ONE*. 2012;7:e50636.
25. Chan JK, Roth J, Oppenheim JJ, et al. Alarmins: awaiting a clinical response. *J Clin Invest*. 2012;122:2711-2719.
26. Teodorczyk-Injeyan JA, Sparkes BG, Peters WJ. Regulation of IgM production in thermally injured patients. *Burns*. 1989;15:241-247.
27. Jeschke MG. The hepatic response to thermal injury: is the liver important for postburn outcomes? *Mol Med*. 2009;15:337-351.
28. Jeschke MG, Barrow RE, Herndon DN. Insulinlike growth factor I plus insulinlike growth factor binding protein 3 attenuates the proinflammatory acute phase response in severely burned children. *Ann Surg*. 2000;231:246-252.
29. Plackett TP, Colantoni A, Heinrich SA, et al. The early acute phase response after burn injury in mice. *J Burn Care Res*. 2007;28:167-172.
30. Kang HJ, Kim JH, Lee EH, et al. Change of complement system predicts the outcome of patients with severe thermal injury. *J Burn Care Rehabil*. 2003;24:148-153.
31. Huber-Lang MS, Younkin EM, Sarma JV, et al. Complement-induced impairment of innate immunity during sepsis. *J Immunol*. 2002;169:3223-3231.
32. Hecke F, Schmidt U, Kola A, et al. Circulating complement proteins in multiple trauma patients – correlation with injury severity, development of sepsis, and outcome. *Crit Care Med*. 1997;25:2015-2024.
33. Ong PY, Ohtake T, Brandt C, et al. Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med*. 2002;347:1151-1160.
34. Murakami M, Lopez-Garcia B, Braff M, et al. Postsecretory processing generates multiple cathelicidins for enhanced topical antimicrobial defense. *J Immunol*. 2004;172:3070-3077.
35. Fort MM, Cheung J, Yen D, et al. IL-25 induces IL-4, IL-5, and IL-13 and Th2-associated pathologies in vivo. *Immunity*. 2001;15:985-995.
36. Soumelis V, Reche PA, Kanzler H, et al. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol*. 2002;3:673-680.
37. Schmitz J, Owyang A, Oldham E, et al. IL-33, an interleukin-1–like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity*. 2005;23:479-490.
38. Milner SM, Ortega MR. Reduced antimicrobial peptide expression in human burn wounds. *Burns*. 1999;25:411-413.
39. Yoshida S, Lee JO, Nakamura K, et al. Lineage$^-$CD34$^+$CD31$^+$ cells that appear in association with severe burn injury are inhibitory on the production of antimicrobial peptides by epidermal keratinocytes. *PLoS ONE*. 2014;9:e82926.
40. Gentile LF, Cuenca AG, Efron PA, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. *J Trauma Acute Care Surg*. 2012;72:1491-1501.
41. Bone RC. Sir Isaac Newton, sepsis, SIRS, and CARS. *Crit Care Med*. 1996;24:1125-1128.
42. Baue AE, Durham R, Faist E. Systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), multiple organ failure (MOF): are we winning the battle? *Shock*. 1998;10:79-89.
43. Gratchev A, Guillot P, Hakiy N, et al. Alternatively activated macrophages differentially express fibronectin and its splice variants and the extracellular matrix protein βG-H3. *Scand J Immunol*. 2001;53:386-392.
44. Schnoor M, Cullen P, Lorkowski J, et al. Production of type VI collagen by human macrophages: a new dimension in macrophage functional heterogeneity. *J Immunol*. 2008;180:5707-5719.
45. Novak ML, Koh TJ. Macrophage phenotypes during tissue repair. *J Leukoc Biol*. 2013;93:875-881.
46. Pardo V, González-Rodríguez Á, Guijas C, et al. Opposite cross-talk by oleate and palmitate on insulin signaling in hepatocytes through macrophage activation. *J Biol Chem*. 2015;290:11663-11677.
47. Wan J, Benkdane M, Teixeira-Clerc F, et al. M2 Kupffer cells promote M1 Kupffer cell apoptosis: a protective mechanism against alcoholic and nonalcoholic fatty liver disease. *Hepatology*. 2014;59:130-142.
48. Wolk K, Döcke W, von Baehr V, et al. Comparison of monocyte functions after LPS- or IL-10-induced reorientation: importance in clinical immunoparalysis. *Pathobiology*. 1999;67:253-256.
49. Hall MW, Knatz NL, Vetterly C, et al. Immunoparalysis and nosocomial infection in children with multiple organ dysfunction syndrome. *Intensive Care Med*. 2011;37:525-532.
50. Mayadas TN, Cullere X, Lowell CA. The multifaceted functions of neutrophils. *Annu Rev Pathol*. 2014;9:181-218.
51. Dahl R, Walsh JC, Lancki D, et al. Regulation of macrophage and neutrophil cell fates by the PU.1:C/EBPα ratio and granulocyte colony-stimulating factor. *Nat Immunol*. 2003;10:1029-1036.
52. Coffelt SB, Wellenstein MD, de Visser KE. Neutrophils in cancer: neutral no more. *Nat Rev Cancer*. 2016;7:431-446.
53. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. *Nat Rev Immunol*. 2013;13:159-175.
54. Loison F, Zhu H, Karatepe K, et al. Proteinase 3-dependent caspase-3 cleavage modulates neutrophil death and inflammation. *J Clin Invest*. 2014;124:4445-4458.

55. Brinkmann V, Zychlinsky A. Beneficial suicide: why neutrophils die to make NETs. Beneficial suicide: why neutrophils die to make NETs. *Nat Rev Microbiol*. 2007;5:577-582.
56. Remijsen Q, Kuijpers TW, Wirawan E, et al. Dying for a cause: NETosis, mechanisms behind an antimicrobial cell death modality. *Cell Death Differ*. 2011;18:581-588.
57. Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. *Nat Immunol*. 2005;6:1191-1197.
58. Summers C, Rankin SM, Condliffe AM, et al. Neutrophil kinetics in health and disease. *Trends Immunol*. 2010;8:318-324.
59. Ley K, Laudanna C, Cybulsky MI, et al. Getting to the site of inflammation: the leukocyte adhesion cascade updated. *Nat Rev Immunol*. 2007;9:678-689.
60. Harada A, Sekido N, Akahoshi T, et al. Essential involvement of interleukin-8 (IL-8) in acute inflammation. *J Leukoc Biol*. 1994;56: 559-564.
61. Vindenes H, Ulvestad E, Bjerknes R. Increased levels of circulating interleukin-8 in patients with large burns: relation to burn size and sepsis. *J Trauma*. 1995;39:635-640.
62. Leliefeld PH, Wessels CM, Leenen LP, et al. The role of neutrophils in immune dysfunction during severe inflammation. *Crit Care*. 2016;20:73.
63. Butler KL, Ambravaneswaran V, Agrawal N, et al. Burn injury reduces neutrophil directional migration speed in microfluidic devices. *PLoS ONE*. 2010;5:e11921.
64. Hickey MJ, Kubes P. Intravascular immunity: the host-pathogen encounter in blood vessels. *Nat Rev Immunol*. 2009;9:364-375.
65. Zins SR, Amare MF, Anam K, et al. Wound trauma mediated inflammatory signaling attenuates a tissue regenerative response in MRL/MpJ mice. *J Inflamm (Lond)*. 2010;7:25.
66. Nomellini V, Faunce DE, Gomez CR, et al. An age-associated increase in pulmonary inflammation after burn injury is abrogated by CXCR2 inhibition. *J Leukoc Biol*. 2008;83:1493-1501.
67. Hazeldine J, Hampson P, Lord JM. The impact of trauma on neutrophil function. *Injury*. 2014;45:1824-1833.
68. Tsuda Y, Takahashi H, Kobayashi M, et al. Three different neutrophil subsets exhibited in mice with different susceptibilities to infection by methicillin-resistant *Staphylococcus aureus*. *Immunity*. 2004;21:215-226.
69. Tsuda Y, Shigematsu K, Kobayashi M, et al. Role of polymorphonuclear neutrophils on infectious complications stemming from *Enterococcus faecalis* oral infection in thermally injured mice. *J Immunol*. 2008;180:4133-4138.
70. Tsuda Y, Takahashi H, Kobayashi M, et al. CCL2, a product of mice early after systemic inflammatory response syndrome (SIRS), induces alternatively activated macrophages capable of impairing antibacterial resistance of SIRS mice. *J Leukoc Biol*. 2004;76:368-373.
71. Shigematsu K, Asai A, Kobayashi M, et al. *Enterococcus faecalis* translocation in mice with severe burn injury: a pathogenic role of CCL2 and alternatively activated macrophages (M2aMϕ and M2cMϕ). *J Leukoc Biol*. 2009;86:999-1005.
72. Shigematsu K, Kogiso M, Kobayashi M, et al. Effect of CCL2 antisense oligodeoxynucleotides on bacterial translocation and subsequent sepsis in severely burned mice orally infected with *Enterococcus faecalis*. *Eur J Immunol*. 2012;42:158-164.
73. Asai A, Kogiso M, Kobayashi M, et al. Effect of IL-10 antisense gene therapy in severely burned mice intradermally infected with MRSA. *Immunobiology*. 2012;217:711-718.
74. Tang D, Kang R, Coyne CB, et al. PAMPs and DAMPs: signal 0s that spur autophagy and immunity. *Immunol Rev*. 2012;249:158-175.
75. Jounai N, Kobiyama K, Takeshita F, et al. Recognition of damage-associated molecular patterns related to nucleic acids during inflammation and vaccination. *Front Cell Infect Microbiol*. 2013;2:168.
76. Simmons JD, Lee YL, Mulekar S, et al. Elevated levels of plasma mitochondrial DNA DAMPs are linked to clinical outcome in severely injured human subjects. *Ann Surg*. 2013;258:591-596.
77. Chou CC, Fang HY, Chen YL, et al. Plasma nuclear DNA and mitochondrial DNA as prognostic markers in corrosive injury patients. *Dig Surg*. 2008;25:300-304.
78. Lantos J, Földi V, Roth E, et al. Burn trauma induces early HMGB1 release in patients: its correlation with cytokines. *Shock*. 2010;33:562-567.
79. Neumann K, Castiñeiras-Vilariño M, Höckendorf U, et al. Clec12a is an inhibitory receptor for uric acid crystals that regulates inflammation in response to cell death. *Immunity*. 2014;40:389-399.
80. Kobayashi M, Jeschke MG, Shigematsu K, et al. M2b monocytes predominated in peripheral blood of severely burned patients. *J Immunol*. 2010;185:7174-7179.
81. O'Sullivan ST, Lederer JA, Horgan AF, et al. Major injury leads to predominance of the T helper-2 lymphocyte phenotype and diminished interleukin-12 production associated with decreased resistance to infection. *Ann Surg*. 1995;222:482-490.
82. Kobayashi M, Kobayashi H, Herndon DN, et al. Burn-associated *Candida albicans* infection caused by $CD30^+$ type 2 T cells. *J Leukoc Biol*. 1998;63:723-731.
83. Guo Z, Kavanagh E, Zang Y, et al. Burn injury promotes antigen-driven Th2–type responses in vivo. *J Immunol*. 2003;171:3983-3990.
84. Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. *Nat Rev Immunol*. 2011;11:723-737.
85. Lawrence T, Natoli G. Transcriptional regulation of macrophage polarization: enabling diversity with identity. *Nat Rev Immunol*. 2011;11:750-761.
86. Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. *J Clin Invest*. 2012;122:787-795.
87. Hume DA. The many alternative faces of macrophage activation. *Front Immunol*. 2015;6:370.
88. Muraille E, Leo O, Moser M. TH1/TH2 paradigm extended: macrophage polarization as an unappreciated pathogen-driven escape mechanism? *Front Immunol*. 2014;5:603.
89. Porta C, Riboldi E, Ippolito A, et al. Molecular and epigenetic basis of macrophage polarized activation. *Semin Immunol*. 2015;27:237-248.
90. Gomez Perdiguero E, Klapproth K, Schulz C, et al. Tissue-resident macrophages originate from yolk-sac-derived erythro-myeloid progenitors. *Nature*. 2015;518:547-551.
91. Italiani P, Boraschi D. New insights into tissue macrophages: from their origin to the development of memory. *Immune Netw*. 2015;15:167-176.
92. Wang J, Kubes P. A reservoir of mature cavity macrophages that can rapidly invade visceral organs to affect tissue repair. *Cell*. 2016;165:668-678.
93. Ley K, Pramod AB, Croft M, et al. How mouse macrophages sense what is going on. *Front Immunol*. 2016;7:204.
94. Perdiguero EG, Geissmann F. The development and maintenance of resident macrophages. *Nat Immunol*. 2016;17:2-8.
95. Yamamoto T, Kaizu C, Kawasaki T, et al. Macrophage colony-stimulating factor is indispensable for repopulation and differentiation of Kupffer cells but not for splenic red pulp macrophages in osteopetrotic (op/op) mice after macrophage depletion. *Cell Tissue Res*. 2008;332:245-256.
96. Butovsky O, Jedrychowski MP, Moore CS, et al. Identification of a unique TGF-β-dependent molecular and functional signature in microglia. *Nat Neurosci*. 2014;17:131-143.
97. Wang Y, Szretter KJ, Vermi W, et al. IL-34 is a tissue-restricted ligand of CSF1R required for the development of Langerhans cells and microglia. *Nat Immunol*. 2012;13:753-760.
98. Shibata Y, Berclaz PY, Chroneos ZC, et al. GM-CSF regulates alveolar macrophage differentiation and innate immunity in the lung through PU.1. *Immunity*. 2001;15:557-567.
99. Okabe Y, Medzhitov R. Tissue-specific signals control reversible program of localization and functional polarization of macrophages. *Cell*. 2014;157:832-844.
100. Rosas M, Davies LC, Giles PJ, et al. The transcription factor Gata6 links tissue macrophage phenotype and proliferative renewal. *Science*. 2014;344:645-648.
101. Ziegler-Heitbrock L. The $CD14^+$ $CD16^+$ blood monocytes: their role in infection and inflammation. *J Leukoc Biol*. 2007;81:584-592.
102. Epelman S, Lavine KJ, Randolph GJ. Origin and functions of tissue macrophages. *Immunity*. 2014;41:21-35.
103. Jeschke MG, Mlcak RP, Finnerty CC, et al. Burn size determines the inflammatory and hypermetabolic response. *Crit Care*. 2007;11:R90.
104. Wang N, Liang H, Zen K. Molecular mechanisms that influence the macrophage m1–m2 polarization balance. *Front Immunol*. 2014;5:614.
105. Date D, Das R, Narla G, et al. Kruppel-like transcription factor 6 regulates inflammatory macrophage polarization. *J Biol Chem*. 2014;289:10318-10329.
106. Kobayashi M, Nakamura K, Cornforth M, et al. Role of M2b macrophages in the acceleration of bacterial translocation and subsequent sepsis in mice exposed to whole body ^{137}Cs γ-irradiation. *J Immunol*. 2012;189:296-303.

107. Ohama H, Asai A, Ito I, et al. M2b macrophage elimination and improved resistance of mice with chronic alcohol consumption to opportunistic infections. *Am J Pathol*. 2015;185:420-431.
108. Laskin DL, Sunil VR, Gardner CR, et al. Macrophages and tissue injury: agents of defense or destruction? *Annu Rev Pharmacol Toxicol*. 2011;51:267-288.
109. Choudhry MA, Kovacs EJ. A role for CD1d-restricted NKT cells in injury-associated T cell suppression. *J Leukoc Biol*. 2003;73:747-755.
110. Hutchins AP, Diez D, Miranda-Saavedra D. The IL-10/STAT3–mediated anti-inflammatory response: recent developments and future challenges. *Brief Funct Genomics*. 2013;12:489-498.
111. Dallagi A, Girouard J, Hamelin-Morrissette J, et al. The activating effect of IFN-γ on monocytes/macrophages is regulated by the LIF-trophoblast-IL-10 axis via Stat1 inhibition and Stat3 activation. *Cell Mol Immunol*. 2015;12:326-341.
112. Martinez FO, Sica A, Mantovani A, et al. Macrophage activation and polarization. *Front Biosci*. 2008;13:453-461.
113. Wilmore DW, Long JM, Mason AD Jr, et al. Catecholamines: mediator of the hypermetabolic response to thermal injury. *Ann Surg*. 1974;180:653-669.
114. Asai A, Nakamura K, Kobayashi M, et al. CCL1 released from M2b macrophages is essentially required for the maintenance of their properties. *J Leukoc Biol*. 2012;92:859-867.
115. Ito I, Bhopale KK, Nishiguchi T, et al. Polarization of M2b monocytes in cultures of burn patient monocytes treated with a selected CCL1 antisense oligodeoxynucleotide. *Nucleic Acid Ther*. 2016;26:269-276.
116. Nishiguchi T, Ito I, Lee JO, et al. Macrophage polarization and MRSA infection in burned mice. *Immunol Cell Biol*. 2016;doi:10.1038/icb.2017;95:198-206.
117. Squadrito ML, Etzrodt M, De Palma M, et al. MicroRNA-mediated control of macrophages and its implications for cancer. *Trends Immunol*. 2013;34:350-359.
118. Das A, Ganesh K, Khanna S, et al. Engulfment of apoptotic cells by macrophages: a role of microRNA-21 in the resolution of wound inflammation. *J Immunol*. 2014;192:1120-1129.
119. Fadok VA, Bratton DL, Konowal A, et al. Macrophages that have ingested apoptotic cells in vitro inhibit proinflammatory cytokine production through autocrine/paracrine mechanisms involving TGF-beta, PGE2, and PAF. *J Clin Invest*. 1998;101:890-898.
120. Sen CK. MicroRNAs as new maestro conducting the expanding symphony orchestra of regenerative and reparative medicine. *Physiol Genomics*. 2011;43:517-520.
121. Ishii M, Wen H, Corsa CA, et al. Epigenetic regulation of the alternatively activated macrophage phenotype. *Blood*. 2009;114:3244-3254.
122. Artis D, Spits H. The biology of innate lymphoid cells. *Nature*. 2015;517:293-301.
123. Sonnenberg GF, Artis D. Innate lymphoid cells in the initiation, regulation and resolution of inflammation. *Nat Med*. 2015;21:698-708.
124. Spits H, Artis D, Colonna M, et al. Innate lymphoid cells – a proposal for uniform nomenclature. *Nat Rev Immunol*. 2013;13:145-149.
125. Klose CS, Artis D. Innate lymphoid cells as regulators of immunity, inflammation and tissue homeostasis. *Nat Immunol*. 2016;17:765-774.
126. Serafini N, Vosshenrich CA, Di Santo JP. Transcriptional regulation of innate lymphoid cell fate. *Nat Rev Immunol*. 2015;15:415-428.
127. Klose CS, Flach M, Möhle L, et al. Differentiation of type 1 ILCs from a common progenitor to all helper-like innate lymphoid cell lineages. *Cell*. 2014;157:340-356.
128. Stein MD, Gamble DN, Klimpel KD, et al. Natural killer cell defects resulting from thermal injury. *Cell Immunol*. 1984;86:551-556.
129. Blazar BA, Rodrick ML, O'Mahony JB, et al. Suppression of natural killer-cell function in humans following thermal and traumatic injury. *J Clin Immunol*. 1986;6:26-36.
130. Klimpel GR, Herndon DN, Fons M, et al. Defective NK cell activity following thermal injury. *Clin Exp Immunol*. 1986;66:384-392.
131. Haik J, Nardini G, Goldman N, et al. Increased serum NKG2D-ligands and downregulation of NKG2D in peripheral blood NK cells of patients with major burns. *Oncotarget*. 2016;7:2220-2228.
132. Halim TY, MacLaren A, Romanish MT, et al. Retinoic-acid-receptor-related orphan nuclear receptor alpha is required for natural helper cell development and allergic inflammation. *Immunity*. 2012;37:463-474.
133. Kumar N, Kojetin DJ, Solt LA, et al. Identification of SR3335 (ML-176): a synthetic RORα selective inverse agonist. *ACS Chem Biol*. 2011;6:218-222.
134. Moro K, Koyasu S. Innate lymphoid cells, possible interaction with microbiota. *Semin Immunopathol*. 2015;37:27-37.
135. Dudakov JA, Hanash AM, Jenq RR, et al. Interleukin-22 drives endogenous thymic regeneration in mice. *Science*. 2012;336:91-95.
136. Mortha A, Chudnovskiy A, Hashimoto D, et al. Microbiota-dependent crosstalk between macrophages and ILC3 promotes intestinal homeostasis. *Science*. 2014;343:1249288.
137. Bernink JH, Peters CP, Munneke M, et al. Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues. *Nat Immunol*. 2013;14:221-229.
138. Wood JJ, Rodrick ML, O'Mahony JB, et al. Inadequate interleukin 2 production. A fundamental immunological deficiency in patients with major burns. *Ann Surg*. 1984;200:311-320.
139. D'Arpa N, Accardo-Palumbo A, Amato G, et al. Circulating dendritic cells following burn. *Burns*. 2009;35:513-518.
140. Williams KN, Szilagyi A, He LK, et al. Dendritic cell depletion in burn patients is regulated by MafB expression. *J Burn Care Res*. 2012;33:747-758.
141. Howell K, Posluszny J, He LK, et al. High MafB expression following burn augments monocyte commitment and inhibits DC differentiation in hemopoietic progenitors. *J Leukoc Biol*. 2012;91:69-81.
142. Johnson NB, Posluszny JA, He LK, et al. Perturbed MafB/GATA1 axis after burn trauma bares the potential mechanism for immune suppression and anemia of critical illness. *J Leukoc Biol*. 2016;[Epub ahead of print].
143. D'Arpa N, D'Amelio L, Accardo-Palumbo A, et al. Skin dendritic cells in burn patients. *Ann Burns Fire Disasters*. 2009;22:175-178.
144. van den Berg LM, de Jong MA, Witte Ld, et al. Burn injury suppresses human dermal dendritic cell and Langerhans cell function. *Cell Immunol*. 2011;268:29-36.
145. Patenaude J, D'Elia M, Hamelin C, et al. Selective effect of burn injury on splenic CD11c(+) dendritic cells and CD8alpha(+)CD4(-)CD11c(+) dendritic cell subsets. *Cell Mol Life Sci*. 2010;67:1315-1329.
146. Shen H, de Almeida PE, Kang KH, et al. Burn injury triggered dysfunction in dendritic cell response to TLR9 activation and resulted in skewed T cell functions. *PLoS ONE*. 2012;7:e50238.
147. Kawasaki T, Kawasaki C, Sata T, et al. Depressed production of beta-defensins from mouse splenic dendritic cells following thermal injury and its influence on susceptibility to infection. *J Anesth*. 2015;29:78-86.
148. Toliver-Kinsky TE, Lin CY, Herndon DN, et al. Stimulation of hematopoiesis by the Fms-like tyrosine kinase 3 ligand restores bacterial induction of Th1 cytokines in thermally injured mice. *Infect Immun*. 2003;71:3058-3067.
149. Bohannon J, Cui W, Cox R, et al. Prophylactic treatment with fms-like tyrosine kinase-3 ligand after burn injury enhances global immune responses to infection. *J Immunol*. 2008;180:3038-3048.

21 Biomarkers in Burn Patient Care

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Introduction

Each year, more than 8 million people are burned. Approximately 1 million sustain severe burn injuries covering more than 30% of the total body surface area (TBSA). Burns cause considerable morbidity and mortality; burn injuries are often complicated by inhalation injury, infections, and sepsis, all of which can lead to systemic inflammation, acute respiratory distress syndrome (ARDS), multiple organ dysfunction (MODS), and death.[1] Despite advances in critical care and resuscitation, infections develop and lead to sepsis in 40–60% of burn patients.[2–6] The ability to prospectively identify or monitor organ function, infections, clinical trajectory, or patient outcome in severely burned patients would enable early intervention, reduce morbidity and mortality, and significantly lower the cost of clinical care. In recent years, biomarkers ranging from single proteins (e.g., procalcitonin, interleukin-8 [IL-8]) to the combination of variables (e.g., proteins, urinary markers, clinical parameters) have been used to predict or identify the risk of infection, sepsis, organ failure, or likelihood of survival, in patients with severe burns. The first 72 hours postinjury are critical for the prevention of complications, so the ability to use biomarkers to guide care during this period enhances our ability to improve patient care. We and others have identified candidate biomarkers that can be used to identify infection or sepsis, predict patient survival, reveal injury severity, or monitor organ function or wound healing. Biomarkers can take the form of single molecules, gene or protein families, injury characteristics, or clinical parameters. A good biomarker can be used for either diagnostic or prognostic purposes, be sensitive, specific, easy to measure, and reproducible.[7] When applicable, the expression of the biomarker of interest can be modified by pharmacologic interventions, and this altered expression then monitored to determine impact on patient outcome.

Burn injury also affects long-term health and quality of life. With the many body systems that are impacted and negative sequelae that can result, the ability to predict patient outcomes or to determine whether therapy is efficacious would enable targeted therapies to improve patient outcomes. Here we review candidate biomarkers in burn patients for infections and sepsis, survival, inhalation injury, organ function, and wound healing.

Prediction of Sepsis and Infection

The expression of pro- and antiinflammatory cytokines is significantly altered following burn injury,[8] and the concentration of these cytokines alone or with respect to each other (the expression profile) can be used to predict patient outcome.[9] Characterization of the post-burn cytokine response shows an immediate spike in the expression of mediators such as IL-6 and IL-8, among others, that then slowly returns to levels detected in nonburned patients over the next several weeks to months.[8–10] The cytokine expression profile at the time of admission and during the course of the hospital stay can predict which patients may develop sepsis or multiple organ failure (MOF).[11–13] The expression of the following pro- and antiinflammatory cytokines has been linked to patient outcome: tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), IL-1β, IL-I7, IL-4, IL-6, and IL-8. Increased expression of inflammatory cytokines contributes significantly to the burn-induced hypermetabolic response and to the increased incidence of infection and sepsis. While initial studies focused on the correlation of single cytokines with patient outcomes,[14–18] technologies allowing detection of multiple proteins at a single time enable the correlation of analyte expression profiles back to clinical trajectory or other outcome.[11,13] The standard criteria for diagnosing sepsis in the critically ill are not used in the burn population due to overlap with the pathophysiological response to burn injury. Because the clinical presentation of sepsis in the burn patient is sufficiently unique, a burn-specific definition of sepsis was developed.[19] Given the massive inflammatory, acute-phase, and coagulopathic responses induced by burn injury[10,20,21] and the perturbations of these responses that occur with infection, there are many candidate biomarkers for the identification and/or prediction of sepsis and infection.

TNF-α

TNF-α is mainly secreted by activated macrophages immediately postburn. The host immune response is activated by TNF-α, as is the subsequent release of cytokines following trauma and infection. TNF-α also plays a role in angiogenesis and wound healing.[22] Several studies have identified TNF-α as a predictive marker for the development of septic complications in burn patients.[11,23] In fact, TNF-α expression is increased immediately post-burn, triggering the inflammatory response, and then decreasing again.[8,9,24] A later elevation in TNF-α expression appears to be indicative of the onset of infection or sepsis.[23,25]

IL-8

IL-8 (or CXCL8) is a chemokine that is released early postinjury mainly by macrophages. IL-8 is an important protein related to inflammation, where it plays a key role in the recruitment of neutrophils and other immune cells to the site of infection.[26] In addition to macrophages, IL-8 is also released by epithelial cells, airway smooth muscle cells, and endothelial cells. This chemokine has been shown to be

involved in many cellular processes including cell proliferation, tissue remodeling, and angiogenesis.[27]

IL-8 has been proposed as a survival biomarker following burn injury. Expression of IL-8 has been consistently shown to be greater in burn patients who do not survive than in those who do.[11,13,14,24] Whereas IL-8 expression returns to baseline within 8–10 days of injury in burn survivors, IL-8 concentrations remained significantly elevated in the nonsurvivors until the time of death.[24] When assayed over the course of hospitalization, the temporal increase in IL-8 expression in nonsurvivors occurs approximately 8–10 days post-burn, which may indicate the initiation of infection or sepsis. A more recent study has shown that in 468 pediatric burn patients, concentrations of IL-8 that met or exceeded a cutoff limit of 234 pg/mL were associated with higher incidence of MOF, sepsis, and mortality.[28]

IL-6

IL-6 is released by T cells and activated macrophages during the acute-phase response following injury or trauma and may lead to inflammation or infection. IL-6 has both pro- and antiinflammatory properties.[29] In burns, IL-6 concentrations are significantly increased when compared to IL-6 levels in nonburn volunteers.[24] Although the initial spike in IL-6 elevation reflects the early antiinflammatory response, chronic and excessive increases in serum IL-6 concentrations following burn injury are associated with a higher incidence of infection, sepsis, and death.[11,16,24] Detection of IL-6 in serum is significantly greater in nonsurviving versus surviving burn patients at all time points between the time of admission and time of death or discharge.[11,24]

C-REACTIVE PROTEIN

C-reactive protein (CRP) is a serum amyloid P component belonging to the pentraxin family of calcium-dependent ligand-binding proteins; it serves as a marker of inflammation. Synthesis of CRP occurs in the liver and is triggered by the release of IL-6 in response to tissue damage or infectious stimuli. Elevation of CRP expression occurs several hours after the onset of the increase in IL-6.[30] CRP measurements are inexpensive and readily available. High concentrations of CRP occur with inflammation; however this response is not specific. In burns, elevation of serum CRP is well documented.[31–33] CRP has been proposed as an early predictor of sepsis in burned children.[34] In a study of 918 pediatric burn patients, we found that CRP levels correlate significantly with burn size and mortality, but the changes in CRP expression did not correlate with the incidence of major infections or sepsis in severely burned children.[35] Additional studies showed that although CRP may correlate with burn size or mortality, the relationship to infection or sepsis is not well-supported.[36]

PROCALCITONIN

Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin, synthesized by the parafollicular cells of the thyroid gland, and involved in calcium homeostasis. The major function of calcitonin is to decrease calcium absorption by osteoclastic cells, which increases circulating calcium levels. The half-life of PCT is 25–30 hours. Serum PCT concentrations are significantly increased in response to infectious stimuli, fungal infections, trauma, and surgery. In burn patients, elevation of PCT concentrations begins approximately 4 hours postinjury.[37] Following burn injury, significantly higher concentrations of PCT are reported in septic versus nonseptic patients.[1,37–39] Furthermore it has been suggested that PCT concentrations be incorporated into the burn-specific definition of sepsis.[37] At present, the utility of the PCT assay is somewhat limited due to the lack of availability of rapid, cost-effective tests.

LEPTIN

Leptin is a circulating hormone primarily secreted by adipose tissue and involved in the regulation of feeding and energy homeostasis through central nervous system afferent pathways.[40] Leptin also plays a role in angiogenesis[41] and stimulates T cells and monocytes to induce cytokine release.[42] Recent reports suggest a possible role for leptin as a biomarker in burns; serum leptin levels are significantly increased following burn injury.[25,41] Leptin concentrations are elevated in septic burn patients compared to nonseptic patients and in burn survivors compared to nonsurvivors.[25] The increased expression of leptin by septic patients may be related to leptin's role in regulating the stress response.[27] Elevated expression of leptin may play a crucial role in survival of acute sepsis. The high leptin concentrations in septic burn survivors may represent a host defense mechanism against bacterial infection.[43]

COMBINED PANELS

The combination of multiple proteins may offer greater predictive ability of patient outcomes. The popularity of technologies allowing detection of a variety of proteins at a single time, such as a bead-based multiplex approach or mass spectrometry, has made the measurement of many proteins in small amounts of sample easy. As a result, it is now possible to collect the expression data for a panel of proteins to determine whether there is a correlation with patient outcome. By using these techniques, relationships between protein expression and burn injury or patient outcome can be established. Using these approaches, it has been shown that the risk of dying of sepsis is elevated in pediatric burn patients with increased expression of IL-6 and IL-12p70 alongside reduced TNF-α expression.[11]

Prediction of Patient Survival with Clinical Characteristics

The ability to accurately predict which patients have a reduced likelihood of survival will enable the clinician to develop a more aggressive treatment strategy in order to maximize the patient's chance of survival. Classically, age and percent TBSA burn were used in the initial trial for early assessment of patient outcome.[44] Furthermore, the additive influence of the presence of an inhalation injury or pneumonia could be accounted for in order to refine prediction of death.[45] With improvements in clinical care, such as resuscitation procedures, better control of

infections and septic episodes, and the development of new grafting techniques, mortality following a severe burn injury has significantly decreased. Three risk factors, however, are associated with increased mortality: age greater than 60 years, burn covering more than 40% of TBSA, and presence of inhalation injury.[46]

We have reported that the inflammatory and the metabolic responses are positively correlated with burn size[47] and that patients with massive burns have a higher incidence of sepsis, inhalation injury, mechanical ventilation requirement, myocardial infarction, and death.[48] To evaluate the effects of clinical complications on patient outcome, 952 severely burned pediatric patients were studied. A cutoff of 62% of TBSA burned was identified: patients above this threshold had an increased incidence of sepsis, MOF, and mortality.[48]

The assessment of protein expression panels has shown that these can be used to predict patient survival.[13,24] Although clinical characteristics are frequently used to evaluate the severity of the patient's health, we have found that the inclusion of proteomic data and assay results from the clinical laboratory can improve identification of patients who may have difficult clinical courses.[49] In this study of 322 severely burned children, a panel of biomarkers was identified, including burn size, presence of inhalation injury, age, blood urea nitrogen, α-2-macroglobulin, IL-4, and aspartate aminotransferase. Testing of this model showed that although prediction of death was only accurate 52% of the time when using burn size, age, and presence of inhalation injury, by including clinical chemistry and proteomic data, accuracy could be boosted to 81%.

Inhalation Injury and Mechanical Ventilation

The severity of burn injury is sometimes complicated by inhalation injury, which contributes to mortality. Patients with inhalation injury have an odds of dying nearly three times higher than those without inhalation injury.[48] Morbidity in patients with inhalation injury is further complicated by exposure to inhaled toxins and soot, exposure to which can predispose the patient to development of respiratory tract infections and/or ARDS. Mechanical ventilation is used to alleviate these symptoms. Biomarker studies have been performed in burn patients under various ventilation strategies, such as low tidal volume versus high tidal volumes. Shelhamer et al. reported that, in mechanically ventilated patients, an early increase in plasma IL-8 concentrations, among other cytokines (IL-1β, IL-6, IL-8, GM-CSF, and TNF-α), was associated with a several-fold increase in ventilator-associated pneumonia or death.[50] However a recent study compared serum concentrations of inflammatory cytokines, IL-6, IL-8, and TNF-α before and after using percussive ventilation in patients with minor burns and smoke inhalation to determine whether the plasma levels of these biomarkers are affected by the ventilation strategy.[51] Unexpectedly this study showed that high-frequency percussive ventilation (HFPV) increased blood oxygenation and did not further increase the serum levels of inflammatory cytokines,[51] as was hypothesized by the Shelhamer et al. study.[50]

Protein expression within the bronchoalveolar lavage fluid (BALF) can also be used to give insight into the effects of inhalation injury in the burned patient. Profiling of cytokine expression within the BALF from burned survivors and nonsurvivors revealed that expression of many inflammatory markers, including IL-1RA, IL-1β, IL-2, IL-4, IL-8, IL-10, IFN-γ, MIP-1β, and TNF-α was suppressed in nonsurvivors. Additional studies revealed differences in pulmonary immune hyporesponsiveness in the nonsurvivors that were responsible for decreased cytokine production. Correlation of the expression of these same cytokines in the serum with the clinical determination of the severity of inhalation injury demonstrated that IL-1RA, IL-6, IL-8, granulocyte colony-stimulating factor (GCSF), and monocyte chemotactic protein 1 serve as biomarkers for lung injury severity.[53] Within the BALF, the detection of raised concentrations of IL-10 alongside suppressed expression of IL-12p70 are significantly associated with postburn acute lung injury.[54] Furthermore early detection of increased IL-10, double-stranded DNA, and hyaluronic acid in the airway is associated with subsequent development of pulmonary bacterial infections.[54]

Resuscitation and Kidney Function

Fluid resuscitation is guided by the type of fluids to be administered, flow rate, volume, and frequency. The goal of fluid management is to correct the hypovolemic shock associated with the loss of the skin barrier function without overresuscitating. Formulae such as the Parkland formula or the Galveston formula are used to determine the burn patient's resuscitation goals. While overresuscitation is often reported,[5] no one protocol has been established for use by all burn centers. The most recent work by Cancio et al. promotes the use of computerized tools to assist providers in the resuscitation of burn patients.[55]

Volume requirements for resuscitation can be estimated by patient weight and TBSA burned.[56] Inhalation injury, burn thickness, and time since injury are also involved in these calculations.[57] The actual infusion rate is titrated over time based on urine output.[5] While several studies have suggested using intrathoracic blood volumes to guide resuscitation rates, higher ratios of serum pro- to antiinflammatory cytokines were found in these patients when compared to patients with urine output-guided resuscitation.[58] In the same study, granulocyte, lymphocyte, and monocyte CD markers were also higher in the urine-guided resuscitation group compared to patients who receive intrathoracic blood volume-guided resuscitation, suggesting a shift to an anti-inflammatory status in this group.

Studies to determine reliable biomarkers for intravascular volume and renal perfusion in critical care have pointed to neutrophil gelatinase-associated lipocalin (NGAL) and B-type natriuretic peptide (BNP) as useful markers to determine resuscitation strategies. Acute kidney injury was identified by measurement of NGAL 12 hours earlier than when using creatinine levels; in patients who had been overresuscitated, BNP levels were significantly higher.[59,60] During resuscitation following burn, measurement of creatinine, NGAL, and BNP at the point of care facilitate determination

of vascular volume and assessment of renal function.[59,61] Additional studies are needed to optimize the cutoffs for BNP and NGAL that will be used to guide resuscitation.

Wound Healing

Wound closure is predicted based on injury location, wound perfusion, and the gross appearance of the wound bed and granulation tissue.[62] In the absence of credible algorithms or biomarkers, quantitation of these factors is subjective. Therefore determination of biomarkers that can be used to monitor wound healing or be modulated to achieve optimal wound healing while avoiding hypertrophic scarring is of utmost importance in this field. Wound healing is accomplished via a precisely orchestrated cascade of interrelated cellular and biochemical events that lead to repaired tissue and is accomplished via the following events: inflammation, migration, proliferation, and remodeling. These phases are tightly regulated, and each phase overlaps with the previous one and is characterized by specific markers. The initial inflammatory phase of wound healing prevents wound infection through the early immune response and is characterized by vasodilation, fluid extravasation, edema formation ensured by neutrophils, monocytes, and macrophages, respectively. The second phase is the proliferative phase, characterized by activation of fibroblasts and keratinocytes, which leads to wound closure and revascularization. Finally the remodeling phase is characterized by collagen and elastin deposition and differentiation of fibroblasts into myofibroblasts to help with wound contracture and ultimately wound closure. Finally apoptosis of keratinocytes, myofibroblast, and immune cells will take place to terminate wound healing and avoid overgrowing extracellular components that may lead to unwanted hypertrophic scarring.

Acute wounds heal by an interdependent sequence of events mediated by pro- or antiinflammatory cytokines and chemokines. Determining the levels of these cytokines may reflect the status of the healing wound. Biomarker studies aim to determine specific markers that drive each phase of wound healing in order to tailor therapeutic strategies that will optimize functional recovery. Possible biomarkers have been identified by analyzing cytokine levels in the serum, wound exudate, blister fluid, and wound tissues. From these studies, increased serum levels of IL-3, IL-12p70, and PCT have emerged as biomarker candidates indicating delayed wound healing.[63] Hawksworth et al. analyzed the levels of proinflammatory cytokines in the serum, wound effluent, and biopsies of the wound bed collected during each débridement procedure.[64] Serum IL-6, IL-8, MIP-l α, and effluent inducible protein [IP]-10 protein were predictive of wound dehiscence.[64] Additionally, expression of mRNA transcripts for MCP-l, IL-lα, TNF-α, IL-8, MIP-lα, GM-CSF, IL-lβ, and IL-6 were also predictive of wound dehiscence.[64]

In elderly patients, delayed wound healing was associated with increased levels of CD44 and keratin-6.[65] Modulation of matrix metalloproteinase-9 in these patients accelerates wound healing.[65] IL-33, a member of the IL-lβ cytokine family, was shown to accelerate wound healing, increase extracellular matrix (ECM) production, facilitate the development of activated macrophages, and inhibit meticillin-resistant *Staphylococcus aureus* (MRSA) colonization by activating neutrophil proliferation while increasing expression of ECM-associated genes.[66] Leptin also improved wound healing by stimulating angiogenesis[40] and neovascularization in ischemic wounds as part of the autocrine/paracrine regulation of wound healing.[67] TNF-α is an important factor in wound healing due to its role in the early immune response when secreted by activated macrophages. TNF-α may also influence wound healing through direct action on keratinocytes and endothelial cells, thereby impacting epithelialization and vascularization.[68] Therefore TNF-α may be a good therapeutic target to improve wound healing in burns.

Conclusion

The utilization of proteomic, genomic, and clinical measurements to predict patient outcomes, monitor injury severity or organ recovery, or monitor wound healing following severe burn injury is the topic of much research. With current efforts to precisely define the patient population or injury severity (including defining sepsis), future efforts to identify biomarkers for patient outcomes should yield markers with greater specificity and utility. By pursuing these efforts, identification and validation of biological markers that can be used to guide clinical decisions or to monitor efficacy of therapy will be possible.

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Further Reading

Davis CS, Albright JM, Carter SR, et al. Early pulmonary immune hyporesponsiveness is associated with mortality after burn and smoke inhalation injury. *J Burn Care Res*. 2012;33(1):26-35.

Finnerty CC, Jeschke MG, Qian WJ, et al. Determination of burn patient outcome by large-scale quantitative discovery proteomics. *Crit Care Med*. 2013;41(6):1421-1434.

Finnerty CC, Ju H, Spratt H, et al. Proteomics improves the prediction of burns mortality: results from regression spline modeling. *Clin Translat Sci*. 2012;5(3):243-249.

Jeschke MG, Gauglitz GG, Kulp GA, et al. Long-term persistence of the pathophysiologic response to severe burn injury. *PLoS ONE*. 2011;6(7):e21245.

Kraft R, Herndon DN, Al-Mousawi AM, et al. Burn size and survival probability in paediatric patients in modern burn care: a prospective observational cohort study. *Lancet*. 2012;379(9820):1013-1021.

Ruiz-Castilla M, Roca O, Masclans JR, Barret JP. Recent advances in biomarkers in severe burns. *Shock*. 2016;45(2):117-125.

References

1. Lavrentieva A, Kontakiotis T, Lazaridis L, et al. Inflammatory markers in patients with severe burn injury. What is the best indicator of sepsis? *Burns*. 2007;33(2):189-194.
2. Mann-Salinas EA, Baun MM, Meininger JC, et al. Novel predictors of sepsis outperform the American Burn Association sepsis criteria in the burn intensive care unit patient. *J Burn Care Res*. 2013;34(1):31-43.
3. Mann EA, Baun MM, Meininger JC, Wade CE. Comparison of mortality associated with sepsis in the burn, trauma, and general intensive care unit patient: a systematic review of the literature. *Shock*. 2012;37(1):4-16.
4. Williams FN, Herndon DN, Hawkins HK, et al. The leading causes of death after burn injury in a single pediatric burn center. *Crit Care*. 2009;13(6).
5. Dries DJ. Management of burn injuries – recent developments in resuscitation, infection control and outcomes research. *Scand J Trauma Resuscit Emerg Med*. 2009;17:14.
6. Park MS, Salinas J, Wade CE, et al. Combining early coagulation and inflammatory status improves prediction of mortality in burned and nonburned trauma patients. *J Trauma*. 2008;64(2 suppl):S188-S194.
7. Samraj RS, Zingarelli B, Wong HR. Role of biomarkers in sepsis care. *Shock*. 2013;40(5):358-365.
8. Finnerty CC, Jeschke MG, Herndon DN, et al. Temporal cytokine profiles in severely burned patients: a comparison of adults and children. *Mol Med*. 2008;14(9-10):553-560.
9. Finnerty CC, Herndon DN, Przkora R, et al. Cytokine expression profile over time in severely burned pediatric patients. *Shock*. 2006;26(1):13-19.
10. Jeschke MG, Gauglitz GG, Kulp GA, et al. Long-term persistence of the pathophysiologic response to severe burn injury. *PLoS ONE*. 2011;6(7):e21245.
11. Finnerty CC, Herndon DN, Chinkes DL, Jeschke MG. Serum cytokine differences in severely burned children with and without sepsis. *Shock*. 2007;27(1):4-9.
12. Kraft R, Herndon DN, Finnerty CC, Shahrokhi S, Jeschke MG. Occurrence of multiorgan dysfunction in pediatric burn patients: incidence and clinical outcome. *Ann Surg*. 2014;259(2):381-387.
13. Finnerty CC, Jeschke MG, Qian WJ, et al. Determination of burn patient outcome by large-scale quantitative discovery proteomics. *Crit Care Med*. 2013;41(6):1421-1434.
14. Yeh FL, Lin WL, Shen HD, Fang RH. Changes in levels of serum IL-8 in burned patients. *Burns*. 1997;23(7-8):555-559.
15. Yeh FL, Lin WL, Shen HD. Changes in circulating levels of an anti-inflammatory cytokine interleukin 10 in burned patients. *Burns*. 2000;26(5):454-459.
16. Yeh FL, Lin WL, Shen HD, Fang RH. Changes in circulating levels of interleukin 6 in burned patients. *Burns*. 1999;25(2):131-136.
17. Yeh FL, Lin WL, Shen HD, Fang RH. Changes in serum tumour necrosis factor-alpha in burned patients. *Burns*. 1997;23(1):6-10.
18. Yeh FL, Shen HD, Fang RH. Deficient transforming growth factor beta and interleukin-10 responses contribute to the septic death of burned patients. *Burns*. 2002;28(7):631-637.
19. Greenhalgh DG, Saffle JR, Holmes JHt, et al. American Burn Association consensus conference to define sepsis and infection in burns. *J Burn Care Res*. 2007;28(6):776-790.
20. Finnerty CC, Jeschke MG, Qian WJ, et al. Determination of burn patient outcome by large-scale quantitative discovery proteomics. *Crit Care Med*. 2013.
21. Jeschke MG, Chinkes DL, Finnerty CC, et al. Pathophysiologic response to severe burn injury. *Ann Surg*. 2008;248(3):387-401.
22. Barrientos S, Brem H, Stojadinovic O, Tomic-Canic M. Clinical application of growth factors and cytokines in wound healing. *Wound Repair Regen*. 2014;22(5):569-578.
23. de Bandt JP, Chollet-Martin S, Hernvann A, et al. Cytokine response to burn injury: relationship with protein metabolism. *J Trauma*. 1994;36(5):624-628.
24. Jeschke MG, Gauglitz GG, Finnerty CC, et al. Survivors versus nonsurvivors postburn: differences in inflammatory and hypermetabolic trajectories. *Ann Surg*. 2014;259(4):814-823.
25. Abdel-Hafez NM, Saleh Hassan Y, El-Metwally TH. A study on biomarkers, cytokines, and growth factors in children with burn injuries. *Ann Burns Fire Disasters*. 2007;20(2):89-100.
26. Gauglitz GG, Finnerty CC, Herndon DN, Mlcak RP, Jeschke MG. Are serum cytokines early predictors for the outcome of burn patients with inhalation injuries who do not survive? *Crit Care*. 2008;12(3):R81.
27. Ning Y, Manegold PC, Hong YK, et al. Interleukin-8 is associated with proliferation, migration, angiogenesis and chemosensitivity in vitro and in vivo in colon cancer cell line models. *Int J Cancer*. 2011;128(9):2038-2049.
28. Kraft R, Herndon DN, Finnerty CC, et al. Predictive value of IL-8 for sepsis and severe infections after burn injury: a clinical study. *Shock*. 2015;43(3):222-227.
29. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. *Biochimica Biophysica Acta*. 2011;1813(5):878-888.
30. Li HX, Liu ZM, Zhao SJ, et al. Measuring both procalcitonin and C-reactive protein for a diagnosis of sepsis in critically ill patients. *J Int Med Res*. 2014;42(4):1050-1059.
31. Daniels JC, Larson DL, Abston S, Ritzmann SE. Serum protein profiles in thermal burns. II. Protease inhibitors, complement factors, and c-reactive protein. *J Trauma*. 1974;14(2):153-162.
32. Faymonville ME, Micheels J, Bodson L, et al. Biochemical investigations after burning injury: complement system, protease-antiprotease balance and acute-phase reactants. *Burns, Incl Thermal Inj*. 1987;13(1):26-33.
33. Gottschlich MM, Baumer T, Jenkins M, Khoury J, Warden GD. The prognostic value of nutritional and inflammatory indices in patients with burns. *J Burn Care Rehabil*. 1992;13(1):105-113.
34. Neely AN, Smith WL, Warden GD. Efficacy of a rise in C-reactive protein serum levels as an early indicator of sepsis in burned children. *J Burn Care Rehabil*. 1998;19(2):102-105.
35. Jeschke MG, Finnerty CC, Kulp GA, Kraft R, Herndon DN. Can we use C-reactive protein levels to predict severe infection or sepsis in severely burned patients? *Int J Burns Trauma*. 2013;3(3):137-143.
36. Barati M, Alinejad F, Bahar MA, et al. Comparison of WBC, ESR, CRP and PCT serum levels in septic and non-septic burn cases. *Burns*. 2008;34(6):770-774.
37. Mann EA, Wood GL, Wade CE. Use of procalcitonin for the detection of sepsis in the critically ill burn patient: a systematic review of the literature. *Burns*. 2011;37(4):549-558.
38. Seoane L, Pertega S, Galeiras R, Astola I, Bouza T. Procalcitonin in the burn unit and the diagnosis of infection. *Burns*. 2014;40(2):223-229.
39. Ren H, Li Y, Han C, Hu H. Serum procalcitonin as a diagnostic biomarker for sepsis in burned patients: a meta-analysis. *Burns*. 2015;41(3):502-509.
40. Hausman GJ, Richardson RL. Adipose tissue angiogenesis. *J Animal Sci*. 2004;82(3):925-934.
41. Kino Y, Kato M, Ikehara Y, et al. Plasma leptin levels in patients with burn injury: a preliminary report. *Burns*. 2003;29(5):449-453.
42. Santos-Alvarez J, Goberna R, Sanchez-Margalet V. Human leptin stimulates proliferation and activation of human circulating monocytes. *Cell Immunol*. 1999;194(1):6-11.
43. Correia ML, Morgan DA, Mitchell JL, et al. Role of corticotrophin-releasing factor in effects of leptin on sympathetic nerve activity and arterial pressure. *Hypertension*. 2001;38(3):384-388.
44. Zawacki BE, Azen SP, Imbus SH, Chang YT. Multifactorial probit analysis of mortality in burned patients. *Ann Surg*. 1979;189(1):1-5.
45. Shirani KZ, Pruitt BA Jr, Mason AD Jr. The influence of inhalation injury and pneumonia on burn mortality. *Ann Surg*. 1987;205(1):82-87.
46. Ryan CM, Schoenfeld DA, Thorpe WP, et al. Objective estimates of the probability of death from burn injuries. *N Engl J Med*. 1998;338(6):362-366.
47. Jeschke MG, Mlcak RP, Finnerty CC, et al. Burn size determines the inflammatory and hypermetabolic response. *Crit Care*. 2007;11(4):R90.
48. Kraft R, Herndon DN, Al-Mousawi AM, et al. Burn size and survival probability in paediatric patients in modern burn care: a prospective observational cohort study. *Lancet*. 2012;379(9820):1013-1021.
49. Finnerty CC, Ju H, Spratt H, et al. Proteomics improves the prediction of burns mortality: results from regression spline modeling. *Clin Translat Sci*. 2012;5(3):243-249.
50. Shelhamer MC, Rowan MP, Cancio LC, et al. Elevations in inflammatory cytokines are associated with poor outcomes in mechanically ventilated burn patients. *J Trauma Acute Care Surg*. 2015;79(3):431-436.
51. Reper P, Heijmans W. High-frequency percussive ventilation and initial biomarker levels of lung injury in patients with minor burns after smoke inhalation injury. *Burns*. 2015;41(1):65-70.
52. Reference deleted at revises.

53. Davis CS, Janus SE, Mosier MJ, et al. Inhalation injury severity and systemic immune perturbations in burned adults. *Ann Surg*. 2013;257(6):1137-1146.
54. Maile R, Jones S, Pan Y, et al. Association between early airway damage-associated molecular patterns and subsequent bacterial infection in patients with inhalational and burn injury. *Am J Physiol Lung Cell Mol Physiol*. 2015;308(9):L855-L860.
55. Cancio LC, Salinas J, Kramer GC. Protocolized resuscitation of burn patients. *Crit Care Clin*. 2016;32(4):599-610.
56. Lawrence A, Faraklas I, Watkins H, et al. Colloid administration normalizes resuscitation ratio and ameliorates "fluid creep". *J Burn Care Res*. 2010;31(1):40-47.
57. Pham TN, Cancio LC, Gibran NS. American Burn Association practice guidelines burn shock resuscitation. *J Burn Care Res*. 2008;29(1):257-266.
58. Foldi V, Lantos J, Bogar L, et al. Effects of fluid resuscitation methods on the pro- and anti-inflammatory cytokines and expression of adhesion molecules after burn injury. *J Burn Care Res*. 2010;31(3):480-491.
59. Howell E, Sen S, Palmieri T, et al. Point-of-care B-type natriuretic peptide and neutrophil gelatinase-associated lipocalin measurements for acute resuscitation: a pilot study. *J Burn Care Res*. 2015;36(2):e26-e33.
60. Hong DY, Lee JH, Park SO, Baek KJ, Lee KR. Plasma neutrophil gelatinase-associated lipocalin as early biomarker for acute kidney injury in burn patients. *J Burn Care Res*. 2013;34(6):e326-e332.
61. Lee HE, Lee SH, Baek M, Choi H, Park K. Urinary measurement of neutrophil gelatinase associated lipocalin and kidney injury molecule-1 helps diagnose acute pyelonephritis in a preclinical model. *J Biomarkers*. 2013;2013:413853.
62. Finnerty CC, Jeschke MG, Branski LK, et al. Hypertrophic scarring: the greatest unmet challenge after burn injury. *Lancet*. 2016;388(10052):1427-1436.
63. Forsberg JA, Potter BK, Polfer EM, Safford SD, Elster EA. Do inflammatory markers portend heterotopic ossification and wound failure in combat wounds? *Clin Orthopaed Related Res*. 2014;472(9):2845-2854.
64. Hawksworth JS, Stojadinovic A, Gage FA, et al. Inflammatory biomarkers in combat wound healing. *Ann Surg*. 2009;250(6):1002-1007.
65. Simonetti O, Lucarini G, Cirioni O, et al. Delayed wound healing in aged skin rat models after thermal injury is associated with an increased MMP-9, K6 and CD44 expression. *Burns*. 2013;39(4):776-787.
66. Yin H, Li X, Hu S, et al. IL-33 accelerates cutaneous wound healing involved in upregulation of alternatively activated macrophages. *Mol Immunol*. 2013;56(4):347-353.
67. Murad A, Nath AK, Cha ST, et al. Leptin is an autocrine/paracrine regulator of wound healing. *FASEB J*. 2003;17(13):1895-1897.
68. Sander AL, Henrich D, Muth CM, et al. In vivo effect of hyperbaric oxygen on wound angiogenesis and epithelialization. *Wound Repair Regen*. 2009;17(2):179-184.

22 Hematology, Hemostasis, Thromboprophylaxis, and Transfusion Medicine in Burn Patients

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Introduction

Severe burn injury causes a myriad of hematologic perturbations. Burn excision as well as substantial in-hospital phlebotomy causes severe blood loss anemia and even hemorrhagic shock, requiring substantial transfusion. Large-scale fluid resuscitation and shock cause a significant coagulopathy. Surgical extirpation can similarly cause a significant dilutional coagulopathy requiring transfusion. Hematopoiesis, the generation of new blood cells, is directed away from red blood cell (RBC) production toward myeloid blood cell production by the hyperinflammatory cytokine cascade. The hyperinflammatory nature of burn injury further makes the patient hypercoagulable, generally requiring significant anticoagulation or thromboprophlyactic therapy. Providing total burn care requires knowledge of hematology, hemostasis, thromboprophylaxis, and transfusion medicine to overcome the substantial pathophysiology experienced by these patients.

Etiology of Anemia in Burn Patients

Anemia is the condition occurring when the RBC concentration, or hemoglobin (Hb) concentration, falls below normal laboratory limits for healthy adults. These normative values do not correlate with sufficient oxygen delivery. Weiskopf and Feiner classically demonstrated normal oxygen delivery despite dramatic acute anemias while examining Hb concentrations as low as 5 g/dL in euvolemic subjects.[1] Anemia is common in burn patients, especially in those with severe thermal injuries. Burn patients suffer from anemia due to acute surgical blood loss and the anemia of critical illness. This can occur in patients with as little as 10% total body surface area (TBSA) burned.[2] A mild reduction of RBCs mass is of little clinical significance[3]; when the concentration is significantly reduced, or total blood volume loss is beyond 30%, it becomes clinically relevant, leading to impaired end-organ perfusion and oxygenation.[4] The initial 2 weeks post-burn feature anemia mainly resulting from blood loss through the burn wound, dilution due to resuscitation, and surgical blood loss from repeated débridement to prepare the wound bed with well-vascularized tissue.[5] Subsequently, anemia is characterized as the anemia of critical illness and develops from inadequate nutrition,[6,7] stunted erythropoiesis,[8] or phlebotomy and dressing changes.[8] Specifically, bone marrow dysfunction leading to dampened erythropoiesis has been explored in autopsy studies and in the mouse model of burn injury in vitro.[8] In an autopsy study of patients who died from myocardial infarction, sepsis, or burns, the bone marrow of burn patients contained significantly fewer erythroblasts compared to the other groups.[9]

Acute blood loss results in at least 2% blood volume loss per percent body surface area excised; thus during major burn excisions, there is significant blood loss often requiring massive transfusions (MTs).[10] MT is defined as the transfusion of packed red blood cells (pRBCs) of 10 units or more within 24 hours of admission.[11] While acute surgical blood loss is obvious and prominent during the treatment phase, burn patients suffer a prolonged anemia of critical illness during their recoveries, which is insidious. The anemia of critical illness is the inability of RBC production to meet RBC demand and losses during critical illness.[12,13] More than 50% of transfusions during a burn patient's hospital course may be caused by the anemia of critical illness.[14] It has been equated to an acute form of the anemia of chronic disease[15–17] and anemia of inflammation in conjunction with nutritional deficiencies.[12] Acute blood loss anemia is controlled with surgical technique, while the anemia of critical illness can be restrained with reduced phlebotomy, decreased blood loss with dressing changes, improved nutrition, and resolving the critical illness by covering the patient with skin, thereby abating his disease. Prevention of anemia is accomplished through alteration of its sources, acute blood loss, and the anemia of critical illness, while the mainstay of treatment for both types of anemia is the transfusion of pRBCs.

Hemostasis in Burn Patients

Controlling blood loss and hemorrhage during burn care is important to prevent episodes of hemorrhagic shock and limit total transfusion need. While Barbosa and Rowel demonstrated that a 6-h RBC transfusion requirement is one of the mortality predictors in MT trauma patients, it is unclear

if these findings extend to controlled blood loss during a burn extirpation.[18] In these cases, a skilled anesthesiologist can match the transfusion rate and blood product mix to the bleeding rate, thus preventing hemorrhagic shock, maintaining euvolemia, and avoiding coagulopathy while the surgeon removes burned and diseased tissue and engrafts the patient.

As with burn-susceptible infections, preventing burn-derived anemia from developing is more optimal than treating the anemia or subsequent sequela. Several methods have been established to mitigate acute surgical blood loss, including epinephrine tumescence, thrombin-soaked dressings, and tourniquet use.[19] Additionally, excision with electrocautery at a fascial or subcutaneous level can limit blood loss significantly in large, full-thickness burns.[20] Regardless of excision methodology employed, many studies found the injection of dilute epinephrine into the subdermal space promoted vasoconstriction and reduced blood loss during surgical management of the wound.[21–24] In a pediatric trial, epinephrine tumescence alone decreased blood loss from 3.5% to 5% to 0.98% of total blood volume per percent of body excised and grafted.[24] Importantly sufficient time must be allotted for the epinephrine to take effect, with an ideal interval of 25 minutes.[25] Epinephrine tumescence has no significant hemodynamic consequences, nor does it alter wound healing.[26–30] A recent study confirmed that subcutaneous epinephrine injection had no adverse effect on perfusion, pain, or scar quality versus the saline-administered control group.[26] Of interest lately has been tumescent infiltration of lidocaine and epinephrine by clysis. Gumus showed that this technique resulted in more facile excision with diminished blood loss.[31] Similarly, clysis has been demonstrated to reduce the need for blood transfusions.[32] The use of thrombin-soaked pads for additional hemostasis support postoperatively has been studied in the context of epinephrine tumescence and provides supplementary hemostasis by reducing unnecessary ooze from the dressing site.[19,33–35] New silicone gel dressings also significantly reduced the amount of blood loss per percent excised and the amount of blood transfused.[36,37] We employ nonadherent dressings (Telfa) soaked with epinephrine intraoperatively. This facilitates hemostasis and does not restart the bleeding upon removal of the pads, as often occurs with epinephrine-soaked laparotomy pads that avulse the clots they helped induce on the wound surface when they are removed. Finally the use of an extremity tourniquet during excision and débridement can decrease acute surgical blood loss without compromising graft adherence.[19,38–41] Kragh et al. found tourniquet use efficacious in both adults[42] and children.[43] In combination, all three techniques (epinephrine tumescence, thrombin-soaked dressings, and tourniquet use) can reduce intraoperative transfusion from 3.3 to 0.1 units per operative case with 96% graft take and total units transfused from 15.7 to 7.9 units per patient.[34] However recent analysis indicates that utilizing the epinephrine-tumescent technique obviates the need for tourniquets.[44] Of note, administration of topical bovine thrombin must be avoided in burn patients with prior exposure because they have been shown to develop coagulation derangements and severe bleeding complications from an acquired factor V deficiency.[45] Mullins et al. reported safe and effective hemostasis through recombinant human thrombin applied as a spray.[46] Due to rampant overestimations of operative transfusion needs and the expenses incurred by blood typing and cross-matching,[47] a preoperative estimate of 1.78 units of pRBCs per 1000 cm^2 of burn wound excised best utilizes blood bank resources.[48]

Coagulopathy in Burn Patients

In addition to anemia, thermal injuries are associated with systemic coagulopathy, and the hemostatic changes seen in patients with severe burns appear similar to those in patients with other major traumas. The severity of the burn correlates with the extent of hemostatic changes[49,50]; typically only severely burned patients (≥30% TBSA) develop extensive coagulopathy.[51–53] However, no consensus currently exists on the definition of coagulopathy in burn injuries.[54] Despite being documented since the 1970s, the physiology of coagulopathy in burns is still ill-defined.[49] However, coagulopathy of thermal trauma does present with characteristics common to sepsis-induced coagulopathy: decreased levels of antithrombin and other native anticoagulants, elevated levels of activated factor VII, fibrinogen degradation products, plasminogen activator inhibitor-1 (PAI-1), and thrombin-antithrombin complex (TAT).[53] The three types often discussed in burn- and trauma-related literature are trauma-induced coagulopathy (TIC), disseminated intravascular coagulation (DIC), and acute traumatic coagulopathy (ATC).[54] Acute coagulopathy of trauma shock has largely been subsumed under TIC.[55] Caused by trauma, TIC is characterized by coagulation activation, hyperfibrinolysis, and consumption coagulation.[56] The main pathophysiology of TIC is DIC .[55,57,58] Specifically DIC presents as the fibrinolytic phenotype in the early, acute phase of trauma and burn[54,56,58,59], whereas the thrombolytic phenotype is associated with sepsis-induced DIC, which presents later in the clinical course of burn pathophysiology.[56] As defined by the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis, DIC is an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization originating from and causing damage to the microvasculature, potentially leading to multisystem organ dysfunction (MOD).[55,60] DIC is characterized not by the significant bleeding, transfusion requirements, and fourfold higher mortality associated with TIC,[54,61] but by excessive thrombosis, unchecked inflammation and MOD, insufficient anticoagulation mechanisms, and increased fibrinolysis.[58] Indeed, early coagulopathy is associated with increased incidence of ventilator-associated events among burn patients.[62] MTs are administered more frequently in patients with DIC.[63] ATC is associated with the depletion of fibrinogen, platelet dysfunction, and activation of protein C.[64] This particular coagulopathy is not secondary to other conditions, such as hypothermia, and markers for it can be discerned within 30 minutes of the inciting thermal event.[65,66] In the pediatric population, ATC is defined by an international normalized ratio (INR) of 1.3 or greater, and those who present with fibrinolytic shutdown are more likely to develop deep vein thrombosis (DVT), especially because prophylactic anticoagulant administration is not recommended in the pediatric population due to their lower rates of venous thromboembolism (VTE).[67] Coagulopathy seen in burns is mediated by

preexisting conditions (e.g., age and comorbidities) as well as environmental (e.g., ambient temperature) and therapeutic factors (e.g., pre-hospital fluid administration).[68]

As demonstrated in multiple studies, the timing and onset of coagulopathy correspond with the severity of the burn,[49,52,69,70], and TIC may present without initial hypercoagulopathy.[71] Few burn patients present with coagulopathy at admission, but a large number develop it within a day post-burn.[49] In fact, at admission, no statistically significant differences were observed between nonsurvivors and survivors in coagulation and fibrinolysis markers.[72] The inciting causes of coagulopathy in burned patients include tissue hypoperfusion from fluid resuscitation, systemic inflammatory response syndrome (SIRS), blood loss from surgical excision, hypothermia, endothelial damage, consumption and/or dilution of coagulation factors, and acidemia.[53] Tejiram et al. effectively reviewed the myriad of changes seen in the clotting dynamics of burn patients and related more subtle factor changes as possible markers of mortality than partial thrombin time (PTT) and INR, which were normal in their cohort.[73] Classically, hypothermia, acidosis, and coagulopathy are collectively known as the lethal triad,[71,74,75] corresponding to MTs and mortality in burn and trauma patients.

Prevention of hypothermia in the operative theater is completely within the purview of the operative team and the operating room in the same way that the temperature of a steak is completely within the purview of the chef and the oven. As a manifestation of the First Law of Thermodynamics, a patient cannot cool beyond the temperature of the operating room. The clinical practice guideline in many burn centers is to maintain the ambient temperature of the ICU and operating rooms at 86–104°F (30–40°C) as a component of standard of care in the treatment of burn patients.[76,77] Maintaining sufficient heat in the operating room to prevent hypothermia is essential. In patients undergoing surgery, inadvertent perioperative hypothermia resulted from 50% to 90% of the cases.[78] Singer et al. determined hypothermia to be associated with high mortality, although it was much more commonly found in patients with large burns.[76,77] In fact, it has been shown that hypothermia, the condition where the core temperature falls below 36°C (96.8°F),[79] is not associated with external factors at the time of the burn, but correlates to burn severity and patient physiological status.[80] Burn patients are most vulnerable during excisional surgery due to operative heat loss[81] concurrent with evaporative water loss[82] or massive fluid therapy.[53,77,83]

Acidosis is an ever-present threat for the recovering burn patient. Lactic acidosis from shock states occurs transiently during recovery and surgery and exacerbates bleeding, as does hypercarbia. Uremia causes an anion gap acidosis and reduces platelet aggregation, which can be reversed with desmopressin.[84] Hyperchloremia of normal saline administration is an effect of hemodilution or a decrease in renal excretion of H^+.[85] While administration of natural saline is associated with hyperchloremia-induced metabolic acidosis,[86] Ringer's lactate, the other crystalloid solution typically used, correlates with metabolic alkalosis.[87]

Diagnosis of coagulopathy depends on detection. The INR measured upon admission is the basis for the diagnosis of acute traumatic coagulopathy.[49,64] Initial Hb levels may mask bleeding, and repeated measurements are necessary to use Hb levels diagnostically as a marker for bleeding. Notably, low initial Hb is considered an indicator for hemorrhage-associated coagulopathy.[68] However, assessing specific coagulation markers has proved both time-consuming and expensive, and typical laboratory tests, such as PTT, are limited in diagnostic value.[52,53,88] The markers of the various coagulopathies seen in burns present similarly to the coagulopathy seen in patients with sepsis and severe trauma.[53,89,90] Among the coagulopathic changes are increased levels markers of thrombin activation, activated factor VII (FVIIa), thrombin-antithrombin complex (TAT) and inhibited fibrinolysis with increased levels of PAI-1, as well as decreased levels in proteins C and S, fibrinogen, and antithrombin.[53,90–93] In the first day post-burn, patients with severe burns show marked decreases in fibrinolysis[51,53,72] as well as platelet activity.[94] Lavrentieva et al. demonstrated that, in the early post-burn phase (day 3 to day 7 post-burn), survivors could be distinguished from nonsurvivors by the levels of natural coagulation inhibitors (i.e., proteins C and S and antithrombin), fibrinolytic factors (i.e., PAI-1 and tissue-plasminogen activator), and TAT, a marker of thrombin generation, but not at admission when both groups presented with statistically similar levels in all parameters.[72] While van Haren et al. also found that severely burned patients become hypercoagulable following admission despite pharmacologic thromboprophylaxis, they determined that thromboelastography (TEG) was a more reliable indicator of coagulopathy than were coagulation markers.[89] Interpretation of TEG data is reviewed in Fig. 22.1. Furthermore, TEG provides diagnostic answers in a much shorter time than standard laboratory testing, resulting in faster goal-directed therapies.[91,95] The majority of burn centers worldwide used standard coagulation tests,[96] but the move to using TEG is warranted. With the advent a portable fibrinogen analyzer, fibrinogen levels can be measured in mere minutes.[97] Low levels of fibrinogen have been shown to be predictors for MTs[98]; Hayakawa et al. demonstrated that fibrinogen reached critical diagnostic levels (150 mg/dL) sooner than other coagulation parameters,[63] making it a key factor in determining blood product needs as well as being a coagulation indicator. More recently, other studies showed higher levels of fibrinogen (211 mg/dL and 190 mg/dL) functioned as useful predictors of MT.[98,99]

Not only is there limited consensus on the diagnosis of the type of coagulation associated with burns, there is no agreement on the therapies used to respond to the condition when it presents.[96] It is accepted that the activation of fibrinolysis is inadequate to offset the excessive fibrinogen formation in the early post-burn phase in patients severely burned.[72] Hemostasis depends on fibrinogen for clot formation and platelet aggregation, and the depletion of fibrinogen correlates with poor outcomes.[100] While fibrinogen is the coagulation protein with the highest plasma concentration, plasma transfusions do not correct the fibrinogen depletion seen in TIC and ATC unless massive volumes are infused.[101] Current European Trauma Guidelines suggest the administration of fibrinogen concentrate or cryoprecipitate if a trauma patient presents with both significant bleeding and thromboelastometric signs of functional fibrinogen deficit or a fibrinogen concentration (FIB) of

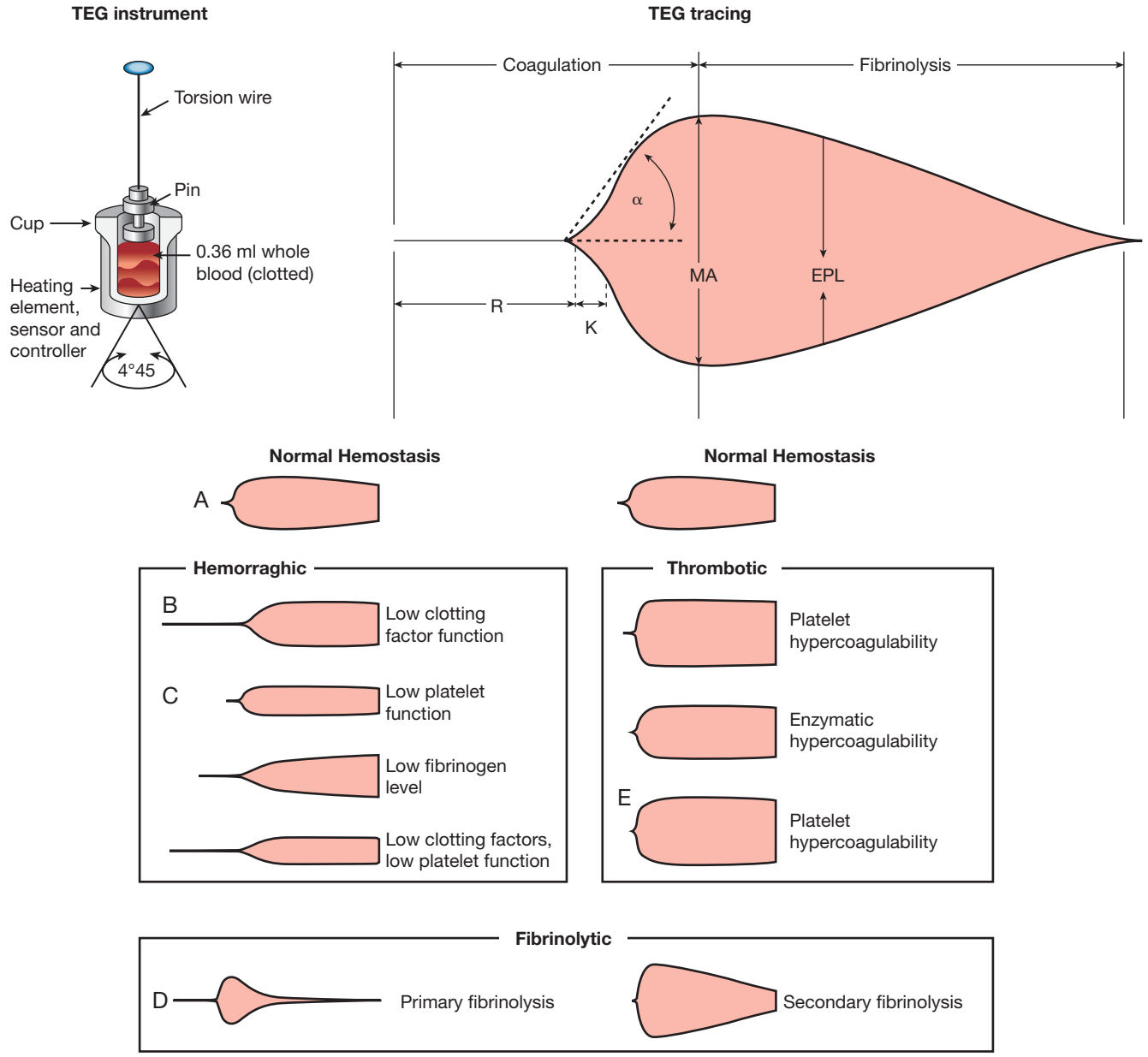

Fig. 22.1 Panel 1 depicts the thromboelastography (TEG) device, in which a cuvette of whole sample blood is incubated with a pin and torsion wire rotates within the sample. The tracing depicted in Panel 2 reflects the **force** required to **spin** the pin **over time** as the fibrin strands form a clot which resists pin movement. R (reaction time) in minutes reflects the latency time to initial fibrin formation. Elevations are typically treated with frozen fresh plasma (FFP) or reversal of anticoagulants, which delay initiation of clot formation. K (kinetics) is the time taken to achieve a clot strength of 20 mm. α is the angle between R and K and measures the speed of fibrin build up and cross-linking, which reflects the availability of fibrinogen; defects are typically treated with cryoprecipitate. TMA (time to maximum amplitude) is another measure of speed to fibrin build up. MA (maximum amplitude) represents the ultimate strength of the fibrin clot and overall stability and is a measure of platelet action and stabilization of the clot. Deficits in MA are typically treated with platelets or ddAVP to augment platelet aggregation. FPL, A30, or LY30 reflects the amplitude of the clot strength at 30 minutes as a measurement of fibrinolysis. Fibrinolytic patterns are treated with TXA typically. (A) Normal TEG tracing. (B) Low clotting factor availability causing a decreased α-angle. (C) various pathological hemorrhagic TEG tracings. (D) Fibrinolytic TEG tracings. (E) Various thrombotic TEG tracings. (From Mauffrey C, Cuellar DO, 3rd, Pieracci F, et al. Strategies for the management of haemorrhage following pelvic fractures and associated trauma-induced coagulopathy. *Bone Joint J.* 2014;96–B(9):1143–1154.[299])

less than 1.5–2 g/L.[68] Topical hemostatic agents such as thrombin spray rely on plasma FIB to effect hemostasis in operative wounds.

Limiting fibrinolysis is another important method to control blood loss during burn excisions. Tranexamic acid (TXA), a synthetic derivative of lysine, has found great utility in treating burn patients. In the landmark CRASH2 randomized controlled trial, Roberts et al. demonstrated a reduction of blood loss and mortality with TXA use in trauma patients.[102] Not only does TXA safely and significantly reduce the mortality rates of trauma patients with, or at risk of, substantial bleeding when administered early in the course of treatment,[103] but its de minimis side-effect profile in conjunction with its low cost and ease of use have

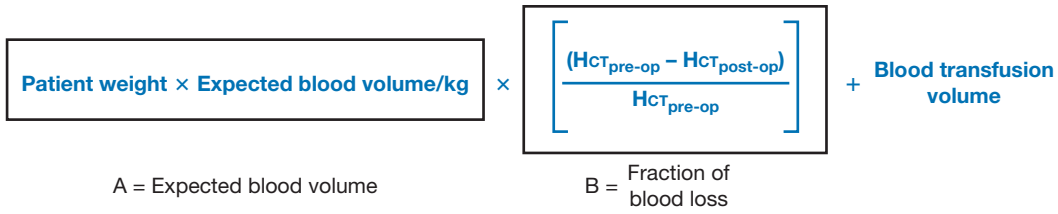

Fig. 22.2 An algebraic formula to estimate surgical blood loss. In the first group of terms, labeled A, the patient's weight is multiplied by the expected blood volume for age: adult men 75 cc/kg, adult women 65 cc/kg, infants 80 cc/kg, term infants 85 cc/kg, and premature neonates 95 cc/kg. The second portion of the equation utilizes preoperative and postoperative hemocrit (Hct) to derive the fraction of blood lost to account for the observed change in Hct. Finally, blood transfused is added in to account for intraoperative transfusion effects.

made it an integral component of resuscitation protocols worldwide.[104] However, the benefits of TXA are seen only when administered within 3 hours of injury; after that window, it has been shown to increase mortality.[65,105] Thus it is most efficacious to treat acute traumatic coagulopathy. Fibrinolysis is less likely to be fully activated the sooner patients receive TXA; fibrinolysis continues unceasingly once activated, and only restoration of endogenous antifibrinolytic elements can then abate the activity.[106] Some practitioners feel that the potential risk is too great for use in patients whose bleeding is not life threatening.[107] Although reports exist highlighting the prothrombotic effects resulting from each antifibrinolytic drug,[65] we advocate the use of TXA perioperatively for large burn excisions.

Transfusion of Blood Cells

Burn patients have many disparate indications for transfusion. In the setting of active operative hemorrhage, the rapid transfusion of pRBC, plasma, and other products is essential to prevent hemorrhagic shock. In the postoperative period, transfusion is necessary to treat blood loss anemia, coagulopathies, and consumptive thrombocytopenias. As a component of resuscitation, plasma transfusion is often required to treat coagulopathies resulting from consumption and under-production of factors, as well as for volume expansion, as discussed in Chapter 8 on the pathophysiology of burn shock and burn edema and in Chapter 9 on fluid resuscitation and early management. Understanding the vastly disparate indications for transfusion in burn patients allows clarity in the urgency and aggressiveness of transfusion used in these patients with ever-changing status.

The first major indication for transfusion is intraoperative blood loss during burn wound excision. The anesthesia team must monitor overall preload while estimating blood loss to prevent hypovolemia and hemorrhagic shock. Surgical control of hemorrhage is critical, but large blood loss is expected, especially in the setting of large burns. Surgical blood loss has been estimated and measured in a variety of ways,[33,108–112] but reports based on surgical and anesthesia team estimates[113] are simple and reliable. Following serial hematocrit value along with hemodynamic markers is a standard method of monitoring blood loss and transfusion success. Various formulae have been developed to calculate the estimated blood loss. Total blood volume is estimated using the patient's weight, preoperative and postoperative Hb, and presumed normal adult Hb of 70 cc/kg. Generally accepted and employed constants are adult men 75 cc/kg, adult women 65 cc/kg, infants 80 cc/kg, term infants 85 cc/kg, and premature neonates 95 cc/kg. Gross initially described the mathematics of the formula in 1983[114]; we have derived an equation estimating allowable operative blood loss with which we estimate blood loss for all our operations.[115] Fig. 22.2 reflects the formula we utilize, and, although patient conditions, such as venous capacitance and changes in vascular tone, can significantly alter blood volume of distribution, this formula has proved the best estimator of blood loss in our experience.

Due to blood type and cross-match expenses and overestimation of operative transfusion needs[47] a preoperative estimate of 1.78 units of pRBCs per 1000 cm^2 of burn wound excised best utilizes blood bank resources.[48] However, even since publication of the prior edition of this book, studies show 25% of patients received cross-match orders exceeding national guidelines, with surgeons being most responsible for this overestimation.[116] Interestingly, change in hematocrit, not Hb, is considered the most reliable indicator for continuing blood loss,[117] and, at admission, is the best predictor of 24-hour blood product requirements,[118] as well as being associated with signs of shock and hemorrhage in trauma patients, both adult[119] and pediatric.[120] Additionally multiple studies have found massive blood transfusion in trauma, surgery, and critical care to be a predictor of SIRS, multiple organ failure, and increased infection and mortality,[74] although it is unclear if the need for significant transfusion is a marker for disease severity rather than the transfusion itself being the etiologic cause.

In the setting of active operative hemorrhage, transfusion rates should match the rate of blood loss. Estimation of ongoing rates of bleeding and matching transfusion rates requires careful coordination between the anesthesia and operative teams. MT protocols have been demonstrably life-saving in these cases.[121] In the setting of operative hemorrhage, the standard transfusion ratio is 1 pRBC to 1 flash frozen plasma (FFP).[121] Electrolytes must be monitored to prevent hypocalcemia instigated by the citrate anticoagulant in the blood products. As was demonstrated in the PROPPR study, major trauma centers were unable to deliver adequate amounts of thawed plasma for MT sufficiently quickly, so a burn team anticipating significant blood loss intraoperatively is well advised to order appropriate amounts of blood products prior to initiating the surgery.[122] With modern rapid infusers, such as the Belmont, capable of transfusing warmed, mixed blood products at rates of 500 cc/min, there is little reason for insufficient transfusion rates during a burn extirpation.

In the ICU, blood transfusions are typically unnecessary to treat or prevent hemorrhagic shock; rather, they are warranted for less emergent indications, such as blood loss anemia, coagulopathy, or volume expansion. Traditionally a defined Hb trigger of 10g/dL or hematocrit of 30%, the "10-and-30" rule, has guided transfusion practices.[123] These triggers continue in many centers worldwide.[123] However large-scale works in critical care literature[124] and smaller, retrospective reviews of adult[125] and pediatric[126] burn patients have established the benefits of a lower, more restrictive transfusion trigger, indicating that some patients had been receiving blood to no benefit.[123] The Society of Critical Care Medicine addressed transfusions in the intensive care setting. For critically ill patients, a restrictive strategy was found as efficacious as the conventional liberal one, so in patients with evidence of hemorrhagic shock, hemodynamic instability, or acutely bleeding, an Hb trigger of less than 7 g/dL indicates for transfusion, and this should be given as single units in the absence of acute bleeding.[127,128] Recent research supports the theory that pRBC transfusions should not rely on the use of standardized triggers, but rather be tailored to the burn patient's blood volume status, acuity of blood loss, and perfusion requirements.[2]

Transfusion needs increase with burn size,[5,47,129,130] as do complications. Each 1% increase in TBSA of burn has a corresponding 6% increase in mortality risk.[131] In a large study of transfusion trends in burn patients, those with 20% or greater TBSA required 13.7 ± 1.1 units, whereas those with 50% or greater TBSA required more than 30 units of pRBCs.[129] Burn patients often receive multiple transfusions; in one study, more than half the transfusions resulted from anemia of critical illness (nonsurgical).[5] While pRBC transfusion rapidly and reliably corrects anemia, it is associated with many of the consequences of bloodborne transmission, including hepatitis B, hepatitis C, and HIV. While the infectious transmission rate has significantly decreased with improved screening methods,[132,133] it is markedly higher in low- and middle-income countries than in high-income countries like the United States (0.1% and 0.003%, respectively).[134] More importantly, pRBC transfusion is associated with immunomodulation, including increased infectious morbidity,[135] with a 13% increase in risk of developing an infection per unit of blood transfused.[129] Muszynski et al. nicely reviewed the extensive hyperinflammatory and severe immunosuppressive effects of blood transfusions and related these data to critical care outcomes.[136]

Other significant consequences include transfusion-related acute lung injury (TRALI), which is difficult to diagnose in burn patients because simultaneous lung injury from resuscitation or inhalation injury may contribute to TRALI diagnostic criteria,[137] and ABO incompatibility, which can be rapidly fatal.[138] Implementation of restrictive-transfusion strategies in which pRBCs are transfused only for hemodynamic instability or at lower Hb concentrations has reduced overall transfusion and infection rates, benefitting both cost and survival.[68,125,126] FFP transfusion is also associated with TRALI[139] in burn patients, and early transfusion of FFP correlates with increased incidence of other deleterious effects post-burn.[140] However by not administering plasma from women with a history of pregnancy, the risk of TRALI from FFP is significantly mitigated,[141] and using pathogen-inactivated plasma reduces the risk of transmitting infectious diseases.[68] The indicators for increased transfusions of FFP and pRBC were high TBSA and use of argatroban anticoagulation.[142]

Except in the setting where MTs are indicated, greater ratios of FFP and platelets to pRBCs correlate to longer ICU stays and higher mortality rates.[143] When high ratios of FFP to pRBC are unable to be transfused, it has been demonstrated that resuscitating patients with a minimum of 1 L crystalloid per unit pRBC leads to improved mortality rates.[144] However, a recent study showed that TBSA burn and patient age independently correlated to mortality, not RBC or plasma transfusions.[142] Blood product resuscitation was not hemostatic, and coagulopathy and thrombocytopenia combined may contribute to intraoperative hemorrhage, which blood product transfusions would be inadequate to correct.[145] Brakenridge and coworkers showed that, despite prior reports of associations between FFP and large-volume crystalloid transfusions with MOD, it was the MT volumes of pRBC that correspond to MOD, not blood products.[146] Blood component ratios failed to predict inflammatory complications, whereas injury severity, sex, and total pRBC volume did.[147] Additionally transfusion of stored pRBC correlates with increased complications due to microparticles released from RBCs able to induce cellular dysfunction.[148] The poor quality of stored erythrocytes has been documented with dynamic microscopy.[149] Furthermore, recent data would suggest different protocols for transfusion in the operating room (acute blood loss) versus in the setting of critical illness (bedside).[150] A series of studies examining different ratios of FFP to pRBC transfusions have yet to demonstrate any difference in transfusion volume for burned pediatric patients.[10,151] Last, it has been demonstrated that transfusion protocols for adults are not efficacious in children;[152] a new score should be developed for transfusions in the burned pediatric population.

Recently, platelet-rich plasma (PRP), in which the platelet concentration is above baseline in blood plasma, has come under consideration for use in transfusing burn patients because its hemostatic antimicrobial effects have shown promise in wound healing in animal studies.[153] The concentration of growth factors and number of platelets dictate the clinical efficacy of PRP.[154] It is not transfusions of pRBCs but rather of platelets that have recently been correlated to nosocomial infections in the critically ill.[155] Platelet transfusion is not without complications because platelets are stored at room temperature, thereby facilitating higher rates of bacterial contamination than for other blood products. One in 1000–3000 platelet units may be bacterially contaminated;[156] one-sixth of these episodes result in a septic event.[157] In a study of blood bank utilization by a burn unit, 15% of all admitted patients received platelets with either pRBCs or FFP.[47,156] Given that cryopreserved platelets demonstrate superior hemostatic activity over liquid platelets, studying the efficacy of storing platelets at cold temperatures for burn units is warranted.[158,159] Last, immediate administration of pRBCs, plasma, and platelets upon admission has been shown to benefit patient outcome.[121]

Commonly coincident with sepsis,[160] thrombocytopenia requiring platelet transfusion is rare in burn patients. Often platelet counts and function are stable unless there is an infectious or septic event. In coagulopathic patients

with hemodynamically significant oozing from wound and donor sites, the administration of platelets and recombinant factor VIIa has been shown to improve hemostasis.[161,162] Of interest, recombinant factor VIIa seems most efficacious at lower temperatures.[163] Prothrombin complex concentrate (PCC) is gaining utility in treating coagulopathies derived from medications such as warfarin or argatroban and now has an expanding role in treating trauma and perioperative coagulopathies.[164] PCC is also gaining use as an adjunct or replacement for FFP to reverse factor-deficient coagulopathies and expedite operative intervention.[165,166]

Venothromboembolic Prophylaxis

Once burn patients recover from TIC they develop an elevated risk of venous thrombosis and thromboembolism. A recent study indicated that platelet-derived microparticles (PMPs) are responsible for the hypercoagulability seen immediately post-burn, particularly the decline in platelets, and that an ADP-induced platelet activation was crucial to the enhanced clotting seen a week post-burn.[94] Additionally, Levin et al. showed that thermal trauma incites an increase in the number of erythrocyte-derived microvesicles. These, in turn, increase the procoagulant activity while reducing the antithrombin and fibrinolytic activity of erythrocytes, thereby contributing to post-burn hypercoagulability.[167] Furthermore, the typically defined criteria for hypercoagulability described in Virchow's triad exist in all major burn patients: venous stasis from reduced activity such as bed-rest, endothelial activation or injury from shock state and inflammation, and hypercoagulability from acute-phase reactants.[168,169] Meizoso recently characterized the detailed pathophysiology of hypercoagulability in burn patients, concluding that larger-scale studies are needed to protocolize safe and effective thromboprophylaxis.[170] A typical burn ICU patient will be high or highest risk based on the American College of Chest Physician guidelines and Caprini score, indicating both mechanical and chemical prophylaxis.[168] In a 2005 survey of 84 U.S. burn centers, 76.1% routinely provided VTE prophylaxis, 31 utilizing subcutaneous unfractionated heparin (UFH), 16 low-molecular-weight heparin (LMWH), and 1 a heparin infusion.[171] In a 2013 review of their institution's patients in a single year, Mullins et al. reported an incidence of 113 DVTs in 86 patients for an incidence of 5.92%.[172]

The modalities that underlie VTE prophylaxis are mechanical and pharmacological prophylaxis. Mechanical treatments, such as intermittent pneumatic compression, aim to prevent venous pooling and mechanically pump blood from the extremities. These devices also stimulate fibrinolytic pathways, which further decreases the risk of venous thrombosis.[173,174] Chemical prophylaxis, such as heparin, is intended to reduce thrombosis by interfering with the coagulation cascade. Prophylaxis is often complicated in the burn population. For instance, mechanical prophylaxis is often impractical or impossible due to donor sites or wounds on the legs. Pharmacoprophylaxis agents can have inconsistent effects due to altered pharmacokinetics and pharmacodynamics leading to either venous thrombosis or hemorrhage.

Pharmacologic anticoagulants fall under four major classes: antithrombin-III (AT-III) activators, such as UFH; factor X inhibitors, such as LMWHs; direct thrombin inhibitors (DTIs), such as argatroban; and vitamin K antagonists, such as warfarin. The ideal phamacoprophylactic agent for a burn patient has a short half-life allowing dose titration and operative interventions, the ability to monitor resulting effects with laboratory values, an available reversal agent, and limited nursing workload. Warfarin is not used for prophylaxis in hospitalized burn patients due to its long half-life, which requires days to take effect and reestablish normal coagulation, all of which complicates operative management.[175] DTIs carry a high risk of bleeding and are irreversible so typically are employed only in the rare setting of antibody-confirmed heparin-induced thrombocytopenia (HIT) when treating burn patients.[176] Most VTE prophylaxis and treatment in burn patients are carried out using UFH or LMWH.

UFH exerts the principal part of its action by binding to and activating AT-III, the most abundant anticoagulant in the plasma. AT-III, in turn, breaks down activated thrombin, thereby terminating the propagation of coagulation. A minor portion of AT-III's action is attributable to inactivating factor X, the central factor joining the intrinsic and extrinsic coagulation cascades. Anticoagulant activity can be monitored, with a PTT targeting time of 30–41 seconds for prophylaxis and 60–80 seconds for therapeutic anticoagulation.[53] UFH can be administered either subcutaneously or via a continuous intravenous infusion. Subcutaneous dosing of 5000 units every 8 hours is considered an effective prophylactic dose; however in burn patients with unpredictable subcutaneous absorption and variable creatinine clearances due to hypermetabolism, this route is far less predictable. In our critical care population, we prefer a low-dose UFH infusion targeting a PTT of 30–41 seconds. With this protocol, we are able to provide a verifiable prophylactic effect regardless of the physiological state of the patient, although this comes at the cost of greater nursing utilization. UFH also has the benefit of a short half-life, and, in the setting of hemorrhage, it is reversible with protamine. There is a risk of development of HIT with this medication, and platelet levels must be monitored. Should thrombocytopenia develop in a burn patient, all heparin administration should be held until antibody titers can be returned. Because there are a myriad of causes of thrombocytopenia in burn patients, conversion to a secondary agent, such as a DTI, ought to be considered carefully on a case-by-case basis given the increased risk of bleeding associated with these medications and their lack of reversal agents.[177]

LMWH exerts its principal effect by inactivating factor X. Anticoagulant activity can be monitored with an anti-factor Xa level target of 0.2–0.5 IU/mL for prophylaxis and 0.5–1.2 IU/mL for therapeutic anticoagulation. In a review of practice at a large academic medical center, levels were determined to be insufficiently monitored and frequently outside the intended range in patients weighing less than 45 kg, more than 150 kg, or with impaired renal function.[178] These medications are delivered by subcutaneous injection and, as such, carry pharmacodynamic concerns regarding inconsistent absorption. There are also oral factor Xa inhibitors; however, there is not currently sufficient data nor experience to advocate their prophylactic

use in the acute burn patient for VTE prophylaxis. The half-lives of these agents are longer than UFH, and they only require dosing every 12–24 hours, which reduces nursing workload but increases the duration of bleeding, should it occur. In particular, Fondaparinux has a 17- to 21-hour half-life and thus is particularly prone to cause bleeding in our experience with burn patients; the use of fondaparinux is ill-advised. When these medications are chosen for burn patients, factor Xa levels should be monitored due to unpredictable subcutaneous absorption and large changes in creatinine clearance from hypermetabolism or renal impairment, although these pharmacologic issues are most often studied related to antibiotic dosing.[179] There are currently no reversal agents for this class, although scant data suggest that PCC may limit bleeding.[180]

There are circumstances in which VTE prophylaxis may need to be held in a major burn patient, such as bleeding. In these instances, an inferior vena cava (IVC) filter should be considered to reduce the risk of fatal pulmonary embolism. Furthermore, several centers routinely monitor patients for DVT formation with a weekly Doppler exam.

Hematopoiesis

Given the myriad of risks incurred to glean the benefits of transfusion, it is preferable for patients to generate their own replacement blood. Hematopoiesis is the production of the more than 10 distinct mature peripheral blood cell types.[181] Well-regulated hematopoietic differentiation is vital to generate all blood cells necessary for defense against invasive pathogens, gas exchange, and wound healing.[182] This process begins in the yolk sac, continues in the placenta and the aorta-gonad-mesonephros region, progresses to the fetal liver until finally occurring throughout postnatal life in the bone marrow.[183,184] Table 22.1 details the roles of growth factors and cytokines in directing hematopoiesis. Unfortunately, production is often insufficient to meet a burn patient's RBC requirements in the setting of large excisions and grafting procedures combined with critical care. This stems from the large volume of blood loss seen in burn surgeries as well as the fact that thermal trauma directs hematopoiesis away from erythropoiesis and toward immune cell production.

Two pathways exist for hematopoiesis: myeloid and lymphoid. The myeloid lineage ultimately produces RBCs and the cells comprising the innate immune system (e.g., platelets,[185] macrophages, neutrophils, eosinophils, and basophils). The lymphoid lineage forms the cornerstone of the adaptive immune system by generating B and T cells. Dendritic cells (DCs) and natural killer (NK) cells develop from either lineage. While only half the bone marrow is hematopoietically active,[186] an estimated 200 billion erythrocytes (0.5–2% of total RBCs),[187,188] 100 billion leukocytes, and 100 billion platelets (~7% of total platelets) are nonetheless produced daily in a healthy adult.

Accounting for one in every 10^5 nucleated cells in the bone marrow of a healthy adult, hematopoietic stem cells (HSCs) are the fountainhead of the hematopoietic hierarchy. Significantly they are the only cells in this system able to be both self-renewing and multipotent (able to differentiate into all potential blood cells).[181,189–192] The two variants of HSCs, long-term (LT) and short-term (ST), are distinguishable by more than their divergent self-renewal and differentiation capacities.[193–195] Aptly named, LT-HSCs remain permanently self-renewing cells with minimal response to physiologic stress and exhibit a total dearth of lineage-specific surface markers.[182] ST-HSCs derive from LT-HSCs and affect their production and differentiation depending on the existing pathologic state in their niches. ST-HSCs give rise to multipotent progenitor cells (MPPs),[196] which lack self-renewal potential but remain able to differentiate

Table 22.1 The Roles of Growth Factors and Cytokines in Hematopoiesis

Growth Factor or Cytokine	Role in Hematopoiesis
Stem cell factor	Essential for hematopoietic stem cell proliferation and differentiation Activates the c-*kit* receptor
Flt-3 ligand	Enhances multipotent progenitor, early lymphoid, myeloid, natural killer, and dendritic cell proliferation Activates the Flt-3/flk-2/CD135 receptor
IL-3	Plays a role in hematopoietic stem cell, myeloid, and erythroid cell line expansion
IL-6	Increased production following burn injury and infection Essential for expansion of hematopoietic stem and progenitor cells
G-CSF	Stimulates granulocyte proliferation in the bone marrow and augments immune activity of cells in blood Increased immediately following burn injury and in response to infection RhG-CSF use is not indicated for use in burn patients
CSF-1 or M-CSF	Essential for monocyte and macrophage differentiation Increases the survival of monocytes and macrophages
GM-CSF	Regulates the proliferation and differentiation of hematopoietic progenitors Enhances antigen presentation by DCs and macrophages Prophylactic administration accelerates bacterial clearance and killing
IL-7	Necessary for both engagement into lymphoid lineage and maintenance and expansion of lymphoid cells
Erythropoietin	Stimulates erythroid proliferation and prevents apoptosis to increase erythrocyte production May have a role in tissue protection via a related receptor rhEPO has not been shown to benefit burn patients
Thrombopoietin	Enhances megakaryocyte proliferation and reduces apoptosis to increase platelet production May increase following burn injury and contribute to thrombocytosis Evolving role in stem and progenitor cell proliferation

G-CSF, Granulocyte colony-stimulating factor; *GM-CSF*, granulocyte-monocyte colony-stimulating factor; *IL*, interleukin.

into every hematopoietic lineage.[183,197,198] The progression of hematopoiesis, from stem cells to progenitor groups to terminally differentiated cells (Fig. 22.3), allows for the rapid amplification of cell production by the upstream proliferation of stem cells.[199] The hematopoietic hierarchy is not without controversy; other suggested hematopoietic progressions[200,201] differ in the branch points at which certain progenitor populations lose lineage potential[202] or advocate that select cell groups have the potential to dedifferentiate and enter a different lineage.[203] MicroRNAs (miRNAs), growth factors, and cytokines present in the bone marrow influence the commitment patterns of these progenitor cells, yielding mature, fully differentiated bone marrow cells that later populate the bloodstream.

Up-regulation of fetal liver kinase-2 (Flk2) is a shared feature of all lineages of HSC differentiation[203] as is the epigenetic regulation exerted by microRNAs on every stage of hematopoiesis.[204] The expression of a limited set of transcription factors, controlled by growth factors, cytokines, and miRNAs present in the bone marrow milieu, control lineage commitment, cell fate,[205–207] and, ultimately, the composition of cells in the bloodstream. As patients age, there is an HSC shift toward myeloid potential.[208]

Bone marrow hematopoiesis demonstrated an overall increase in the HSC population (identified as LSKs [Lineage^{negative}, Sca-1^{+} cKit^{+}] in mice) as early as 48 hours following burn injury,[209] and the expansion of LSKs persisted for at least 21 days post-burn.[210] Despite their multilineage potential (Fig. 22.3), LSKs do not differentiate evenly across all lineages. Only ST-HSCs and MPPs increase, with no significant change in LT-HSCs.[211] In the progenitor compartment, there is a significant increase in granulocyte-monocyte progenitors (GMPs) with a concomitant decrease in megakaryocyte-erythroid progenitor (MEP) production. Given the hierarchical nature of hematopoiesis, changes in ST-HSC and MPP production, and the lineage shift toward greater GMP and lesser MEP production may herald the overall problems present after burn injury: erythropoietic production (anemia) and myeloid function (immune dysfunction).[209,210] In a recent work, myelo-erythroid commitment following thermal insult was shown to be under β-adrenergic control via MafB regulation, indicating that burn injury perturbs the hematopoietic paradigm.[212] For more details please refer to Chapter 23 on the significance of the hormonal, adrenal, and sympathetic responses to burn injury. Further work on HSCs and progenitor cell responses may provide avenues for early therapeutic intervention, which may ameliorate the negative hematopoietic consequences of burn injury.

HSCs have considerable potential in treating blood disorders.[213–215] The utilization of these cells as a possible therapy for the anemia or immune dysfunction present in severely burned patients is currently not in progress. Rea and colleagues assayed the cells present in the healing burn wound, finding that hematopoietic cells were merely transient and predominantly present only in the acute inflammatory phase, with a small number persisting in the healing dermis.[216] Ascertaining the long-term hematopoietic response to various degrees of burn wounds will be crucial in developing HSC-based therapies for burn injuries.

Due to burn-associated anemia, erythropoietin (EPO) levels should be increased during treatment and recovery from the burn injury. However, contrary to the expected EPO response to anemia, there is limited increase in EPO following burn. Earlier studies had small sample sizes, used unreliable urine bioassays, and could not overwhelmingly support an appropriate EPO response, leading to contradictory results.[217,218] Later comparison of serum bioassays and radioimmunoassays showed no correlation between the two methods, and their results suggested significant differences between the sensitivity of these tests.[219,220] More recent larger studies using serum radioimmunoassays demonstrated an increase in EPO in response to decreased Hb concentrations but inconsistent erythropoietic response to this EPO increase.[130,221]

While only erythroid-committed cells in the bone marrow possess the EPO receptor, a related EPO receptor and response to EPO have been identified in nonhematopoietic tissues, including neurons, glial cells, retina, heart, skeletal muscle, kidney, ovary, uterus, testis, and endothelial cells.[222–225] Consequently the ability of EPO to reduce apoptosis and prevent damage to these tissues has been explored. RhEPO in particular can reduce apoptosis after cerebral ischemia[226]; protect the myocardium and promote remodeling following myocardial ischemia, allowing for restoration of cardiac function;[227,228] and protect against renal injury from ischemia, improving renal function.[229] Despite these findings and the expected erythropoietic response to rhEPO, its use in burn patients has not been substantiated.

Recombinant human erythropoietin (rhEPO) helps augment erythropoiesis in patients with chronic anemias (e.g., end-stage renal disease and HIV with antiretroviral use), decreasing transfusion rates and improving quality of life. To decrease transfusion rates and correct the anemia of critical illness, multiple trials have explored rhEPO use in the critically ill, including burn patients. Unfortunately both large clinical trials and meta-analyses of critically ill medical, surgical, and trauma patients show no significant reduction in transfusion rates with rhEPO use.[230,231] JM Still and others performed a study of rhEPO in burn patients resulting in no significant increase in hematocrit percentage or decrease in transfusion rates.[232–234] Critically ill patients may possess a resistance to EPO,[235] which may be a function of antierythropoietin antibodies[236] or a relative reduction in erythropoietic response due to less EPO-responsive erythroid precursors after burn-induced hematopoietic hierarchy shift.[237] As such, rhEPO is not indicated for use in burn patients. However a recent study showed that rhEPO significantly reduced the markers of multisystem organ failure and, in the lung, specifically reduced apoptosis and histological signs of tissue injury in mice with second-degree scald burns.[238] While the use of rhEPO has been shown to increase the rate of reepithelialization in scald injury and decrease time to close the wound when injected directly into the injury site,[239] we still cannot recommend the use of rhEPO in burn patients to decrease transfusion rates. These new data highlight the potential use for other burn-induced complications beyond the purview of this chapter.

MYELOID GROWTH FACTORS

Granulocyte Colony-Stimulating Factor

Granulocyte colony-stimulating factor (G-CSF) is the primary growth factor responsible for the proliferation and

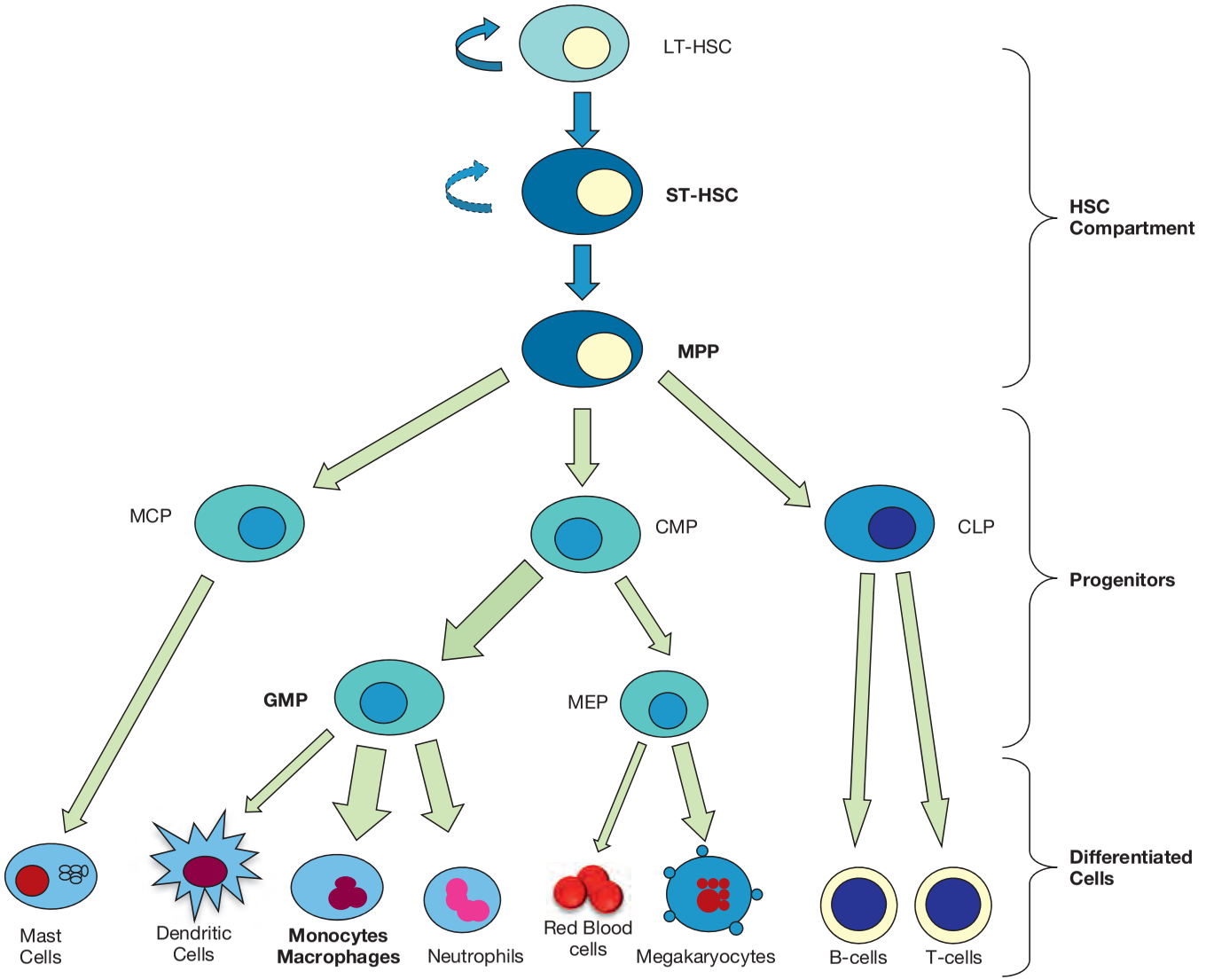

Fig. 22.3 A Hierarchical Model of Hematopoiesis The model here shows the three compartments of hematopoietic cells: stem cells, lineage-commited progenitors, and terminally differentiated cells. The first step in lineage commitment occurs at the branch point from multipotent progenitors (MPPs) to myeloid (CMP, common myeloid progenitor) or lymphoid lineages (CLP, common lymphoid progenitor) or MCP, mast cell progenitors). CLPs differentiate into T and B cells. The CMP population can branch in to GMPs (granulocyte-monocyte progenitors) or MEPs (megakaryocyte-erythroid progenitors), which then lead to their respective terminally differentiated populations.

differentiation of bone marrow granulocyte progenitors into mature granulocytes.[240,241] G-CSF is produced by monocytes, fibroblasts, and endothelial cells stimulated to produce G-CSF in response to inflammatory cytokines (tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6], IL-1).[222] Although it stimulates the production of neutrophils in the bone marrow, in the periphery G-CSF augments the bactericidal activity of neutrophils by priming the oxidative burst, increases neutrophil half-life by preventing apoptosis, and down-regulates the overall inflammatory response by decreasing the cytokine production of monocytes and macrophages.[242] In various animal models of burn and burn sepsis, the benefits of G-CSF were shown to be the killing of translocated bacteria,[243] regulating the pro-inflammatory response to injury,[244] enhancing neutrophil chemotaxis,[245] and improving survival in combination with antibiotic therapy.[246,247]

At baseline, there are very low levels of G-CSF present in the blood. However following an inflammatory or infectious process, G-CSF levels dramatically increase. Following a burn injury, G-CSF levels in the blood are initially increased and then gradually decline to baseline 3–4 weeks following injury.[248–250] The initial increase in G-CSF may prime the neutrophilic component of the immune response for future bacterial insult. However, the immune dysfunction seen following burn injury or burn sepsis may be related to hyporesponsiveness of bone marrow progenitors and peripheral neutrophils to G-CSF.[251] Recent studies suggest that the increase in serum G-CSF post-burn corresponds to an increase in the resistance to infection, activation of innate immune responses, and prioritization of bone marrow responses, indicating that it plays a central role for burn patient survival, especially in the setting of infection.[252]

Administration of recombinant human G-CSF (rhG-CSF) to burn septic animals prior to the initiation of septic insult has been shown to improve the survival rate of burn septic mice.[245,246,253] However administration of G-CSF 24 hours after the onset of septic insult had little effect on survival.[254,255] Despite the potential benefit of exogenous G-CSF administration on the inflammatory and infectious response during burn injury, the use of rhG-CSF (Filgrastim)[256] is not indicated in the treatment of burn patients.

CSF-1

CSF-1 (M-CSF) is a preeminent growth factor for the differentiation, proliferation, and survival of monocytes and macrophages.[257] It also stimulates chemotaxis, cytokine, and superoxide production in macrophages.[258,259] Hume et al. first demonstrated that administration of CSF-1 to mice resulted in monocytosis and an increase in peritoneal and tissue macrophages.[260] In response to burn injury, CSF-1-responsive GM-CFU are increased in the bone marrow and this results in enhanced monocytopoiesis.[261] The underpinning of this monocytopoiesis post-burn arises from increased expression of CSF-1 receptors in ERMP-20$^+$ bone marrow compartment, which comprises monoblasts and promonocytes,[261] which begins to be initiated much earlier at progenitor level in GMPs[209] and CMPs.[210] Additionally burn injury and sepsis also alter the inflammatory cytokine phenotype of CFU-GM-derived macrophages in that they predominately result in hyporesponsive macrophages.[262,263] Similar hyporesponsiveness in monocytes has been demonstrated in trauma patients.[264] These findings provide a plausible mechanism and a role for CSF-1 and its cognate receptor interactions in monocyte/macrophage biology following burn injury.

GM-CSF

Granulocyte-monocyte colony-stimulating factor (GM-CSF) regulates proliferation and differentiation of hematopoietic progenitor cells, as well as modulating the function of mature leukocytes.[265] GM-CSF enhances the antigen-presenting capacity of macrophages and DCs, increases complement-mediated phagocytosis, and augments bacterial killing by both innate immune cells[266,267] and chemotaxis of leukocytes.[268,269] GM-CSF is produced by a variety of cells, including macrophages, B lymphocytes, pulmonary epithelial cells, neutrophils, and stromal cells.[270,271] In response to burn injury, bone marrow GM progenitors respond by producing more GM-CFU colonies .[261] Administration of GM-CSF prior to burn injury and *E. coli* sepsis enhanced bacterial clearance and survival of experimental animals.[272] Similarly, GM-CSF improved the survival of neonatal rats when administered prophylactically prior to *S. aureus* infection.[273] However, GM-CSF administration after the onset of infection did not provide a survival benefit.[274] While the inactivation of GM-CSF or GM-CSF receptor genes in mice did not alter the number of granulocytes and monocytes, these animals exhibited significant alveolar macrophage dysfunction. Furthermore GM-CSF-deficient mice are very susceptible to pulmonary group B streptococcal infection.[271] Cioffi et al. studied the effects of GM-CSF in burned adults. They found a 50% increase in mean leukocyte counts after the first week post-burn in treated patients. Application of GM-CSF did increase myeloperoxidase activity (cytosolic oxidative function) 1 week post-burn, but these levels returned to unburned control levels during weeks 2 and 3 of treatment, while remaining elevated in the untreated patients. Extracellular oxidative function, measured by superoxide production, was initially depressed in both burned groups compared to nonburned controls, although GM-CSF-treated patients demonstrated a return to nonburned control levels after week 1, while these levels remained below control levels in the untreated burn patients.[275] In a multicenter clinical trial, administration of rhGM-CSF in hydrogel to deep second-degree burn wounds has been shown to be both safe and to accelerate wound healing.[276,277] A subsequent study found topical application of GM-CSF reduced healing time of partial-thickness burn wounds by 5.1 days compared to standard treatment with no significant increase in adverse effects. The same study examined two other growth factors, fibroblast and epidermal, and found a decrease in healing time by 5.02 and 3.12 days, respectively, as well as improvement in scar color, height, pliability, and vascularity.[278] Further research examining the efficacy of topical administration of rhGM-CSF on deep partial-thickness burn wounds similarly found accelerated wound healing with no difference in adverse reactions.[279] These data corroborated other studies that likewise found accelerated wound healing with application of topical rhGM-CSF and no difference in adverse reactions in adult[280] and pediatric burn patients.[281] Given the promising data,

cautious increasing use as a topical treatment to promote wound healing is warranted, but further examination of rhGM-CSF, along with fibroblast and epidermal growth factors, is also recommended.

LYMPHOID GROWTH FACTORS

Several growth factors/cytokines contribute to the formation of lymphoid cells; the most prominent and well studied is IL-7. The IL-7 receptor is unique to lymphoid cells. Thus IL-7 is the cytokine/growth factor that influences the expansion of this cell line. IL-7 receptor engagement is essential not only for lymphoid cell proliferation and survival but also for HSC differentiation into the lymphoid lineage. The IL-7 receptor enhances lymphoid cell survival through maintenance of Bcl-2.[282] Bone marrow stromal cells and the thymus predominantly produce IL-7. T cells are unique since their maturation takes places in the thymus as opposed to the bone marrow, and they undergo a process of positive and negative selection dependent on both IL-7 activation and expression of the transcription factor Notch1.[283] Alterations in IL-7 production, in addition to other cytokines, can negatively impact survival after inhalation injury.[284] Additional growth factors/cytokines contributing to lymphopoiesis include IL-2, IL-15, and IL-23.

MEGAKARYOCYTE GROWTH FACTORS

Megakaryocyte and platelet production are regulated by thrombopoietin. Similar to EPO, thrombopoietin enhances megakaryocyte progenitor proliferation by amplifying cell-cycle regulators and preventing apoptosis.[222] It is the only growth factor necessary for proliferating megakaryocytes and their progenitors.[285] Unlike erythropoietin, thrombopoietin has a synergistic role with other growth factors and cytokines in the maintenance and proliferation of HSCs[286] and can be used in their expansion.[287] Thrombopoietin stimulates platelet release from the bone marrow and in the periphery, thereby up-regulating platelet function and aggregation.[288] Produced in the liver, kidney, skeletal muscle, and stromal cells of the bone marrow,[222,289] thrombopoietin production may be increased in response to increased IL-6 production.[290] Given the elevated IL-6 levels present following burn injury, IL-6-induced thrombopoietin release may be responsible for the thrombocytosis often seen immediately post-burn.[291] Elevated levels of thrombopoietin, and subsequently platelet activation, may be present following burn injury.[292] The evidence from a recent study would support the notion that thrombopoietin blockade could help prevent organ damage in burn patients with sepsis.[293]

TRANSCRIPTION FACTORS

While growth factors control hematopoietic cell fate, the development of terminally differentiated cells is under the control and coordination of a limited set of transcription factors. Ultimately specific sequential and temporal gene expression patterns dictate hematopoietic commitment. These genetic processes are governed though modulations in the rate of gene transcription, which are accomplished through the binding of DNA-binding proteins or transcription factors to specific regions on a gene.[294] Transcription factors are nuclear proteins that act as control points in the conversion of a gene to a functional protein.[294] Since many key proteins are turned over rapidly to meet the changing needs of the tissues, a complex system of cell signaling architecture, with the final common pathway of gene transcription, must exist to produce bioactive proteins on demand. Since cells respond to several signals simultaneously, and many ligand–cell interactions stimulate similar proximal signals, tight control of transcriptional initiation must exist for the proper orchestration of cellular responses.

The role of transcription factors in hematopoietic cell fate is an evolving topic of study. The lineage-restricted proliferation and differentiation program of hematopoiesis is achieved through switching on and off specific sets of genes in response to cell signals. Since thermal injury and sepsis are accompanied by hematologic and hematopoietic changes that determine the overall pathophysiological response of burn patients, it is reasonable to assume that transcriptional regulation of hematopoietic developmental genes play a significant role. It is known that GATA-1, sct/tal1, and Klf1 form the transcriptional core of the erythroid lineage and are all expressed by the earliest hematopoietic progenitors.[295] The relationship between transcription factors is complex because they are not independent of one another but demonstrate antagonism. In fact, the inability of one transcription factor to suppress the other has been linked to the development of hematologic malignancies. However little is known about hematopoietic transcription factor changes following pathologic injury, even though they may control the dramatic hematopoietic shifts following severe trauma and burn injury. Given the importance of these transcription factors to cell fate and the significant shifts in lineage commitment patterns, knowledge of these transcription factors and their roles in hematopoiesis may help in providing a foundation for future reference. Furthermore recent studies indicating the poor correlation of animal models to humans with regards to transcriptional response after burn/trauma/endotoxemia highlight the need for medical research to shift from a reliance on animal models,[296] especially mouse models,[297] although the clinical translation efficacy is debated.[298]

Conclusion

Hematology plays a major role in burn care. Patients suffer from anemia due to RBC losses in surgery as well as the anemia of critical illness. Operative hemostasis is important both to limit RBC loss and prevent shock. Coagulopathies develop due to factor consumption and insufficient production as well as hypothermia. Transfusion of various blood products is critical to the management of patients. Hematopoiesis is directed away from erythropoiesis to the production of the immune cells vital to fight off invading microbes and heal wounds. Venous thrombosis becomes a major risk in these critically ill patients, adding another mortality risk. Hematologic management is a central component of burn critical care and ought to be carefully considered.

Complete references available online at
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References

1. Weiskopf RB, Viele MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA*. 1998;279(3):217-221.
2. Curinga G, Jain A, Feldman M, et al. Red blood cell transfusion following burn. *Burns*. 2011;37(5):742-752.
3. Hebert PC, Van der Linden P, Biro G, Hu LQ. Physiologic aspects of anemia. *Crit Care Clin*. 2004;20(2):187-212.
4. Scharte M, Fink MP. Red blood cell physiology in critical illness. *Crit Care Med*. 2003;31(12 suppl):S651-S657.
5. Posluszny JA Jr, Conrad P, Halerz M, Shankar R, Gamelli RL. Classifying transfusions related to the anemia of critical illness in burn patients. *J Trauma*. 2011;71(1):26-31.
6. Pieracci FM, Henderson P, Rodney JR, et al. Randomized, double-blind, placebo-controlled trial of effects of enteral iron supplementation on anemia and risk of infection during surgical critical illness. *Surg Infect (Larchmt)*. 2009;10(1):9-19.
7. Pieracci FM, Stovall RT, Jaouen B, et al. A multicenter, randomized clinical trial of IV iron supplementation for anemia of traumatic critical illness. *Crit Care Med*. 2014;42(9):2048-2057.
8. Posluszny JA Jr, Muthumalaiappan K, Kini AR, et al. Burn injury dampens erythroid cell production through reprioritizing bone marrow hematopoietic response. *J Trauma*. 2011;71(5):1288-1296.
9. Wallner SF, Warren GH. The haematopoietic response to burning: an autopsy study. *Burns Incl Therm Inj*. 1985;12(1):22-27.
10. Palmieri TL, Greenhalgh DG, Sen S. Prospective comparison of packed red blood cell-to-fresh frozen plasma transfusion ratio of 4: 1 versus 1: 1 during acute massive burn excision. *J Trauma Acute Care Surg*. 2013;74(1):76-83.
11. Smith CE, Bauer AM, Pivalizza MB, et al. Massive Transfusion Protocol (MTP) for Hemorrhagic Shock: ASA Committee on Patient Blood Management; 2011 [Sample massive transfusion protocol and treatment of the hemorrhaging trauma patient.]. Available from: https://www.asahq.org/~/media/sites/asahq/files/public/resources/asa%20committees/mtp%20for%20asa%20transfusion%20committee%20final.pdf?la=en.
12. Hayden SJ, Albert TJ, Watkins TR, Swenson ER. Anemia in critical illness: insights into etiology, consequences, and management. *Am J Respir Crit Care Med*. 2012;185(10):1049-1057.
13. Posluszny JA Jr, Gamelli RL. Anemia of thermal injury: combined acute blood loss anemia and anemia of critical illness. *J Burn Care Res*. 2010;31(2):229-242.
14. Posluszny JA Jr, Conrad P, Halerz M, Shankar R, Gamelli RL. Classifying transfusions related to the anemia of critical illness in burn patients. *J Trauma*. 2011;71(1):26-31.
15. Walsh TS, Saleh EE. Anaemia during critical illness. *Br J Anaesth*. 2006;97(3):278-291.
16. Corwin HL, Krantz SB. Anemia of the critically ill: "acute" anemia of chronic disease. *Crit Care Med*. 2000;28(8):3098-3099.
17. Madu AJ, Ughasoro MD. Anaemia of chronic disease: an in-depth review. *Med Princ Pract*. 2017;26(1):1-9.
18. Barbosa RR, Rowell SE, Sambasivan CN, et al. A predictive model for mortality in massively transfused trauma patients. *J Trauma*. 2011;71(2 suppl 3):S370-S374.
19. Sterling JP, Heimbach DM. Hemostasis in burn surgery – a review. *Burns*. 2011;37(4):559-565.
20. Mosier MJ, Gibran NS. Surgical excision of the burn wound. *Clin Plast Surg*. 2009;36(4):617-625.
21. Djurickovic S, Snelling CF, Boyle JC. Tourniquet and subcutaneous epinephrine reduce blood loss during burn excision and immediate autografting. *J Burn Care Rehabil*. 2001;22(1):1-5.
22. Kahalley L, Dimick AR, Gillespie RW. Methods to diminish intraoperative blood loss. *J Burn Care Rehabil*. 1991;12(2):160-161.
23. Robertson RD, Bond P, Wallace B, Shewmake K, Cone J. The tumescent technique to significantly reduce blood loss during burn surgery. *Burns*. 2001;27(8):835-838.
24. Sheridan RL, Szyfelbein SK. Staged high-dose epinephrine clysis is safe and effective in extensive tangential burn excisions in children. *Burns*. 1999;25(8):745-748.
25. Bashir MM, Qayyum R, Saleem MH, Siddique K, Khan FA. Effect of time interval between tumescent local anesthesia infiltration and start of surgery on operative field visibility in hand surgery without tourniquet. *J Hand Surg Am*. 2015;40(8):1606-1609.
26. Blome-Eberwein S, Abboud M, Lozano DD, et al. Effect of subcutaneous epinephrine/saline/local anesthetic versus saline-only injection on split-thickness skin graft donor site perfusion, healing, and pain. *J Burn Care Res*. 2013;34(2):e80-e86.
27. Cartotto R, Kadikar N, Musgrave MA, Gomez M, Cooper AB. What are the acute cardiovascular effects of subcutaneous and topical epinephrine for hemostasis during burn surgery? *J Burn Care Rehabil*. 2003;24(5):297-305.
28. Maguina P, Velez M. Review of epinephrine solution use in 400 consecutive cases of burn reconstruction. Are infusion pumps safe? *J Burn Care Res*. 2013;34(5):e305-e307.
29. Missavage AE, Bush RL, Kien ND, Reilly DA. The effect of clysed and topical epinephrine on intraoperative catecholamine levels. *J Trauma*. 1998;45(6):1074-1078.
30. Papp AA, Uusaro AV, Ruokonen ET. The effects of topical epinephrine on haemodynamics and markers of tissue perfusion in burned and non-burned patients requiring skin grafting. *Burns*. 2009;35(6):832-839.
31. Gumus N. Tumescent infiltration of lidocaine and adrenaline for burn surgery. *Ann Burns Fire Disasters*. 2011;24(3):144-148.
32. Allorto NL, Bishop DG, Rodseth RN. Vasoconstrictor clysis in burn surgery and its impact on outcomes: systematic review and meta-analysis. *Burns*. 2015;41(6):1140-1146.
33. Cartotto R, Musgrave MA, Beveridge M, Fish J, Gomez M. Minimizing blood loss in burn surgery. *J Trauma*. 2000;49(6):1034-1039.
34. Gomez M, Logsetty S, Fish JS. Reduced blood loss during burn surgery. *J Burn Care Rehabil*. 2001;22(2):111-117.
35. Sheridan RL, Szyfelbein SK. Trends in blood conservation in burn care. *Burns*. 2001;27(3):272-276.
36. Osuka A, Kuroki Y, Nakajima S, et al. Haemostatic technique using a novel silicone gel dressing for tangential excisions in burn surgery. *Burns*. 2014;40(1):165-166.
37. Osuka A, Kuroki Y, Ueyama M. A haemostatic technique using silicone gel dressing for burn surgery. *Int Wound J*. 2016;13(6):1354-1358.
38. O'Mara MS, Goel A, Recio P, et al. The use of tourniquets in the excision of unexsanguinated extremity burn wounds. *Burns*. 2002;28(7):684-687.
39. Rosenberg JL, Zawacki BE. Reduction of blood loss using tourniquets and 'compression' dressings in excising limb burns. *J Trauma*. 1986;26(1):47-50.
40. Smoot EC 3rd. Modified use of extremity tourniquets for burn wound débridement. *J Burn Care Rehabil*. 1996;17(4):334-337.
41. Warden GD, Saffle JR, Kravitz M. A two-stage technique for excision and grafting of burn wounds. *J Trauma*. 1982;22(2):98-103.
42. Kragh JF Jr, O'Neill ML, Walters TJ, et al. Minor morbidity with emergency tourniquet use to stop bleeding in severe limb trauma: research, history, and reconciling advocates and abolitionists. *Mil Med*. 2011;176(7):817-823.
43. Kragh JF Jr, Cooper A, Aden JK, et al. Survey of trauma registry data on tourniquet use in pediatric war casualties. *Pediatr Emerg Care*. 2012;28(12):1361-1365.
44. Prasetyono TO, Koswara AF. Retrospective analysis of the one-per-million tumescent technique in post-burn hand deformity surgeries. *Arch Plast Surg*. 2015;42(2):164-172.
45. Foster KN, Kim H, Potter K, et al. Acquired factor V deficiency associated with exposure to bovine thrombin in a burn patient. *J Burn Care Res*. 2010;31(2):353-360.
46. Foster KN, Mullins RF, Greenhalgh DG, et al. Recombinant human thrombin: safety and immunogenicity in pediatric burn wound excision. *J Pediatr Surg*. 2011;46(10):1992-1999.
47. Yogore MG 3rd, Boral L, Kowal-Vern A, et al. Use of blood bank services in a burn unit. *J Burn Care Res*. 2006;27(6):835-841.
48. Criswell KK, Gamelli RL. Establishing transfusion needs in burn patients. *Am J Surg*. 2005;189(3):324-326.
49. Mitra B, Wasiak J, Cameron PA, et al. Early coagulopathy of major burns. *Injury*. 2013;44(1):40-43.
50. King DR, Namias N, Andrews DM. Coagulation abnormalities following thermal injury. *Blood Coagul Fibrinolysis*. 2010;21(7):666-669.
51. Hofstra JJ, Vlaar AP, Knape P, et al. Pulmonary activation of coagulation and inhibition of fibrinolysis after burn injuries and inhalation trauma. *J Trauma*. 2011;70(6):1389-1397.
52. Sherren PB, Hussey J, Martin R, et al. Acute burn induced coagulopathy. *Burns*. 2013;39(6):1157-1161.
53. Glas GJ, Levi M, Schultz MJ. Coagulopathy and its management in patients with severe burns. *J Thromb Haemost*. 2016;14(5):865-874.
54. Dobson GP, Letson HL, Sharma R, Sheppard FR, Cap AP. Mechanisms of early trauma-induced coagulopathy: the clot thickens or not? *J Trauma Acute Care Surg*. 2015;79(2):301-309.

55. Gonzalez E, Moore EE, Moore HB. *Trauma Induced Coagulopathy*. New York, NY: Springer Science+Business Media; 2016.
56. Hayakawa M. Pathophysiology of trauma-induced coagulopathy: disseminated intravascular coagulation with the fibrinolytic phenotype. *J Intensive Care.* 2017;5(14).
57. Gando S, Otomo Y. Local hemostasis, immunothrombosis, and systemic disseminated intravascular coagulation in trauma and traumatic shock. *Crit Care*. 2015;19:72.
58. Gando S, Wada H, Thachil J, Scientific, Standardization Committee on DICotISoT, Haemostasis. Differentiating disseminated intravascular coagulation (DIC) with the fibrinolytic phenotype from coagulopathy of trauma and acute coagulopathy of trauma-shock (COT/ACOTS). *J Thromb Haemost*. 2013;11(5):826-835.
59. Gando S, Sawamura A, Hayakawa M. Trauma, shock, and disseminated intravascular coagulation: lessons from the classical literature. *Ann Surg*. 2011;254(1):10-19.
60. Taylor FB Jr, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost*. 2001;86(5):1327-1330.
61. Schochl H, Schlimp CJ, Maegele M. Tranexamic acid, fibrinogen concentrate, and prothrombin complex concentrate: data to support prehospital use? *Shock*. 2014;41(suppl 1):44-46.
62. Younan D, Griffin R, Thompson M, et al. Early coagulopathy is associated with increased incidence of ventilator-associated events among burn patients. *Shock*. 2017;47(1):107-110.
63. Hayakawa M, Gando S, Ono Y, et al. Fibrinogen level deteriorates before other routine coagulation parameters and massive transfusion in the early phase of severe trauma: a retrospective observational study. *Semin Thromb Hemost*. 2015;41(1):35-42.
64. Simmons JW, Powell MF. Acute traumatic coagulopathy: pathophysiology and resuscitation. *Br J Anaesth*. 2016;117(suppl 3):iii31-iii43.
65. Gruen RL, Mitra B. Tranexamic acid for trauma. *Lancet*. 2011;377 (9771):1052-1054.
66. Davenport R, Curry N, Manson J, et al. Hemostatic effects of fresh frozen plasma may be maximal at red cell ratios of 1:2. *J Trauma*. 2011; 70(1):90-95, discussion 95-96.
67. Leeper CM, Neal MD, McKenna C, Sperry JL, Gaines BA. Abnormalities in fibrinolysis at the time of admission are associated with deep vein thrombosis, mortality, and disability in a pediatric trauma population. *J Trauma Acute Care Surg*. 2017;82(1):27-34.
68. Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. *Crit Care*. 2016;20:100.
69. Lu RP, Ni A, Lin FC, et al. Major burn injury is not associated with acute traumatic coagulopathy. *J Trauma Acute Care Surg*. 2013;74(6):1474-1479.
70. Lavrentieva A. Replacement of specific coagulation factors in patients with burn: a review. *Burns*. 2013;39(4):543-548.
71. Hanke AA, Rahe-Meyer N. Trauma-induced coagulopathy]. *Unfallchirurg*. 2014;117(2):95-98.
72. Lavrentieva A, Kontakiotis T, Bitzani M, et al. Early coagulation disorders after severe burn injury: impact on mortality. *Intensive Care Med*. 2008;34(4):700-706.
73. Tejiram S, Brummel-Ziedins KE, Orfeo T, et al. In-depth analysis of clotting dynamics in burn patients. *J Surg Res*. 2016;202(2):341-351.
74. Sihler KC, Napolitano LM. Complications of massive transfusion. *Chest*. 2010;137(1):209-220.
75. Sherren PB, Hussey J, Martin R, et al. Lethal triad in severe burns. *Burns*. 2014;40(8):1492-1496.
76. Rizzo JA, Rowan MP, Driscoll IR, Chan RK, Chung KK. Perioperative temperature management during burn care. *J Burn Care Res*. 2017; 38(1):e277-e283.
77. Singer AJ, Taira BR, Thode HC Jr, et al. The association between hypothermia, prehospital cooling, and mortality in burn victims. *Acad Emerg Med*. 2010;17(4):456-459.
78. Moola S, Lockwood C. Effectiveness of strategies for the management and/or prevention of hypothermia within the adult perioperative environment. *Int J Evid Based Healthc*. 2011;9(4):337-345.
79. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. *N Engl J Med*. 1996;334(19):1209-1215.
80. Steele JE, Atkins JL, Vizcaychipi MP. Factors at scene and in transfer related to the development of hypothermia in major burns. *Ann Burns Fire Disasters.* 2016;29(2):103-107.
81. Williams D, Leslie G, Kyriazis D, et al. Use of an esophageal heat exchanger to maintain core temperature during burn excisions and to attenuate pyrexia on the burns intensive care unit. *Case Rep Anesthesiol*. 2016;2016:7306341.
82. Busche MN, Roettger A, Herold C, Vogt PM, Rennekampff HO. Evaporative water loss in superficial to full thickness burns. *Ann Plast Surg*. 2016;77(4):401-405.
83. Prunet B, Asencio Y, Lacroix G, et al. Maintenance of normothermia during burn surgery with an intravascular temperature control system: a non-randomised controlled trial. *Injury*. 2012;43 (5):648-652.
84. Kim JH, Baek CH, Min JY, et al. Desmopressin improves platelet function in uremic patients taking antiplatelet agents who require emergent invasive procedures. *Ann Hematol*. 2015;94(9):1457-1461.
85. El Gkotmi N, Kosmeri C, Filippatos TD, Elisaf MS. Use of intravenous fluids/solutions: a narrative review. *Curr Med Res Opin*. 2017;33(3):459-471.
86. Soussi S, Ferry A, Chaussard M, Legrand M. Chloride toxicity in critically ill patients: what's the evidence? *Anaesth Crit Care Pain Med*. 2017;36(2):125-130.
87. Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med*. 2013;369 (13):1243-1251.
88. Lavrentieva A. Coagulopathy in burn patients: one part of a deadly trio. *Burns*. 2015;41(3):419-420.
89. Van Haren RM, Thorson CM, Valle EJ, et al. Hypercoagulability after burn injury. *J Trauma Acute Care Surg*. 2013;75(1):37-43, discussion.
90. Koyama K, Madoiwa S, Nunomiya S, et al. Combination of thrombin-antithrombin complex, plasminogen activator inhibitor-1, and protein C activity for early identification of severe coagulopathy in initial phase of sepsis: a prospective observational study. *Crit Care*. 2014;18 (1):R13.
91. Davenport R, Manson J, De'Ath H, et al. Functional definition and characterization of acute traumatic coagulopathy. *Crit Care Med*. 2011;39 (12):2652-2658.
92. Floccard B, Rugeri L, Faure A, et al. Early coagulopathy in trauma patients: an on-scene and hospital admission study. *Injury*. 2012;43 (1):26-32.
93. Moore HB, Moore EE, Gonzalez E, et al. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: the spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. *J Trauma Acute Care Surg*. 2014;77(6):811-817, discussion 817.
94. Midura EF, Kuethe JW, Rice TC, et al. Impact of platelets and platelet-derived microparticles on hypercoagulability following burn injury. *Shock*. 2016;45(1):82-87.
95. Haas T, Spielmann N, Mauch J, et al. Comparison of thromboelastometry (ROTEM(R)) with standard plasmatic coagulation testing in paediatric surgery. *Br J Anaesth*. 2012;108(1):36-41.
96. Lavrentieva A, Depetris N, Kaimakamis E, Berardino M, Stella M. Monitoring and treatment of coagulation abnormalities in burn patients. an international survey on current practices. *Ann Burns Fire Disasters*. 2016;29(3):172-177.
97. Hayakawa M, Gando S, Ono Y, et al. Rapid evaluation of fibrinogen levels using the CG02N whole blood coagulation analyzer. *Semin Thromb Hemost*. 2015;41(3):267-271.
98. Nakamura Y, Ishikura H, Kushimoto S, et al. Fibrinogen level on admission is a predictor for massive transfusion in patients with severe blunt trauma: analyses of a retrospective multicentre observational study. *Injury*. 2017;48(3):674-679.
99. Umemura T, Nakamura Y, Nishida T, Hoshino K, Ishikura H. Fibrinogen and base excess levels as predictive markers of the need for massive blood transfusion after blunt trauma. *Surg Today*. 2016;46 (7):774-779.
100. Stinger HK, Spinella PC, Perkins JG, et al. The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. *J Trauma*. 2008; 64(2 suppl):S79-S85.
101. Chowdary P, Saayman AG, Paulus U, Findlay GP, Collins PW. Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. *Br J Haematol*. 2004;125(1):69-73.
102. Roberts I, Shakur H, Coats T, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technol Assess*. 2013;17(10):1-79.

103. Williams-Johnson JA, McDonald AH, Strachan GG, Williams EW. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2) A randomised, placebo-controlled trial. *West Indian Med J*. 2010;59(6):612-624.
104. Guerriero C, Cairns J, Perel P, et al. Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. *PLoS ONE*. 2011;6(5):e18987.
105. CRASH-2 trial collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376(9734):23-32.
106. Bolliger D, Szlam F, Levy JH, Molinaro RJ, Tanaka KA. Haemodilution-induced profibrinolytic state is mitigated by fresh-frozen plasma: implications for early haemostatic intervention in massive haemorrhage. *Br J Anaesth*. 2010;104(3):318-325.
107. Tranexamic acid and thrombosis. *Prescrire Int*. 2013;22(140):182-183.
108. Moran KT, O'Reilly TJ, Furman W, Munster AM. A new algorithm for calculation of blood loss in excisional burn surgery. *Am Surg*. 1988;54(4):207-208.
109. Brown RA, Grobbelaar AO, Barker S, Rode H. A formula to calculate blood cross-match requirements for early burn surgery in children. *Burns*. 1995;21(5):371-373.
110. Drew PJ, Ciampolini J, Dickson WA. Blood crossmatching for burn surgery: potential for reduced wastage using a modified dye formula. *Burns*. 1999;25(7):651-654.
111. Dye DJ. Requirements for cross-matched blood in burns surgery. *Burns*. 1993;19(6):524-528.
112. Janezic T, Prezelj B, Brcic A, Arnez Z, Zaletelj-Kragelj L. Intraoperative blood loss after tangential excision of burn wounds treated by subeschar infiltration of epinephrine. *Scand J Plast Reconstr Surg Hand Surg*. 1997;31(3):245-250.
113. Budny PG, Regan PJ, Roberts AH. The estimation of blood loss during burns surgery. *Burns*. 1993;19(2):134-137.
114. Gross JB. Estimating allowable blood loss: corrected for dilution. *Anesthesiology*. 1983;58(3):277-280.
115. Desai MH, Herndon DN, Broemeling L, et al. Early burn wound excision significantly reduces blood loss. *Ann Surg*. 1990;211(6):753-759, discussion 759-762.
116. Ejaz A, Frank SM, Spolverato G, et al. Variation in the use of type and crossmatch blood ordering among patients undergoing hepatic and pancreatic resections. *Surgery*. 2016;159(3):908-918.
117. Thorson CM, Ryan ML, Van Haren RM, et al. Change in hematocrit during trauma assessment predicts bleeding even with ongoing fluid resuscitation. *Am Surg*. 2013;79(4):398-406.
118. Thorson CM, Van Haren RM, Ryan ML, et al. Admission hematocrit and transfusion requirements after trauma. *J Am Coll Surg*. 2013;216(1):65-73.
119. Ryan ML, Thorson CM, Otero CA, et al. Initial hematocrit in trauma: a paradigm shift? *J Trauma Acute Care Surg*. 2012;72(1):54-59, discussion 9-60.
120. Allen CJ, Tashiro J, Valle EJ, et al. Initial hematocrit predicts the use of blood transfusion in the pediatric trauma patient. *J Pediatr Surg*. 2014;49(11):1678-1682.
121. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015;313(5):471-482.
122. Novak DJ, Bai Y, Cooke RK, et al. Making thawed universal donor plasma available rapidly for massively bleeding trauma patients: experience from the Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial. *Transfusion*. 2015;55(6):1331-1339.
123. Fuzaylov G, Anderson R, Lee J, et al. Blood transfusion trigger in burns: a four-year retrospective analysis of blood transfusions in eleven burn centers in Ukraine. *Ann Burns Fire Disasters*. 2015;28(3):178-182.
124. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340(6):409-417.
125. Kwan P, Gomez M, Cartotto R. Safe and successful restriction of transfusion in burn patients. *J Burn Care Res*. 2006;27(6):826-834.
126. Palmieri TL, Lee T, O'Mara MS, Greenhalgh DG. Effects of a restrictive blood transfusion policy on outcomes in children with burn injury. *J Burn Care Res*. 2007;28(1):65-70.
127. Napolitano LM, Kurek S, Luchette FA, et al. Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. *Crit Care Med*. 2009;37(12):3124-3157.
128. Lelubre C, Vincent JL, Taccone FS. Red blood cell transfusion strategies in critically ill patients: lessons from recent randomized clinical studies. *Minerva Anestesiol*. 2016;82(9):1010-1016.
129. Palmieri TL, Caruso DM, Foster KN, et al. Effect of blood transfusion on outcome after major burn injury: a multicenter study. *Crit Care Med*. 2006;34(6):1602-1607.
130. Vasko SD, Burdge JJ, Ruberg RL, Verghese AS. Evaluation of erythropoietin levels in the anemia of thermal injury. *J Burn Care Rehabil*. 1991;12(5):437-441.
131. Farina JA Jr, Rosique MJ, Rosique RG. Curbing inflammation in burn patients. *Int J Inflam*. 2013;2013:715645.
132. Alter HJ, Klein HG. The hazards of blood transfusion in historical perspective. *Blood*. 2008;112(7):2617-2626.
133. Goodnough LT. Risks of blood transfusion. *Crit Care Med*. 2003;31(12 suppl):S678-S686.
134. Organization WH Global Database on Blood Safety 2011. Available from: http://www.who.int/bloodsafety/global_database/GDBS_Summary_Report_2011.pdf.
135. Graves TA, Cioffi WG, Mason AD Jr, McManus WF, Pruitt BA Jr. Relationship of transfusion and infection in a burn population. *J Trauma*. 1989;29(7):948-952, discussion 952-954.
136. Muszynski JA, Spinella PC, Cholette JM, et al. Transfusion-related immunomodulation: review of the literature and implications for pediatric critical illness. *Transfusion*. 2017;57(1):195-206.
137. Higgins S, Fowler R, Callum J, Cartotto R. Transfusion-related acute lung injury in patients with burns. *J Burn Care Res*. 2007;28(1):56-64.
138. Linden JV, Wagner K, Voytovich AE, Sheehan J. Transfusion errors in New York State: an analysis of 10 years' experience. *Transfusion*. 2000;40(10):1207-1213.
139. Jones LM, Deluga N, Bhatti P, et al. TRALI following fresh frozen plasma resuscitation from burn shock. *Burns*. 2017;43(2):397-402.
140. Johnson JL, Moore EE, Kashuk JL, et al. Effect of blood products transfusion on the development of postinjury multiple organ failure. *Arch Surg*. 2010;145(10):973-977.
141. Pandey S, Vyas GN. Adverse effects of plasma transfusion. *Transfusion*. 2012;52(suppl 1):65S-79S.
142. Lu RP, Lin FC, Ortiz-Pujols SM, et al. Blood utilization in patients with burn injury and association with clinical outcomes (CME). *Transfusion*. 2013;53(10):2212-2221, quiz 2221.
143. Sambasivan CN, Kunio NR, Nair PV, et al. High ratios of plasma and platelets to packed red blood cells do not affect mortality in nonmassively transfused patients. *J Trauma*. 2011;71(2 suppl 3):S329-S336.
144. Spoerke N, Michalek J, Schreiber M, et al. Crystalloid resuscitation improves survival in trauma patients receiving low ratios of fresh frozen plasma to packed red blood cells. *J Trauma*. 2011;71(2 suppl 3):S380-S383.
145. Pidcoke HF, Isbell CL, Herzig MC, et al. Acute blood loss during burn and soft tissue excisions: an observational study of blood product resuscitation practices and focused review. *J Trauma Acute Care Surg*. 2015;78(6 suppl 1):S39-S47.
146. Brakenridge SC, Phelan HA, Henley SS, et al. Early blood product and crystalloid volume resuscitation: risk association with multiple organ dysfunction after severe blunt traumatic injury. *J Trauma*. 2011;71(2):299-305.
147. Jones AR, Bush HM, Frazier SK. Injury severity, sex, and transfusion volume, but not transfusion ratio, predict inflammatory complications after traumatic injury. *Heart Lung*. 2017;46(2):114-119.
148. Belizaire RM, Prakash PS, Richter JR, et al. Microparticles from stored red blood cells activate neutrophils and cause lung injury after hemorrhage and resuscitation. *J Am Coll Surg*. 2012;214(4):648-655, discussion 56-57.
149. Zhang Q, Li Z, Zhao S, et al. Analysis of red blood cells' dynamic status in a simulated blood circulation system using an ultrahigh-speed simultaneous framing optical electronic camera. *Cytometry A*. 2017;91(2):126-132.
150. Palmieri TL, Sen S, Falwell K, Greenhalgh DG. Blood product transfusion: does location make a difference? *J Burn Care Res*. 2011;32(1):61-65.
151. Galganski LA, Greenhalgh DG, Sen S, Palmieri TL. Randomized comparison of packed red blood cell-to-fresh frozen plasma transfusion ratio of 4: 1 vs 1: 1 during acute massive burn excision. *J Burn Care Res*. 2016;doi:10.1097/BCR.0000000000000468.

152. Acker SN, Hall B, Hill L, Partrick DA, Bensard DD. Adult-based massive transfusion protocol activation criteria do not work in children. *Eur J Pediatr Surg*. 2017;27(1):32-35.
153. Marck RE, Middelkoop E, Breederveld RS. Considerations on the use of platelet-rich plasma, specifically for burn treatment. *J Burn Care Res*. 2014;35(3):219-227.
154. Lubkowska A, Dolegowska B, Banfi G. Growth factor content in PRP and their applicability in medicine. *J Biol Regul Homeost Agents*. 2012;26(2 suppl 1):3S-22S.
155. Engele LJ, Straat M, van Rooijen IH, et al. Transfusion of platelets, but not of red blood cells, is independently associated with nosocomial infections in the critically ill. *Ann Intensive Care*. 2016;6(1):67.
156. Centers for Disease Control and Prevention. Bacterial contamination of platelets. Atlanta, GA, 2013 [updated March 21, 2013]. Available from: http://www.cdc.gov/bloodsafety/bbp/bacterial-contamination-of-platelets.html.
157. Burns KH, Werch JB. Bacterial contamination of platelet units: a case report and literature survey with review of upcoming american association of blood banks requirements. *Arch Pathol Lab Med*. 2004;128(3):279-281.
158. Johnson L, Reade MC, Hyland RA, Tan S, Marks DC. In vitro comparison of cryopreserved and liquid platelets: potential clinical implications. *Transfusion*. 2015;55(4):838-847.
159. Pidcoke HF, Cap AP. Refrigerated platelets for the treatment of acute bleeding: a review of the literature and reexamination of current standards: reply. *Shock*. 2015;44(6):616-617.
160. Kaur A, Sethi GK, Goyal RK, et al. Thrombocytopenia in paediatric ICU: incidence, transfusion requirement and role as prognostic indicator. *J Clin Diagn Res*. 2015;9(12):SC5-SC7.
161. Johansson PI, Eriksen K, Alsbjorn B. Rescue treatment with recombinant factor VIIa is effective in patients with life-threatening bleedings secondary to major wound excision: a report of four cases. *J Trauma*. 2006;61(4):1016-1018.
162. Martin JT, Alkhoury F, McIntosh BC, Fidler P, Schulz J. Recombinant Factor VIIa: hemostatic adjunct in the coagulopathic burn patient. *Eplasty*. 2009;9:e27.
163. Darlington DN, Kremenevskiy I, Pusateri AE, et al. Effects of In vitro hemodilution, hypothermia and rFVIIa addition on coagulation in human blood. *Int J Burns Trauma*. 2012;2(1):42-50.
164. Tanaka KA, Mazzeffi M, Durila M. Role of prothrombin complex concentrate in perioperative coagulation therapy. *J Intensive Care*. 2014;2(1):60.
165. Joseph B, Pandit V, Khalil M, et al. Use of prothrombin complex concentrate as an adjunct to fresh frozen plasma shortens time to craniotomy in traumatic brain injury patients. *Neurosurgery*. 2015;76(5):601-607, discussion 607.
166. Berndtson AE, Huang WT, Box K, et al. A new kid on the block: outcomes with Kcentra 1 year after approval. *J Trauma Acute Care Surg*. 2015;79(6):1004-1008.
167. Levin G, Sukhareva E. The influence of thermal trauma on pro- and anticoagulant activity of erythrocyte-derived microvesicles. *Burns*. 2016;42(7):1528-1533.
168. Lobastov K, Barinov V, Schastlivtsev I, et al. Validation of the Caprini risk assessment model for venous thromboembolism in high-risk surgical patients in the background of standard prophylaxis. *J Vasc Surg Venous Lymphat Disord*. 2016;4(2):153-160.
169. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e419S-e494S.
170. Meizoso JP, Ray JJ, Allen CJ, et al. Hypercoagulability and venous thromboembolism in burn patients. *Semin Thromb Hemost*. 2015;41(1):43-48.
171. Ferguson RE, Critchfield A, Leclaire A, Ajkay N, Vasconez HC. Current practice of thromboprophylaxis in the burn population: a survey study of 84 US burn centers. *Burns*. 2005;31(8):964-966.
172. Mullins F, Mian MA, Jenkins D, et al. Thromboembolic complications in burn patients and associated risk factors. *J Burn Care Res*. 2013;34(3):355-360.
173. Comerota AJ, Chouhan V, Harada RN, et al. The fibrinolytic effects of intermittent pneumatic compression: mechanism of enhanced fibrinolysis. *Ann Surg*. 1997;226(3):306-313, discussion 313-314.
174. Lippi G, Favaloro EJ, Cervellin G. Prevention of venous thromboembolism: focus on mechanical prophylaxis. *Semin Thromb Hemost*. 2011;37(3):237-251.
175. Cruz JL, Moss MC, Chen SL, Hansen KM, Amerine LB. Retrospective evaluation of the clinical use of prothrombin complex concentrate for the reversal of anticoagulation with vitamin K antagonists. *Blood Coagul Fibrinolysis*. 2015;26(4):378-382.
176. Burnett AE, Bowles H, Borrego ME, et al. Heparin-induced thrombocytopenia: reducing misdiagnosis via collaboration between an inpatient anticoagulation pharmacy service and hospital reference laboratory. *J Thromb Thrombolysis*. 2016;42(4):471-478.
177. von Heymann C, Rosenthal C, Kaufner L, Sander M. Management of direct oral anticoagulants-associated bleeding in the trauma patient. *Curr Opin Anaesthesiol*. 2016;29(2):220-228.
178. Sacha GL, Greenlee KM, Ketz JM. The use of anti-factor Xa monitoring in a selection of patients receiving enoxaparin at a large academic medical center. *J Thromb Thrombolysis*. 2016;42(4):479-485.
179. Udy AA, De Waele JJ, Lipman J. Augmented renal clearance and therapeutic monitoring of beta-lactams. *Int J Antimicrob Agents*. 2015;45(4):331-333.
180. Schulman S, Ritchie B, Nahirniak S, et al. Reversal of dabigatran-associated major bleeding with activated prothrombin concentrate: a prospective cohort study. *Thromb Res*. 2017;152:44-48.
181. Seita J, Weissman IL. Hematopoietic stem cell: self-renewal versus differentiation. *Wiley Interdiscip Rev Syst Biol Med*. 2010;2(6):640-653.
182. Montagner S, Deho L, Monticelli S. MicroRNAs in hematopoietic development. *BMC Immunol*. 2014;15:14.
183. Chotinantakul K, Leeanansaksiri W. Hematopoietic stem cell development, niches, and signaling pathways. *Bone Marrow Res*. 2012;2012:270425.
184. Baron MH, Isern J, Fraser ST. The embryonic origins of erythropoiesis in mammals. *Blood*. 2012;119(21):4828-4837.
185. Cox D, Kerrigan SW, Watson SP. Platelets and the innate immune system: mechanisms of bacterial-induced platelet activation. *J Thromb Haemost*. 2011;9(6):1097-1107.
186. Malkiewicz A, Dziedzic M. Bone marrow reconversion – imaging of physiological changes in bone marrow. *Pol J Radiol*. 2012;77(4):45-50.
187. Bouhassira EE. Concise review: production of cultured red blood cells from stem cells. *Stem Cells Transl Med*. 2012;1(12):927-933.
188. Muckenthaler MU, Rivella S, Hentze MW, Galy B. A red carpet for iron metabolism. *Cell*. 2017;168(3):344-361.
189. Bhattacharya D, Bryder D, Rossi DJ, Weissman IL. Rapid lymphocyte reconstitution of unconditioned immunodeficient mice with non-self-renewing multipotent hematopoietic progenitors. *Cell Cycle*. 2006;5(11):1135-1139.
190. Morrison SJ, Wandycz AM, Akashi K, Globerson A, Weissman IL. The aging of hematopoietic stem cells. *Nat Med*. 1996;2(9):1011-1016.
191. Bhattacharya D, Rossi DJ, Bryder D, Weissman IL. Purified hematopoietic stem cell engraftment of rare niches corrects severe lymphoid deficiencies without host conditioning. *J Exp Med*. 2006;203(1):73-85.
192. Uchida N, Tsukamoto A, He D, et al. High doses of purified stem cells cause early hematopoietic recovery in syngeneic and allogeneic hosts. *J Clin Invest*. 1998;101(5):961-966.
193. Yang L, Bryder D, Adolfsson J, et al. Identification of Lin(-)Sca1(+)kit(+)CD34(+)Flt3- short-term hematopoietic stem cells capable of rapidly reconstituting and rescuing myeloablated transplant recipients. *Blood*. 2005;105(7):2717-2723.
194. Spangrude GJ, Heimfeld S, Weissman IL. Purification and characterization of mouse hematopoietic stem cells. *Science*. 1988;241(4861):58-62.
195. Papathanasiou P, Attema JL, Karsunky H, et al. Evaluation of the long-term reconstituting subset of hematopoietic stem cells with CD150. *Stem Cells*. 2009;27(10):2498-2508.
196. Benveniste P, Frelin C, Janmohamed S, et al. Intermediate-term hematopoietic stem cells with extended but time-limited reconstitution potential. *Cell Stem Cell*. 2010;6(1):48-58.
197. Morrison SJ, Wandycz AM, Hemmati HD, Wright DE, Weissman IL. Identification of a lineage of multipotent hematopoietic progenitors. *Development*. 1997;124(10):1929-1939.
198. Camargo FD, Chambers SM, Drew E, McNagny KM, Goodell MA. Hematopoietic stem cells do not engraft with absolute efficiencies. *Blood*. 2006;107(2):501-507.
199. Wilson A, Oser GM, Jaworski M, et al. Dormant and self-renewing hematopoietic stem cells and their niches. *Ann N Y Acad Sci*. 2007;1106:64-75.
200. Adolfsson J, Mansson R, Buza-Vidas N, et al. Identification of Flt3+ lympho-myeloid stem cells lacking erythro-megakaryocytic potential a revised road map for adult blood lineage commitment. *Cell*. 2005;121(2):295-306.

201. Forsberg EC, Serwold T, Kogan S, Weissman IL, Passegue E. New evidence supporting megakaryocyte-erythrocyte potential of flk2/flt3+ multipotent hematopoietic progenitors. *Cell*. 2006;126(2):415-426.
202. Sweeney CL, Teng R, Wang H, et al. Molecular analysis of neutrophil differentiation from human induced pluripotent stem cells delineates the kinetics of key regulators of hematopoiesis. *Stem Cells*. 2016; 34(6):1513-1526.
203. Boyer SW, Schroeder AV, Smith-Berdan S, Forsberg EC. All hematopoietic cells develop from hematopoietic stem cells through Flk2/Flt3-positive progenitor cells. *Cell Stem Cell*. 2011;9(1):64-73.
204. Roden C, Lu J. MicroRNAs in control of stem cells in normal and malignant hematopoiesis. *Curr Stem Cell Rep*. 2016;2(3):183-196.
205. Zon LI. Intrinsic and extrinsic control of haematopoietic stem-cell self-renewal. *Nature*. 2008;453(7193):306-313.
206. Chute JP, Ross JR, McDonnell DP. Minireview: nuclear receptors, hematopoiesis, and stem cells. *Mol Endocrinol*. 2010;24(1):1-10.
207. Hamed M, Trumm J, Spaniol C, et al. Linking hematopoietic differentiation to co-expressed sets of pluripotency-associated and imprinted genes and to regulatory microRNA-transcription factor motifs. *PLoS ONE*. 2017;12(1):e0166852.
208. Pang WW, Schrier SL, Weissman IL. Age-associated changes in human hematopoietic stem cells. *Semin Hematol*. 2017;54(1):39-42.
209. Howell K, Posluszny J, He LK, et al. High MafB expression following burn augments monocyte commitment and inhibits DC differentiation in hemopoietic progenitors. *J Leukoc Biol*. 2012;91(1):69-81.
210. Blanchi B, Kelly LM, Viemari JC, et al. MafB deficiency causes defective respiratory rhythmogenesis and fatal central apnea at birth. *Nat Neurosci*. 2003;6(10):1091-1100.
211. Johnson NB, Posluszny JA, He LK, et al. Perturbed MafB/GATA1 axis after burn trauma bares the potential mechanism for immune suppression and anemia of critical illness. *J Leukoc Biol*. 2016;100 (4):725-736.
212. Hasan S, Johnson NB, Mosier MJ, et al. Myelo-erythroid commitment after burn injury is under beta-adrenergic control via MafB regulation. *Am J Physiol Cell Physiol*. 2016;ajpcell 00139 2016.
213. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354(17):1813-1826.
214. Gratwohl A, Baldomero H, Aljurf M, et al. Hematopoietic stem cell transplantation: a global perspective. *JAMA*. 2010;303(16): 1617-1624.
215. Song K, Li L, Wang Y, Liu T. Hematopoietic stem cells: multiparameter regulation. *Hum Cell*. 2016;29(2):53-57.
216. Rea S, Stevenson A, Giles NL, Wood FM, Fear MW. Cells from the hematopoietic lineage are only present transiently during healing in a mouse model of non-severe burn injury. *Stem Cell Res Ther*. 2015;6:134.
217. Andes WA, Rogers PW, Beason JW, Pruitt BA Jr. The erythropoietin response to the anemia of thermal injury. *J Lab Clin Med*. 1976;88 (4):584-592.
218. Robinson H, Monafo WW, Saver SM, Gallagher NI. The role of erythropoietin in the anemia of thermal injury. *Ann Surg*. 1973;178 (5):565-572.
219. Sanders R, Garcia J, Sheldon GF, et al. Erythropoietin elevation in anemia of thermal injury. *Surg Forum*. 1976;27(62):71-72.
220. Sheldon GF, Sanders R, Fuchs R, Garcia J, Schooley J. Metabolism, oxygen transport, and erythropoietin synthesis in the anemia of thermal injury. *Am J Surg*. 1978;135(3):406-411.
221. Deitch EA, Sittig KM. A serial study of the erythropoietic response to thermal injury. *Ann Surg*. 1993;217(3):293-299.
222. Kaushansky K. Lineage-specific hematopoietic growth factors. *N Engl J Med*. 2006;354(19):2034-2045.
223. Lappin T. The cellular biology of erythropoietin receptors. *Oncologist*. 2003;8(suppl 1):15-18.
224. Rossert J, Eckardt KU. Erythropoietin receptors: their role beyond erythropoiesis. *Nephrol Dial Transplant*. 2005;20(6):1025-1028.
225. Juul SE, Yachnis AT, Christensen RD. Tissue distribution of erythropoietin and erythropoietin receptor in the developing human fetus. *Early Hum Dev*. 1998;52(3):235-249.
226. Siren AL, Fratelli M, Brines M, et al. Erythropoietin prevents neuronal apoptosis after cerebral ischemia and metabolic stress. *Proc Natl Acad Sci USA*. 2001;98(7):4044-4049.
227. Calvillo L, Latini R, Kajstura J, et al. Recombinant human erythropoietin protects the myocardium from ischemia-reperfusion injury and promotes beneficial remodeling. *Proc Natl Acad Sci USA*. 2003;100 (8):4802-4806.
228. Parsa CJ, Matsumoto A, Kim J, et al. A novel protective effect of erythropoietin in the infarcted heart. *J Clin Invest*. 2003;112(7):999-1007.
229. Vesey DA, Cheung C, Pat B, et al. Erythropoietin protects against ischaemic acute renal injury. *Nephrol Dial Transplant*. 2004;19(2): 348-355.
230. Corwin HL, Gettinger A, Fabian TC, et al. Efficacy and safety of epoetin alfa in critically ill patients. *N Engl J Med*. 2007;357(10):965-976.
231. Zarychanski R, Turgeon AF, McIntyre L, Fergusson DA. Erythropoietin-receptor agonists in critically ill patients: a meta-analysis of randomized controlled trials. *CMAJ*. 2007;177(7):725-734.
232. Still JM Jr, Belcher K, Law EJ, et al. A double-blinded prospective evaluation of recombinant human erythropoietin in acutely burned patients. *J Trauma*. 1995;38(2):233-236.
233. Fleming RY, Herndon DN, Vaidya S, et al. The effect of erythropoietin in normal healthy volunteers and pediatric patients with burn injuries. *Surgery*. 1992;112(2):424-431, discussion 431-432.
234. Lundy JB, Hetz K, Chung KK, et al. Outcomes with the use of recombinant human erythropoietin in critically ill burn patients. *Am Surg*. 2010;76(9):951-956.
235. Smrzova J, Balla J, Barany P. Inflammation and resistance to erythropoiesis-stimulating agents–what do we know and what needs to be clarified? *Nephrol Dial Transplant*. 2005;20(suppl 8):viii2-viii7.
236. Katagiri D, Shibata M, Katsuki T, et al. Antiepoetin antibody-related pure red cell aplasia: successful remission with cessation of recombinant erythropoietin alone. *Clin Exp Nephrol*. 2010;14(5):501-505.
237. Williams KN, Szilagyi A, Conrad P, et al. Peripheral blood mononuclear cell-derived erythroid progenitors and erythroblasts are decreased in burn patients. *J Burn Care Res*. 2013;34(1):133-141.
238. Rocha J, Eduardo-Figueira M, Barateiro A, et al. Erythropoietin reduces acute lung injury and multiple organ failure/dysfunction associated to a scald-burn inflammatory injury in the rat. *Inflammation*. 2015;38(1):312-326.
239. Bader A, Ebert S, Giri S, et al. Skin regeneration with conical and hair follicle structure of deep second-degree scalding injuries via combined expression of the EPO receptor and beta common receptor by local subcutaneous injection of nanosized rhEPO. *Int J Nanomedicine*. 2012;7:1227-1237.
240. Broxmeyer HE, Williams DE. Actions of hematopoietic colony-stimulating factors in vivo and in vitro. *Pathol Immunopathol Res*. 1987;6 (3):207-220.
241. Metcalf D. The hemopoietic regulators–an embarrassment of riches. *Bioessays*. 1992;14(12):799-805.
242. Hareng L, Hartung T. Induction and regulation of endogenous granulocyte colony-stimulating factor formation. *Biol Chem*. 2002;383(10): 1501-1517.
243. Eaves-Pyles T, Alexander JW. Granulocyte colony-stimulating factor enhances killing of translocated bacteria but does not affect barrier function in a burn mouse model. *J Trauma*. 1996;41(6):1013-1017.
244. Peter FW, Schuschke DA, Barker JH, et al. The effect of severe burn injury on proinflammatory cytokines and leukocyte behavior: its modulation with granulocyte colony-stimulating factor. *Burns*. 1999;25(6):477-486.
245. Sartorelli KH, Silver GM, Gamelli RL. The effect of granulocyte colony-stimulating factor (G-CSF) upon burn-induced defective neutrophil chemotaxis. *J Trauma*. 1991;31(4):523-529, discussion 529-530.
246. Silver GM, Gamelli RL, O'Reilly M. The beneficial effect of granulocyte colony-stimulating factor (G-CSF) in combination with gentamicin on survival after *Pseudomonas* burn wound infection. *Surgery*. 1989;106(2):452-455, discussion 455-456.
247. Mooney DP, Gamelli RL, O'Reilly M, Hebert JC. Recombinant human granulocyte colony-stimulating factor and Pseudomonas burn wound sepsis. *Arch Surg*. 1988;123(11):1353-1357.
248. Finnerty CC, Herndon DN, Przkora R, et al. Cytokine expression profile over time in severely burned pediatric patients. *Shock*. 2006;26(1): 13-19.
249. Finnerty CC, Przkora R, Herndon DN, Jeschke MG. Cytokine expression profile over time in burned mice. *Cytokine*. 2009;45(1): 20-25.
250. Struzyna J, Pojda Z, Braun B, et al. Serum cytokine levels (IL-4, IL-6, IL-8, G-CSF, GM-CSF) in burned patients. *Burns*. 1995;21(6):437-440.
251. Gamelli R, He LK, Hahn E. Granulocyte colony-stimulating factor: release is not impaired after burn wound infection. *J Trauma*. 2002;53(2):284-289, discussion 289-290.
252. Gardner JC, Noel JG, Nikolaidis NM, et al. G-CSF drives a posttraumatic immune program that protects the host from infection. *J Immunol*. 2014;192(5):2405-2417.
253. Gamelli RL, He LK, Liu H. Recombinant human granulocyte colony-stimulating factor treatment improves macrophage suppression of

granulocyte and macrophage growth after burn and burn wound infection. *J Trauma*. 1995;39(6):1141-1146, discussion 1146-1147.
254. Toda H, Murata A, Matsuura N, et al. Therapeutic efficacy of granulocyte colony stimulating factor against rat cecal ligation and puncture model. *Stem Cells*. 1993;11(3):228-234.
255. Smith WS, Sumnicht GE, Sharpe RW, Samuelson D, Millard FE. Granulocyte colony-stimulating factor versus placebo in addition to penicillin G in a randomized blinded study of gram-negative pneumonia sepsis: analysis of survival and multisystem organ failure. *Blood*. 1995;86(4):1301-1309.
256. http://www.neupogen.com/pdf/Neupogen_PI.pdf.
257. Hume DA. Differentiation and heterogeneity in the mononuclear phagocyte system. *Mucosal Immunol*. 2008;1(6):432-441.
258. Chitu V, Stanley ER. Colony-stimulating factor-1 in immunity and inflammation. *Curr Opin Immunol*. 2006;18(1):39-48.
259. Pixley FJ, Stanley ER. CSF-1 regulation of the wandering macrophage: complexity in action. *Trends Cell Biol*. 2004;14(11):628-638.
260. Hume DA, Pavli P, Donahue RE, Fidler IJ. The effect of human recombinant macrophage colony-stimulating factor (CSF-1) on the murine mononuclear phagocyte system in vivo. *J Immunol*. 1988;141 (10):3405-3409.
261. Santangelo S, Gamelli RL, Shankar R. Myeloid commitment shifts toward monocytopoiesis after thermal injury and sepsis. *Ann Surg*. 2001;233(1):97-106.
262. Cohen MJ, Carroll C, He LK, et al. Severity of burn injury and sepsis determines the cytokine responses of bone marrow progenitor-derived macrophages. *J Trauma*. 2007;62(4):858-967.
263. Muthu K, Deng J, Gamelli R, Shankar R, Jones SB. Adrenergic modulation of cytokine release in bone marrow progenitor-derived macrophage following polymicrobial sepsis. *J Neuroimmunol*. 2005;158(1-2):50-57.
264. Miller-Graziano CL, Szabo G, Kodys K, Griffey K. Aberrations in post-trauma monocyte (MO) subpopulation: role in septic shock syndrome. *J Trauma*. 1990;30(12 suppl):S86-S96.
265. Grant SM, Heel RC. Recombinant granulocyte-macrophage colony-stimulating factor (rGM-CSF). A review of its pharmacological properties and prospective role in the management of myelosuppression. *Drugs*. 1992;43(4):516-560.
266. Morrissey PJ, Bressler L, Park LS, Alpert A, Gillis S. Granulocyte-macrophage colony-stimulating factor augments the primary antibody response by enhancing the function of antigen-presenting cells. *J Immunol*. 1987;139(4):1113-1119.
267. Collins HL, Bancroft GJ. Cytokine enhancement of complement-dependent phagocytosis by macrophages: synergy of tumor necrosis factor-alpha and granulocyte-macrophage colony-stimulating factor for phagocytosis of *Cryptococcus neoformans*. *Eur J Immunol*. 1992;22 (6):1447-1454.
268. Fleischmann J, Golde DW, Weisbart RH, Gasson JC. Granulocyte-macrophage colony-stimulating factor enhances phagocytosis of bacteria by human neutrophils. *Blood*. 1986;68(3):708-711.
269. Weiser WY, Van Niel A, Clark SC, David JR, Remold HG. Recombinant human granulocyte/macrophage colony-stimulating factor activates intracellular killing of Leishmania donovani by human monocyte-derived macrophages. *J Exp Med*. 1987;166(5):1436-1446.
270. Tarr PE. Granulocyte-macrophage colony-stimulating factor and the immune system. *Med Oncol*. 1996;13(3):133-140.
271. LeVine AM, Reed JA, Kurak KE, Cianciolo E, Whitsett JA. GM-CSF-deficient mice are susceptible to pulmonary group B streptococcal infection. *J Clin Invest*. 1999;103(4):563-569.
272. Gennari R, Alexander JW, Gianotti L, Eaves-Pyles T, Hartmann S. Granulocyte macrophage colony-stimulating factor improves survival in two models of gut-derived sepsis by improving gut barrier function and modulating bacterial clearance. *Ann Surg*. 1994;220(1): 68-76.
273. Frenck RW, Sarman G, Harper TE, Buescher ES. The ability of recombinant murine granulocyte-macrophage colony-stimulating factor to protect neonatal rats from septic death due to Staphylococcus aureus. *J Infect Dis*. 1990;162(1):109-114.
274. Toda H, Murata A, Oka Y, et al. Effect of granulocyte-macrophage colony-stimulating factor on sepsis-induced organ injury in rats. *Blood*. 1994;83(10):2893-2898.
275. Cioffi WG Jr, Burleson DG, Jordan BS, et al. Effects of granulocyte-macrophage colony-stimulating factor in burn patients. *Arch Surg*. 1991;126(1):74-79.
276. Zhang L, Chen J, Han C. A multicenter clinical trial of recombinant human GM-CSF hydrogel for the treatment of deep second-degree burns. *Wound Repair Regen*. 2009;17(5):685-689.
277. Guo QL, Han MY, Zhang L, et al. [Effect of ambient atmosphere on laser micro-plasma radiant intensity]. *Guang Pu Xue Yu Guang Pu Fen Xi*. 2009;29(10):2606-2609.
278. Zhang Y, Wang T, He J, Dong J. Growth factor therapy in patients with partial-thickness burns: a systematic review and meta-analysis. *Int Wound J*. 2016;13(3):354-366.
279. Liu J, Liao ZJ, Zhang Q. [Phase clinical trial for external use of recombinant human granulocyte-macrophage colony-stimulating factor gel in treating deep partial-thickness burn wounds]. *Zhonghua Shao Shang Za Zhi*. 2016;32(9):542-548.
280. Yuan L, Minghua C, Feifei D, et al. Study of the use of recombinant human granulocyte-macrophage colony-stimulating factor hydrogel externally to treat residual wounds of extensive deep partial-thickness burn. *Burns*. 2015;41(5):1086-1091.
281. Chi YF, Chai JK, Luo HM, Zhang QX, Feng R. Safety of recombinant human granulocyte-macrophage colony-stimulating factor in healing pediatric severe burns. *Genet Mol Res*. 2015;14(1):2735-2741.
282. Akashi K, Kondo M, von Freeden-Jeffry U, Murray R, Weissman IL. Bcl-2 rescues T lymphopoiesis in interleukin-7 receptor-deficient mice. *Cell*. 1997;89(7):1033-1041.
283. Vicente R, Swainson L, Marty-Gres S, et al. Molecular and cellular basis of T cell lineage commitment. *Semin Immunol*. 2010;22(5):270-275.
284. Gauglitz GG, Finnerty CC, Herndon DN, Mlcak RP, Jeschke MG. Are serum cytokines early predictors for the outcome of burn patients with inhalation injuries who do not survive? *Crit Care*. 2008;12(3):R81.
285. de Sauvage FJ, Carver-Moore K, Luoh SM, et al. Physiological regulation of early and late stages of megakaryocytopoiesis by thrombopoietin. *J Exp Med*. 1996;183(2):651-656.
286. Sitnicka E, Lin N, Priestley GV, et al. The effect of thrombopoietin on the proliferation and differentiation of murine hematopoietic stem cells. *Blood*. 1996;87(12):4998-5005.
287. Fox N, Priestley G, Papayannopoulou T, Kaushansky K. Thrombopoietin expands hematopoietic stem cells after transplantation. *J Clin Invest*. 2002;110(3):389-394.
288. Kojima H, Shinagawa A, Shimizu S, et al. Role of phosphatidylinositol-3 kinase and its association with Gab1 in thrombopoietin-mediated up-regulation of platelet function. *Exp Hematol*. 2001;29(5):616-622.
289. Sungaran R, Markovic B, Chong BH. Localization and regulation of thrombopoietin mRNa expression in human kidney, liver, bone marrow, and spleen using in situ hybridization. *Blood*. 1997;89(1):101-107.
290. Wolber EM, Jelkmann W. Interleukin-6 increases thrombopoietin production in human hepatoma cells HepG2 and Hep3B. *J Interferon Cytokine Res*. 2000;20(5):499-506.
291. Kaser A, Brandacher G, Steurer W, et al. Interleukin-6 stimulates thrombopoiesis through thrombopoietin: role in inflammatory thrombocytosis. *Blood*. 2001;98(9):2720-2725.
292. Lupia E, Bosco O, Mariano F, et al. Elevated thrombopoietin in plasma of burned patients without and with sepsis enhances platelet activation. *J Thromb Haemost*. 2009;7(6):1000-1008.
293. Cuccurullo A, Greco E, Lupia E, et al. Blockade of thrombopoietin reduces organ damage in experimental endotoxemia and polymicrobial sepsis. *PLoS ONE*. 2016;11(3):e0151088.
294. Macfarlane WM. Demystified ... transcription. *Mol Pathol*. 2000;53 (1):1-7.
295. Yamane T, Ito C, Washino A, Isono K, Yamazaki H. Repression of primitive erythroid program is critical for the initiation of multi-lineage hematopoiesis in mouse development. *J Cell Physiol*. 2017;232 (2):323-330.
296. McIntyre MK, Clifford JL, Maani CV, Burmeister DM. Progress of clinical practice on the management of burn-associated pain: lessons from animal models. *Burns*. 2016;42(6):1161-1172.
297. Seok J, Warren HS, Cuenca AG, et al. Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc Natl Acad Sci USA*. 2013;110(9):3507-3512.
298. Osuchowski MF, Remick DG, Lederer JA, et al. Abandon the mouse research ship? Not just yet! *Shock*. 2014;41(6):463-475.
299. Mauffrey C, Cuellar DO 3rd, Pieracci F, et al. Strategies for the management of haemorrhage following pelvic fractures and associated trauma-induced coagulopathy. *Bone Joint J*. 2014;96-B(9):1143-1154.
300. Ivey KN, Srivastava D. MicroRNAs as regulators of differentiation and cell fate decisions. *Cell Stem Cell*. 2010;7(1):36-41.

23 Significance of the Hormonal, Adrenal, and Sympathetic Responses to Burn Injury

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Introduction

The endocrine system is central to coordinating the systemic response to burn trauma (Table 23.1). Pathological and compensatory changes are seen in the hypothalamic-pituitary-adrenal (HPA) axis, thyroid, pancreatic, and gonadal hormonal secretions. These changes act in concert with the humoral effects of cytokines and immunological mediators discussed in the chapters on burn edema (Chapter 8) and multisystem organ failure (Chapter 31). They mediate the innate adaptive (stress) response critical to survival in patients, particularly those who recover sans medical treatment. However in patients receiving medical treatment, they often prove maladaptive. Understanding these fundamental responses is critical to the appropriate application of critical care to burned and traumatized patients.

Normal Hypothalamic-Pituitary-Adrenal Axis

The physiologic response of the HPA axis begins with the hypothalamic release of corticotrophin-releasing hormone (CRH) into the hypophyseal portal system, which mediates the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary. This, in turn, stimulates the synthesis and release of cortisol from the adrenal cortex. The situation is more complex because the hypothalamus's afferent and efferent connections are numerous and diverse in physiological effect. The hypothalamus is the fountainhead of the autonomic nervous system, being its most rostral component. Hypothalamic nuclei originate central outflow, primarily via the dorsal longitudinal fasciculus, to numerous caudal central autonomic centers (pain modulation, heart rate, respiration, blood pressure, salivation, and the dorsal motor nucleus of the vagus) and to the intermediolateral cell column of the thoracic cord, which includes sympathetic nervous system (SNS) afferents to the adrenal glands. Hypothalamic stimulation thus initiates the release of epinephrine and norepinephrine from the chromaffin cells of the adrenal medulla, which essentially are modified postsynaptic neurons. The action of these hormones and neurotransmitters is traditionally thought to facilitate adaptation to changing conditions. As the terminal signal transducer of the global stress response, the adrenal glands function as two distinct parts: the cortex that produces corticosteroids and the medulla that secretes catecholamines. Both are critical to orchestrating the systemic "storms" required to survive a massive injury.

The cellular and biochemical pathways through which catecholamines work these organism-level alterations are an area of active study. We will discuss the pathological alterations in these systems and how they relate to modern critical care and the remainder of the endocrine response.

Strong Sympathetic Activation Following Burn Trauma

The catecholamine surge following burn trauma was delineated in landmark papers in 1957 demonstrating marked elevations in 24-h urine levels of norepinephrine and epinephrine proportional to burn size, highest in the first 3 days and remaining elevated for weeks.[1,2] Herndon et al. repeated these studies, finding sustained elevation in urinary epinephrine and norepinephrine levels past 35 weeks in pediatric burn patients.[3,4] Jeschke et al. subsequently demonstrated that cortisol, catecholamines, and hypermetabolism are significantly elevated up to 3 years after severe burn injury.[5] In light of the decades of evidence for sympathetic activation following thermal injury, it is critical to understand the resultant physiologic effects.

CARDIOVASCULAR RESPONSE

The chapters on multisystem organ failure and shock describe the physiology of the "ebb" phase from distributive shock and myocardial depression in which cardiac function is depressed. By 48 h post-burn the myocardium becomes hyperdynamic in a β-adrenergic–mediated manner transitioning to the "flow phase."[4,6] Even small burns are associated with significant changes in cardiac function and long-term pathologic changes.[7] One sympathetic reflex arc begins when hypotension stimulates baroreceptor (carotid sinus and aortic arch) afferent nerve activity, with resultant increases in efferent sympathetic outflow. This sympathetic signal for peripheral vasoconstriction and consequent increase in peripheral vascular resistance is mediated in part by the nerve-stimulated release of norepinephrine. Angiotensin II (AII) and arginine vasopressin (AVP) also act to

Table 23.1 Influence of Catecholamines on Cardiovascular, Metabolic, and Immune Response to Thermal Injury

Physiologic Variable	Sympathetic-Mediated Change Following Burn Injury
Resting metabolic rate	Increase[238] Increase[29] Increase[25] Increase (in vitro)[171]
Proteolysis	No change (urea production)[30] No change (protein oxidation)[238] Decrease[39]
Glucose production and oxidation	Decrease secondary to increase in lipid catabolism[29,239] No change[238]
Glycogenolysis	Increase (indirect evidence via cAMP)[240]
Gluconeogenesis	Increase (indirect evidence via cAMP)[240]
Lipolysis	Increase[30] Increase[238] Increase[29] Increase[32]
Cardiac output	Increase[29] Increase[30]
Peripheral vascular resistance	Unknown
Heart rate	Increase[39] Increase[30]
T-cell number and function	Unknown
B-cell number and function	Unknown
Neutrophil number and function	Decrease[71]
Monocyte number and function	Increase (indirect; clonogenic potential)[241] Increase (indirect; clonogenic potential)[242] Increase[71,243]

Citation of studies from the current literature suggesting that sympathetic activation is involved in changing the listed physiologic variables following thermal injury.

increase vascular tone.[8,9] Additionally a complex interplay of AII and catecholamines further modulates vascular tone.[10] Concurrently AVP has been shown to reversibly depress myocardial function in the isolated heart. AVP and catecholamine overstimulation may thus contribute to myocardial depression following burn injury early in the compensation of the "ebb phase."[11,12]

As the heart transitions to the "flow phase" within 48 h after insult, sympathetic outflow is likely an important driver in maintaining supranormal cardiac function during recovery from thermal injury. In a group of burned patients undergoing visceral blood flow and metabolic measurements, the average cardiac index was 8.2 +/−0.5 L/m^2 min.[13] In the same study, liver and kidney metabolic and blood flow measurements were also conducted, and all were found to be elevated. These data allude to a supraphysiologic circulatory need requisite for recovery from severe burn injury. Guillory and Finnerty reviewed the menagerie of animal studies demonstrating the centrality of β-receptor dysfunction in mediating this cardiac pathophysiology and have given mechanistic insight into the efficacy of modern burn therapy with β-blockade.[6]

The sympathetic surge continues long after volume status is restored and baroreceptor signaling ends. Despite elevated levels of circulating norepinephrine and epinephrine, there is a paradoxical decreased peripheral vascular resistance during the hyperdynamic "flow" phase. Accompanying reduced cardiac afterload is increased cardiac preload and thus increased cardiac output. There is abundant evidence that mediators of neural, humoral, and metabolic origins are involved in driving the decrease in vascular resistance following thermal injury. The significance of β_2-adrenergic receptors in vasodilation has been demonstrated using knockout mice,[14] thus pointing to the significance of epinephrine. The situation is complicated in the burn patient by the increase in nerve-stimulated release of norepinephrine, which can potentially mediate vasoconstriction. However evidence exists that the local distribution of adrenergic receptors mediating either vasodilation or vasoconstriction will determine the effect of circulating epinephrine and nerve-stimulated norepinephrine release on peripheral vascular resistance.[15] Blood flow regulation to the burned extremity remains intact: even in legs with 85% surface burned, increasing the surface temperature causes increases in blood flow comparable to unburned legs.[16] In addition, increased tissue metabolism has been recognized to produce metabolites that mediate increased blood flow by reducing vascular resistance.[17] With markedly increased metabolism in major burns, these metabolites, along with catecholamines, nitric oxide (NO),[18] and atrial natriuretic peptide,[9] may contribute to decreased vascular resistance.[19]

When decreases in peripheral vascular resistance compromise tissue perfusion and lead to end-organ damage (e.g., the urinary granular casts of tubular necrosis), pressor agents may be required to maintain adequate tissue perfusion in the setting of adequate volume status. Epinephrine is the drug of choice, providing optimal vasoconstrictor and inotropic effects. In cases of resuscitated burn shock, the additional inotropic support of epinephrine is essential to maintain tissue perfusion without overly constricting the cutaneous vasculature needed to heal burn injuries. For example dobutamine, a β-adrenergic inodilator, is an important inotrope in select burn patients, and the novel non-adrenergic inodilator, levosimendan, may find utility in treating cardiac failure in burn patients.[20]

CATECHOLAMINE RESISTANCE

Acidosis is the most common cause of catecholamine resistance. Macarthur et al.[21] described inactivation of catecholamines by superoxide anions contributing to the observed hypotension of septic shock in rat models. They found treatment with superoxide dismutase not only abrogated endotoxin-induced hypotension in anesthetized rats, but also elevated circulating levels of catecholamines. These findings suggest that compensatory sympathetic activation, which counteracts hypotension during conditions of sepsis, may be blunted by inactivation of catecholamines

by superoxides in the extracellular milieu. In a conscious rat model of sepsis, superoxide inhibition enhanced plasma levels of catecholamines, increased blood pressure, and improved survival.[22] They also found that NO reduces the biologic activity of norepinephrine without altering nerve-stimulated release.[23] Case et al. showed increased superoxide release for T cells in a norepinephrine-stimulated manner.[24] These findings may provide insight into the clinical observations involving critically ill patients in which pharmacologic norepinephrine administration is ineffective in correcting hypotension.

CATECHOLAMINES AND HYPERMETABOLISM

Despite myriad factors reported to promote or inhibit the development of the post-burn hypermetabolic state, many investigators have demonstrated sympathetic catecholamines (norepinephrine more so than epinephrine) to be the effector limb of the transition to and maintenance of this hypermetabolic state.[25] Herndon et al. clearly showed this using a 50% full-thickness scald burn rodent model, with groups pretreated with thyroidectomy, adrenalectomy (+/− dexamethasone replacement), and reserpine depletion of catecholamines.[26] Adrenalectomy or reserpine blunted more than half of the hypermetabolic response. Wilmore et al. demonstrated catecholamines to be the mediator of the human hypermetabolic response to thermal injury.[25] Several key findings were generated by that study: the β-adrenergic (but not α-adrenergic) blockade reduced metabolic rate, pulse, blood pressure, and free fatty acids. Additionally the investigators documented the "nonliving" response to thermal injury: poikilothermia. They noted that when burned patients were placed in cooler environments (21°C), their metabolic rates generally increased, with urinary catecholamine excretions increasing in parallel, excepting four nonsurvivors who showed less catecholamine elaboration, became hypothermic, and did not elevate their metabolic rates. The reason these patients failed to develop sufficient hypermetabolic responses to permit survival remains only partially understood. Burned patients consistently selected a higher room temperature (~30°C) and also had skin and core temperature increases of 1.7°C –2°C above controls.[27] Elevations in energy requirements could be partially modulated through adjustments in environmental temperature. Burn patients treated in warm environments of 32°C exhibited reduced metabolic rates compared to those treated at 25°C, although both groups remained hypermetabolic. After injury, and concurrent with an elevated hypothalamic temperature set-point and cardiac index, qualitative and quantitative changes occur in the flow of biological energy and mass (substrate) through the patient.[28]

Experimental studies of Wolfe and Durkot[29] suggest that the adrenergic drive following burn facilitates lipolysis, influencing fatty acid oxidation. The importance of adrenergic drive on lipid metabolism in burn was shown in human patients through the use of stable isotopic studies as well as adrenergic antagonists.[30–32] The profile of the plasma lipids is dramatically changed as well.[33] These results indicate that not only is lipolysis following thermal injury mediated by β_2-adrenergic receptors, but also suggest increased intracellular and extracellular triglyceride–fatty acid cycling, with resultant heat production. Elijah et al. further elucidated the effects of peroxisome proliferator activated receptor (PPAR) on lipolysis and hyperglycemia in the severely burned.[34]

Wilmore developed experimental paradigms suggesting the role of catecholamines in mediating the hypermetabolic response to thermal injury.[25] Findings included a positive correlation of increased plasma catecholamines and whole-body oxygen consumption following thermal injury,[25] as well as demonstrating that adrenergic blockade lowers the burn-induced increase in metabolic rate and cardiac output to control levels in animal models.[25,29]

Experimental findings in rats suggested that the adrenal medulla, while essential for high rates of heat production following thermal injury, is not the primary driver of the hypermetabolic response.[35,36] Animals with hypothalamic lesions did not increase metabolism following thermal injury and were chronically hypothermic,[37] not unlike experiments in which the adrenal medulla was removed prior to thermal injury.[35] These results are consistent with clinical observations of burn patients in whom reductions in heat loss were achieved with occlusive dressings and for whom elevated environmental temperatures demonstrate partial reductions in metabolic rate and catecholamine secretion.[38]

β-BLOCKADE

Building on findings that catecholamines drive post-burn hypermetabolism, Herndon et al.[39,40] demonstrated that pediatric patients could be treated with the β-adrenergic blocker propranolol to successfully reduce metabolic rate without compromising cardiovascular function. In a more recent study by this group,[41] β-adrenergic blockade in pediatric patients for 4 weeks during recovery from severe burns reduced the elevation in resting energy expenditure and reversed the reduction in net muscle–protein balance by 82%. Such treatment also prevented fatty liver and loss in fat-free whole-body mass and provided for a more efficacious recovery in these children.[42,43] Subsequent studies built on these findings demonstrated improvements when dosing was continued for 1 year post-burn.[44] Recent animal studies have further established a cyclooxygenase-2 role in inflammatory proliferation in the liver.[45] Downregulation of fructose-1,6-bisphosphatase-2 mRNA has been observed in muscle tissue following treatment with propranolol; this enzyme may play a role in gluconeogenesis, although the metabolic significance of this tissue-specific transcriptional alteration remains to be determined.[46] Propranolol leaves α-adrenergic receptors unopposed, resulting in peripheral vasoconstriction and increasing vascular resistance. Reduced blood loss has been observed, with postoperative hematocrit 5–7% higher with propranolol.[47] The exercise-induced enhancements in muscle mass, strength, and VO_2 peak were not impaired by propranolol; instead, aerobic response to exercise was improved in massively burned children.[48] β-Blockade in nonburned septic patients has become an area of active research and, based on these findings in burned patients, demonstrates value for some patients, although the overall indications and patient selection have yet to be fully elucidated.[49,50]

SYMPATHETIC INFLUENCES ON IMMUNE FUNCTION

New data have clarified the interconnections between the immune and sympathetic nervous systems and are well reviewed by Pedro et al.[51] Understanding these interactions may be important to comprehending the implications of our pharmacologic treatments with β-adrenergic antagonists and agonists on immune function.

Immunohistochemical staining demonstrates substantial sympathetic innervation of all primary (thymus and bone marrow) and secondary (spleen and lymph nodes) lymphoid organs.[52–55] Innervation has been shown to reach immune cell compartments of the spleen (the white pulp), periarterial lymphoid sheath, marginal zone, and marginal sinus areas, as well as the splenic capsule and trabeculae.[56–59] Sympathetic nerve terminals have been described in direct apposition to T cells, interdigitating dendritic cells, and B cells.[60]

Immune modulation by adrenergic signaling was recently reviewed by Sanders.[61] Lymphocytes (including activated and resting B cells, naïve $CD4^+$ T cells, T-helper [T_H1] cell clones, and newly generated T_H1 cells) express β-adrenergic receptors, but they are not expressed in newly generated T_H2 cells.[62–64] Furthermore there is significant evidence that norepinephrine can modulate the function of $CD4^+$ T cells, which in turn can modulate antibody production of B cells.[65] Sympathetic neurons suppress $CD8^+$ T-cell receptor response and cytotoxic activity.[66] In addition, norepinephrine can directly influence B-cell antibody production depending on the time of exposure following activation.[67] The physiologic importance of these in vitro findings is supported by a series of in vivo experiments involving severe combined immunodeficient (*scid*) mice depleted of norepinephrine prior to reconstitution with antigen-specific T_H2 and B cells. These experiments demonstrate that norepinephrine is necessary to maintain a normal level of antibody production in vivo.[62] Furthermore other whole-animal experiments also involving *scid* mice provide evidence that the immune response itself stimulates the release of norepinephrine from adrenergic nerve terminals in bone marrow and the spleen, which in turn can influence antibody production by B cells.[68] β-Blockade in 20 pediatric burn patients significantly reduced serum tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β).[69] The parasympathetic system further conditions the immunomodulatory role of the SNS. Recently it was shown that the vagal synapses trigger acetylcholine release from memory T cells, in turn reducing TNF-α through α-7-nicotinic acetylcholine receptor.[70] These findings suggest the potential of sympathetic/parasympathetic activation in mediating immune responses.

In animal models, blocking β-adrenergic receptors soon after injury partially restored the lipopolysaccharide (LPS)-stimulated TNF-α secretory potential of circulating monocytes lost during the course of burn injury and sepsis.[71] Apart from adrenergic inhibition of LPS-stimulated TNF-α release in isolated macrophages,[72–75] similar inhibition of LPS-stimulated TNF-α production has also been demonstrated in human mast cells,[76] microglial cells,[77] astrocytes,[78] and cytotoxic T lymphocytes.[79] In contrast to adrenergic stimulation of TNF-α release, experiments with isolated atria,[80,81] myenteric plexus,[82] and brain tissue[83] have proved that TNF-α can negatively affect the release of norepinephrine.

Although the precise mechanisms of the negative modulation of proinflammatory cytokines by catecholamines are poorly understood, it may be achieved through the ability of catecholamines to induce the antiinflammatory cytokine IL-10.[84–87] Whole-animal studies involving assessment of circulating levels of IL-10[87] as well as studies of human whole blood and mononuclear cells stimulated with LPS in the presence of adrenergic agonists[84,86,88] support this premise. Immunomodulatory effects were further elucidated by Takenaka et al. demonstrating the effects on T-cell differentiation to CD4+ via a dendritic cell-mediated pathway.[89] Additionally experimental neurotrauma resulted in increased IL-10 consequent to endogenous adrenergic stimulation in the absence of LPS or other evidence of infectious challenge.[90]

SYMPATHETIC RESPONSE TO SEPSIS

Burn injury is commonly complicated by transient bacteremia, infection, and sepsis (see chapters on Infection [Chapter 12] and Multisystem Organ Failure [Chapter 31]). Infection causes a marked sympathetic response proportional to the degree of insult[91] in which there are simultaneous and opposing forces of hyperinflammation versus immunosuppression. Sepsis is accompanied by an enormous catecholamine surge leading to changes in cardiovascular output, immunomodulatory effects, and catabolism. Propranolol has been shown to attenuate those changes.[92] The use of an adrenergic blockade as an immunomodulator has found further utility in other traumatic injuries.[93] Furthermore animal models of septic peritonitis suggest that initial sympathetic activation, as measured by elevated levels of plasma norepinephrine and greater norepinephrine turnover, persists for many hours.[94,95]

Collectively these data clearly support a complex trophic interconnection between the SNS and immune system. Burn- and sepsis-induced sympathetic responses exert significant influence on bone marrow cellular events. Evidence for norepinephrine regulation of myelopoiesis in experimental thermal injury with sepsis is detailed in Chapter 22 on hematology.[212]

Role of Thyroid Function

An early rat study showed that thyroidectomy did not alter the post-burn increase in metabolism, although adrenalectomy or catecholamine depletion with reserpine did reduce post-burn metabolic rates.[26] Subsequent human studies demonstrated generally normal total triiodothyronine (T3) and thyroxine (T4), free T3 and T4, and thyroid-stimulating hormone (TSH) levels in uncomplicated burn patients. However in those patients with infection or sepsis, decreased amounts of free T4 and T3 were observed.[96] T3 replacement did not alter metabolic rate or mortality post burn[97] but may have decreased circulating levels of norepinephrine and epinephrine. These and other studies suggest that the hypermetabolic response to burn is independent of thyroid hormones.[98] More importantly, these data, in

conjunction with more recent work by Senel et al., allude to a post-burn shift in metabolic control away from thyroid signaling in favor of other mediators.[99]

SEX STEROIDS FOLLOWING BURN TRAUMA

Androgens

Release of C_{19} Steroids. In the normal physiologic state, dehydroepiandrosterone sulfate (DHEAS), a weak androgen, is the major secretory product of the adrenal cortex. In burn patients, there is an increase in cortisol secretion and a distinct decrease in serum DHEAS levels[100] owing to a reduction in synthesis.[101] Testosterone and androstenedione levels decrease abruptly. In burn patients, subnormal testosterone levels persist for 3–18 months post burn, whereas cortisol levels normalize earlier.[101] The decrease in testosterone secretion may be the direct effect of excessive cortisol levels on the testes.[102,103] Wilmore, Long, Mason, and Pruitt wrote a masterful review of the coordinated hypothalamic response to injury in 1976: "Stress in Surgical Patients as a Neurophysiological Reflex Response."[104]

Burned men exhibit hypogonadism and Leydig cell failure following thermal injury, resulting in depressed testosterone levels. Plymate et al. measured levels of sex hormones (e.g., sex hormone-binding globulin [SHBG] and luteinizing hormone [LH]) and thyroid hormones in the weeks following burn injury. They showed an increase in estradiol levels and a concomitant decrease in the secretion of bioactive LH following burn injury, suggestive of an alteration in hypothalamic control of the gonadal axis leading to suppression of testosterone release. SHBG also exhibited significant changes, with an initial decrease and subsequent rise in concentration as compared to controls. This increase in SHBG results in a further suppression of testosterone by reducing the amounts of the unbound hormone. The levels of SHBG strongly correlated with levels of T3 and free T3 as well. This study helped elucidate the complex relationships of alterations in hypothalamic, thalamic, and gonadal regulation in the burned male.[105] Taken together, these studies allude to a pervasive shift from normal hypothalamic function to a post-injury "mobilization" that remains but partly understood.

It appears that synthesis of C_{19} steroids by the adrenals and testes is compromised as a result of enhanced production of C_{21} steroids, such as cortisol. Aldosterone levels are also subnormal, despite elevated plasma renin activity. This suggests a shift in pregnenolone metabolism away from mineralocorticoid and adrenal androgen pathways toward the glucocorticoid pathway.[100] DHEAS also has a profound influence on the immune response, and a role for DHEAS as a modulator of the immune response is now well established.[106–109] Given that immunostimulatory properties of T_H1 cells are low during severe illness,[100] DHEAS deficiency may be a contributing factor to the immune suppression in burn patients. In vitro treatment of human T cells with DHEAS increases IL-2 production (which is required for clonal expansion) and IL-2 mRNA synthesis.[109] Interestingly this effect was seen only in $CD4^+CD8^-$ and not in $CD4^-CD8^+$ cells. DHEAS-treated cells were also able to mediate a more potent cytotoxic effect than were untreated cells.

Under conditions of severe physical stress and chronic illness, dopamine levels have been shown to be elevated;[110,111] consequently dopamine may also influence immune status and adrenal steroid secretion in burn patients. Exogenous dopamine is often used in the treatment of critically ill patients because of its vasopressor, renal vasodilator, and cardiac inotropic properties. Povoa et al. reviewed vasopressor use in septic shock and found a need for a multimodal selection of these agents.[112] However several other studies indicate that dopamine treatment may undermine an already depressed immune system. This effect appears to act via the suppression of prolactin release from the anterior pituitary. Dopamine suppresses serum prolactin and DHEAS levels but not cortisol levels.[113,114] In vitro, prolactin has a synergistic effect on ACTH-induced DHEAS secretion by human adrenal cells.[115] Thus it is possible that the dopamine-induced suppression of prolactin is responsible for lowering DHEAS levels and hence suppression of the T-cell proliferative response. The in vitro proliferative

Table 23.2 Influence of Glucocorticoids on Metabolic and Immune Response to Thermal Injury

Physiologic Variable	Glucocorticoid-Mediated Change Following Burn Injury
Resting energy expenditure	Increased[152,176,179]
Oxygen consumption	Increased[244,245]
Primary fuel	Lipids, glucose[190]
Proteolysis	Increased in skeletal muscle[160,161,163,164,246]
Acute-phase protein synthesis	Increased[133,247,248]
Nitrogen excretion	Increased[244]
Glycogenolysis	Increased via effect on glucagon[157,158]
Gluconeogenesis	Increased[153,154,247]
Lipolysis	Increased[191]
Ketone body formation	Normal[193]
Triglyceride level	Increased[193,247]
Thymic changes T-cell population T-cell proliferation B-cell population	Involution[218] Decreased[217,249] Inhibited[219,220,248] Not conclusive from current data
Neutrophil population —chemotaxis —demargination —bactericidal activity	Increased[223,249,250] Suppressed[223] Increased[223,226] Suppressed[228]
Monocyte population	Increased transiently with corticosteroids but decreased in burn patients[250–252]
—chemotaxis	Suppressed[224]
—bactericidal activity	Suppressed[224,227]
Bone formation	Decreased[200]

Citation of studies from the current literature suggesting that glucocorticoid release is involved in changing the listed physiologic variables following thermal injury.

response of T cells from patients on dopamine therapy is diminished,[113] and cells treated with DHEAS mediate a more potent T-cell cytotoxic effect.[109]

Extensive studies and clinical experiences were undertaken over the past decade with androgen supplementation using oxandrolone. Reeves and Finnerty detailed the 5-year outcomes of long-term oxandrolone treatments following a 24-month administration in severely burned children. They found significantly increased bone mineral content, greater height velocity, reduced cardiac work, and augmented muscle strength.[116] This is described in greater detail in the chapter on hypermetabolism (Chapter 30). Overall there is a hypoandrogeneric state post burn, and supplementation with the anabolic steroid oxandrolone is effective at both ameliorating hypermetabolism as well as shifting the patient toward anabolism.

Estrogens

The impact of xenoestrogens on mortality in burned patients has been investigated. Found in insecticides used from the 1950s to the 1970s, xenoestrogens are compounds that can act as estradiol receptor agonists or antagonists and that are stored in fat. During the hypermetabolic state following thermal injury, the xenoestrogens are released along with mobilized lipids from these fat stores. In older burn patients who were more likely to have higher concentrations of these compounds in their bodies, it was discovered that nonsurvivors had significantly increased levels of two xenoestrogens, heptachlor epoxide and oxychlordane. It was suggested that these compounds may induce the inactivation of estradiol, progesterone, testosterone, and glucocorticoids via the induction of steroid hydroxylases, as well as antagonizing estradiol receptors, which may result in decreased inflammation and cytokine release.[117]

ADRENAL CORTICAL STEROIDS FOLLOWING BURN TRAUMA

Adrenocortical response is critical to coordinating the systemic response to thermal injury. The glucocorticoid surge following burn injury has long been measured by both serum and urinary excretion markers. Regulation of glucocorticoid secretion is complex, with multiple determinants of the adrenal cortex secretion of cortisol, including pituitary ACTH, but also afferent neural control and hyperthermia, which blunts the adrenal response to ACTH. Furthermore the usual circadian rhythm of cortisol secretion is dampened after burn injury. In 1982, Vaughn et al. showed elevated circulating and urinary cortisol, with a weak correlation to the level of ACTH. Superior correlations were noted between cortisol and total body surface area (TBSA), metabolic rate, and average body temperature. These observations in burned patients indicate that adrenal hypersecretion of cortisol is in response to temperature, circulating mediators of hypermetabolism, direct adrenal innervation, and a decrease in adrenal cortex responsiveness to ACTH. As a result, the authors concluded that cortisol may play a secondary role in permitting and promoting the changes seen in post-injury hypermetabolism.[118] On this basis, they attributed post-injury metabolic and thermal changes primarily to sympathetic tone and circulating catecholamines (norepinephrine and epinephrine).

Danner and colleagues carefully mapped the HPA axis response to a massive septic insult in their lethal canine pneumonia model as they attempted to define the "critical illness-related corticosteroid insufficiency" (CIRCI). They found a massive surge in total, bound, and free serum cortisol and in ACTH. Additionally they determined that ACTH failed to promote a further increase in cortisol and that dexamethasone did not suppress cortisol, possibly because the adrenals were already maximally stimulated. Significantly in sepsis-surviving animals, the HPA axis recovered to normal levels whereas ACTH and dexamethasone responsiveness recovered by 10 h compared to nonsurvivors. In contrast, the mineralocorticoid response with hyperaldosteronism remained past 72 h and did not regain dexamethasone suppression. Thus mineralocorticoids are ACTH-independent in the setting of sepsis. These data support the adrenal exhaustion hypothesis.[119]

In a postmortem study of adrenal glands of ICU patients, it was found that the adrenocortical structure was disrupted following critical illness. These patients tended to have adrenal glands that weighed less than controls, with significantly less protein content and greater fluid content. There was also considerable downregulation of ACTH-regulated genes.[120]

Elevated plasma-cortisol levels have been shown during critical illness, especially during an episode of systemic inflammatory response syndrome (SIRS). However cortisol production during the day in patients with SIRS, although elevated, is less than doubled. ACTH is suppressed in these patients, implying a non-ACTH-driven response. It has been demonstrated that during critical illness clearance of plasma cortisol is significantly reduced, playing a significant role in the hypercortisolism of the critically ill stress response.[120] Other investigators determined in the setting of septic shock that only serial hormonal measurements and provocative testing were useful for HPA axis function assessment. They further identified high aldosterone levels in a population with poor outcomes from sepsis.[119]

Norbury et al. followed urinary cortisol levels in 212 severely burned children, finding three- to fivefold increases in cortisol excretion up to 100 days post-burn. Urinary norepinephrine levels were significantly increased up to 20 days,[4] as shown in Fig. 23.1. Hypercortisolemia has been suggested as a driver of whole-body catabolism following severe burn. To test this hypothesis, Jeschke et al. blocked cortisol production with ketoconazole in 55 severely burned children. They found normalization of the eightfold elevation in urine cortisol in the treatment group. Counterintuitively, no change was seen in inflammatory response, acute-phase proteins, body composition, muscle protein breakdown or synthesis, or organ function. Their data suggest that post-burn hypercortisolemia does not play a central role in the catabolic response.[121]

Jeschke and Herndon characterized the long-term inflammatory and acute-phase responses in 977 pediatric burn patients with greater than 30% TBSA with 24-h urinary excretion. They found significant elevations of cortisol, catecholamines, cytokines, and acute-phase proteins for up to 3 years, as seen in Fig. 23.2. They also observed insulin resistance, increased fracture risk, hepatomegaly, increased cardiac output and cardiac dysfunction, and impaired strength over the same period.[4,5]

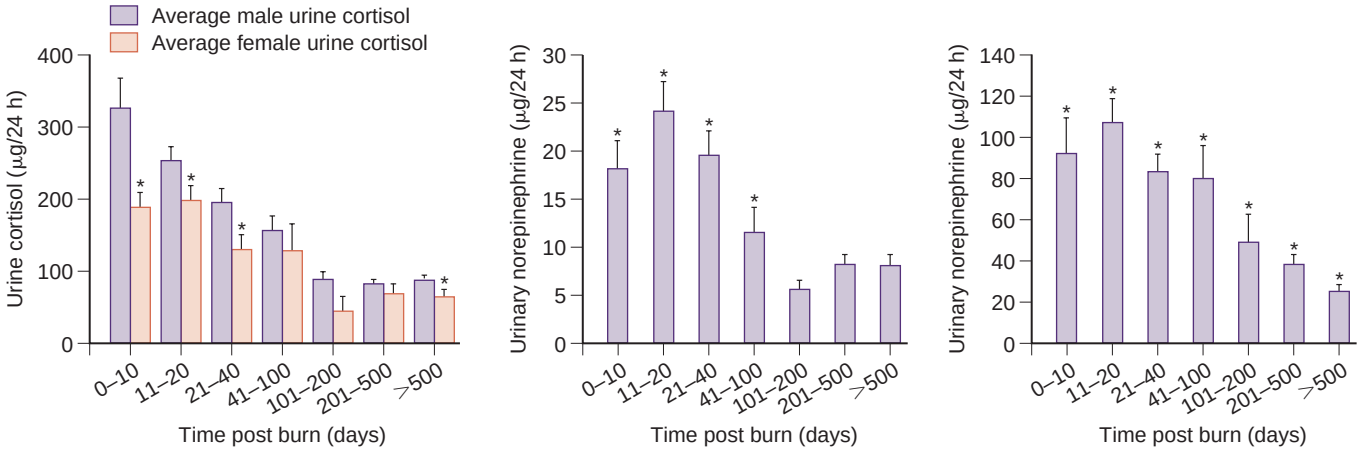

Fig. 23.1 Urinary cortisol and catecholamine excretion after burn injury in children. (From Norbury WB, Herndon DN, Branski LK, Chinkes DL, Jeschke MG. Urinary cortisol and catecholamine excretion after burn injury in children. *J Clin Endocrinol Metab*. Apr 2008;93(4):1270–1275.)

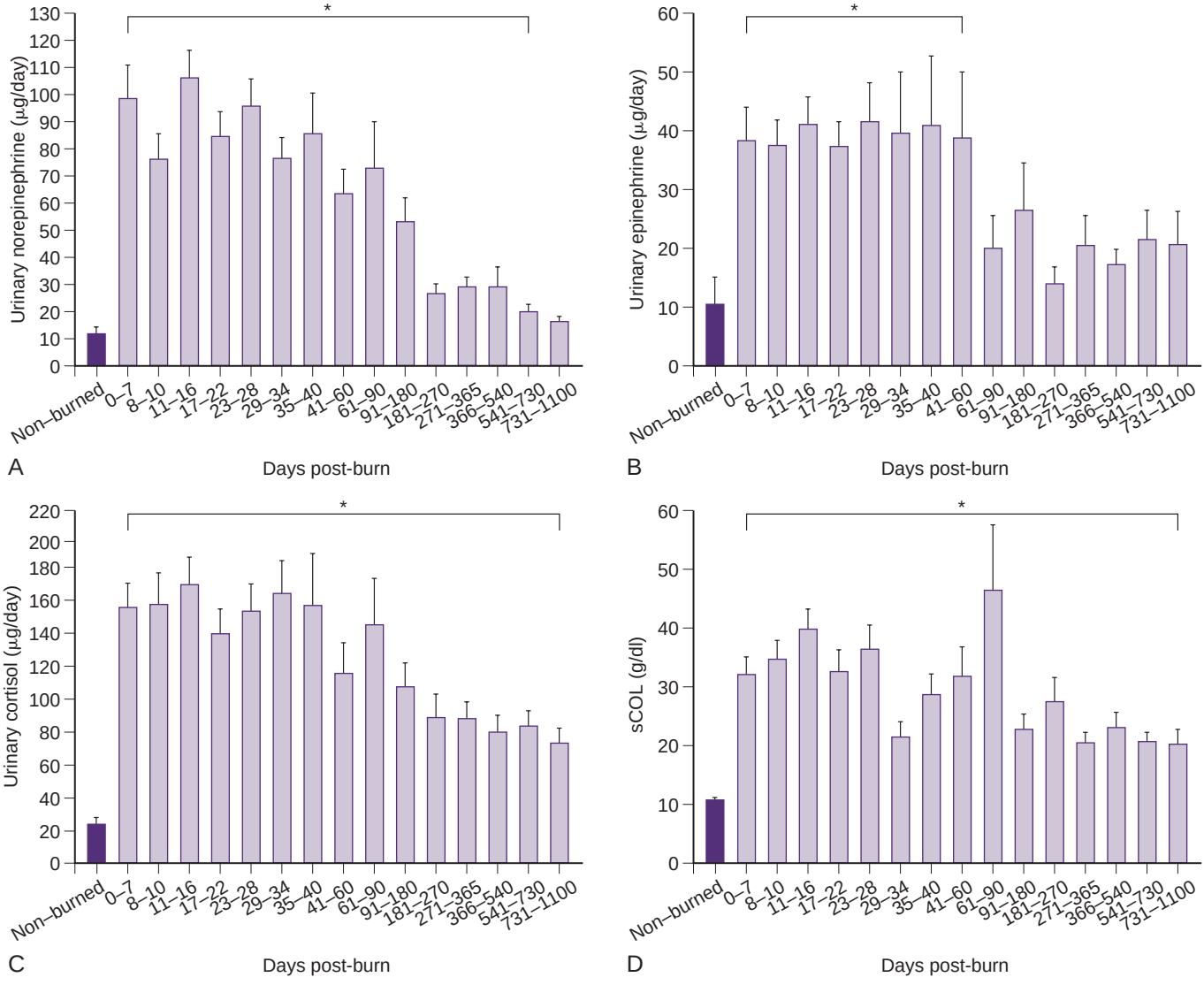

Fig. 23.2 Long-term persistence of the pathophysiologic response to severe burn injury. (From Jeschke MG, Gauglitz GG, Kulp GA, et al. Long-term persistence of the pathophysiologic response to severe burn injury. *PLoS One* 2011;6(7):e21245.)

Free versus Total Cortisol

Glucocorticoids circulate in the body bound to cortisol-binding globulin (CBG), such as transcortin, as an inactive complex. Only 1–10% of total plasma cortisol circulates unbound and is responsible for the biological activity of glucocorticoids. Free plasma cortisol is a surrogate for the difficult-to-measure tissue cortisol.[122,123] Burn injury shifts the equilibrium between unbound and total cortisol toward an elevation in the unbound fraction.[124] Serum CBG and CBG-binding capacity are low in burn injury, severe infection, and septic shock.[124–126] In burn patients, CBG levels have been shown to decrease markedly, with the lowest values occurring 48 h after injury.[127] Even a minor burn, such as 3% TBSA, results in a reduction of serum CBG levels by 30%,[128] which return to normal levels 1–2 weeks later. The net effect of the decrease in CBG levels following thermal injury may not only result in increased levels of free cortisol but also in the amount of excreted cortisol, which is reflected in high urinary corticosteroid levels. The urinary cortisol concentration was observed to increase progressively with burn size, with the highest levels in the 60–99% TBSA burn groups.[129] Additional explanations for increased levels of corticosteroids in burn patients may be due to the direct inhibitory effect of corticosteroids on the biosynthesis of CBG.[130–132] Furthermore IL-6 elevation associated with massive burns has also been implicated in reducing CBG synthesis.[133]

Evidence exists suggesting that cortisol elevation with corresponding decreased ACTH may be driven by endothelin or atrial natriuretic peptide/hormone (ANP/H). Vermes et al.[134] demonstrated significant elevation in both plasma endothelin and ANP levels for 8 days following hospitalization in severely ill patients with sepsis or trauma. Fittingly endothelin has been shown to be a modulator of the sympathetic response.[135] In addition, infusion of ANP in humans has been demonstrated to block CRH-stimulated secretion of ACTH and cortisol,[136] while endothelin-1 and endothelin-3 enhance secretion of steroid hormones from the adrenal cortex.[137] However endothelin-3 has been reported to elevate ACTH and corticosterone levels in rats,[138] whereas endothelin-1 results in elevated ACTH in humans.[139] Based on this, Vermes et al.[134] suggest that endothelin may be responsible for stimulating steroid secretion, whereas ANP's action on the HPA axis may suppress ACTH secretion, thereby explaining the paradoxical increase in cortisol with concomitant low ACTH levels in severely stressed patients.

By precisely measuring cortisol, Cohen et al. found no significant correlation between total plasma, free plasma, and tissue microdialysis cortisol levels. Tissue microdialysis cortisol levels were significantly increased in burned patients compared with healthy controls. Furthermore via subcutaneous microdialysis of cortisol levels in burned and non-burned tissue of severely burned patients, they discerned no significant difference in local cortisol concentrations. This indicates that local microenvironmental changes in burned tissue, such as more cortisol cleaved from CBG by the neutrophil elastase, failed to significantly affect local cortisol levels. They concluded that free cortisol demonstrated a better correlation with TBSA than total cortisol.[140] Given the sensitivity of cortisol to pain and stress as well as diurnal variations, Brown et al. advocate the utilization of salivary α-amylase as a surrogate in the setting of outpatient investigations.[141]

SUBSTRATE CYCLING

Influence on Metabolic Pathways

Elevated energy expenditure and hyperglycemia are hallmarks of thermal injury. The heavy demand for energy stems from the increase in essential functions, such as the synthesis of proteins required for wound healing, the synthesis of acute-phase proteins, and inflammatory mediators. The increase in substrate cycling is partly responsible for the elevation in resting energy expenditure in burn patients. This occurs when enzymes catalyzing opposing reactions of the same pathway are simultaneously active. For example, in the conversion of glucose to glucose-6-phosphate and back to glucose, the demand for energy increases to resynthesize adenosine triphosphate (ATP) used in this and similar reactions. In burn patients, the rate of glucose production and glycolysis, as well as of lipolysis and re-esterification of triglycerides, is elevated.[31] This cycling of substrates generates heat through the hydrolysis of high-energy phosphate bonds in ATP, thereby contributing to thermogenesis as well as increased energy requirements in burn patients.[142] Concurrently muscle mitochondrial decoupling and fat browning adaptions occur to increase thermogenic capacity.

Hormonal Determinants of Glucose Utilization

In 1986, glucose and alanine fluxes were studied in adult burn patients with stable isotope tracer infusions, somatostatin infusion (suppressing insulin and glucagon), and insulin + glucose replacement (isolated glucagon suppression). Insulin and glucagon levels were both significantly elevated above those in unburned individuals. Somatostatin infusion reduced both insulin and glucagon levels and induced a stable decrease in glucose production at 30 min with a progressive decrease in glucose uptake over the course of 30–180 min. When glucagon was selectively reduced via the reinfusion of insulin to restore basal levels in conjunction with glucose infusions to maintain euglycemia, glucose production was suppressed significantly below levels when somatostatin was infused alone, and glucose clearance was restored to pre-infusion levels. This study provided evidence for glucagon control of hepatic glucose production (HGP) in the post-burn state, with basal levels of insulin further suppressing HGP while exerting greater influence to increase (peripheral) glucose uptake. Glucagon reduction (via somatostatin + insulin infusion) did not alter the alanine clearance or flux rates; however suppression of insulin and glucagon (from somatostatin infusion alone) increased the alanine flux rate, consistent with increased peripheral protein catabolism when the insulin signal is diminished. The authors noted prior observations indicating tachyphylactic hepatic gluconeogenesis in response to glucagon. However in the setting of hypercortisolemia (observed in these patients), prolonged HGP in response to glucagon signaling manifests.[143]

A concurrent study of unburned adults differentiated the response to endogenous insulin infusions from the response to a proximate glucose infusion using somatostatin suppression of endogenous insulin and glucagon + insulin replacement to basal levels during the glucose infusion. This study established that glucose infusion (1 and 4 mg/kg per minute), independent of endogenous insulin effect, suppresses endogenous glucose production, stimulates alanine

production, and suppresses urea production.[144] A further analysis of data collected as part of the T3 replacement trial described earlier showed that the metabolic rate increased proportionally with and was independently predicted by plasma glucagon.[145]

In the setting of an adequate, constant nitrogen intake, increasing carbohydrate feeding spared protein catabolism and mitigated negative nitrogen balance, whereas intravenous fat emulsion did not affect nitrogen balance independently.[146,147] These studies indicated the primary determinants for nitrogen excretion were carbohydrate intake and metabolic rate. Nitrogen excretion was minimized when the carbohydrate intake approximated the metabolic rate. Insulin was additively anabolic to carbohydrate intake in further decreasing nitrogen excretion when patients were provided constant and sufficient protein intake.[148]

GLUCOCORTICOIDS FOLLOWING BURN INJURY

In burn patients likely to recover, plasma glucocorticoid levels are moderately elevated or in the upper normal range, can persist beyond a month,[124,149] and return to normal as healing progresses.[150] In contrast, patients with severe thermal injury (90% TBSA) have markedly lower levels of glucocorticoids, suggesting that they are unable to mount an adequate response.[124]

Glucocorticoids and Carbohydrate Metabolism

Glucocorticoids contribute to hyperglycemia by enhancing endogenous production of glucose in the liver.[151–154] Following burn, elevated glucose levels are sustained through gluconeogenesis and impaired glucose utilization. The increased plasma lactate produced by peripheral tissues following burn, as documented by Wolfe et al.,[155] is an essential substrate for gluconeogenesis by the liver. Burn injury causes intrinsic alterations in the liver, which increase the conversion of pyruvate to oxaloacetate at the expense of nontricarboxylic acid cycle sources.[156] Efficient mobilization of glucose from glycogen and skeletal muscle amino acids for gluconeogenesis requires glucagon secretion,[145,157] which is stimulated by glucocorticoids.[145,157,158] Glucocorticoids sustain the action of glucagon and prevent the usual development of tachyphylaxis from high levels of glucagon. In addition to gluconeogenesis, impaired glucose utilization and insulin resistance can also play a role in sustaining high circulating levels of glucose in burn patients.[152]

Glucocorticoids and Protein Metabolism

Protein catabolism is a part of burn hypermetabolism, resulting in negative nitrogen balance. Cuthbertson's[159] landmark studies were the first to suggest the important concept that nitrogen loss is a whole-body rather than a local burn wound response. The increase in proteolysis seen in burn injury is at least partly mediated by glucocorticoids. In humans[160] and in animal models,[161] administration of glucocorticoids enhances muscle proteolysis. Furthermore burn injury-induced muscle proteolysis can be inhibited by a glucocorticoid receptor antagonist.[162] Amino acids mobilized from peripheral tissues are transported to the liver where, unlike in other tissues, cortisol stimulates protein synthesis. The increased hepatic protein synthesis in response to cortisol can drive the new synthesis of gluconeogenic enzymes and acute-phase proteins in response to burn injury.

The complete details of the mechanisms involved in burn-mediated alterations in protein metabolism are unknown. However some information can be gleaned from studies on other states of excessive catabolism. In conditions such as metabolic acidosis, adrenalectomy halts muscle proteolysis and does not increase expression of components of the ubiquitin–proteasome pathway.[163,164] These effects can be reversed by dexamethasone administration. Further support for this premise is provided by in vitro studies, which show that dexamethasone-induced increases in proteolytic degradation in myocytes can be abolished by the glucocorticoid inhibitor RU486.[165] Ding and coworkers[166] suggest that partial inhibition of the ubiquitin–proteasome pathway may be beneficial in enhanced catabolic states. Taken together, these data suggest that interaction of glucocorticoids and the ATP-requiring ubiquitin–proteosome system may play an important role in burn-induced proteolysis.[167–171]

Another aspect of protein catabolism following burn is the generation of gluconeogenic amino acids. Plasma levels of alanine are increased following burn.[172] Nitrogen produced as a result of transaminating alanine to the gluconeogenic intermediate, pyruvate, is subsequently converted into glutamine and then to urea for excretion by the liver. In muscle tissue, alanine aminotransferase (ALT/SGPT) transfers an amino group from glutamine to pyruvate, forming alanine and α-ketoglutarate. Alanine is then dumped into the bloodstream, taken to the liver, and returns to the muscle as glucose (the glucose–alanine cycle). This is one reason why plasma alanine increases after burn. By contrast, in the liver, glutamine enters the mitochondria, and eventually nitrogen is processed via the urea cycle.[173] Glutamine is one of the major participants in the translocation of amino acids from peripheral tissues to the liver for nitrogen excretion. Expression of glutamine synthase is increased to compensate for glutamine depletion in peripheral tissues. Following burn injury, glutamine synthase mRNA is increased first in the lung and later in muscle.[174] Adrenalectomy partially reduces burn-induced glutamine synthase mRNA[174] in a tissue-specific manner, with no such effect in the kidney or liver. There is evidence suggesting that glucocorticoids may augment glutamine synthesis in lung and muscle tissues.[175] Mobilization of protein from peripheral tissues is also indicated by the increase in phenylalanine in the blood of burn patients.[172] Phenylalanine is the only amino acid not degraded by peripheral tissue; hence it accumulates in the circulation when uptake by the liver is compromised.

The hypermetabolic and catabolic states seen in thermal injury remain long after the burn wound completely heals:[152,176–179] reduction in protein catabolism and enhancement of lean body mass were seen only 9–12 months following the initial injury.[177] Therefore the post-burn treatment of growth deficiency must be prolonged beyond wound healing.

Many treatment algorithms to modulate this growth retardation and hypermetabolism have been examined and subsequently reviewed by Diaz.[180] Indirect effects of glucocorticoids on glucose levels in burn include modulation of insulin-like growth factor-1 (IGF-1), an important mediator of growth hormone (GH) action.[181,182] Marked depression of all components of the IGF-1 complex is seen following burn.[183–187] Elevated glucocorticoid levels in burn patients

may contribute to the suppression of the acid labile subunit (ALS) of the IGF-1 complex. Treatment of rats with dexamethasone results in low levels of serum ALS as well as liver ALS mRNA.[188,189]

In addition to amino acids released from peripheral tissue,[190] free fatty acids are released from adipose tissue by cortisol.[191] In burned children and adults, increased lipolysis is reflected in the elevated plasma levels of palmitic and oleic acids.[32,192,193] Collectively these effects lead to hepatomegaly and a cushingoid phenotype.

Glucocorticoids on Bone Metabolism

Aside from combating the increased demand for energy, glucocorticoids also affect bone development. Abnormal bone metabolism in burn injury has been demonstrated in animals and humans.[194,195] In children, the reduction in bone mineral density persists for at least 5 years after severe burn injury (>40% TBSA) and results in permanent retardation of linear growth.[196,197] The reasons for loss of bone mineral density include increased production of endogenous glucocorticoids, the inflammatory response, immobilization, aluminum loading, and production of cytokines (e.g., IL-1 and IL-6) that facilitate bone resorption.[198] In an animal study, Hoscheit et al. found increased markers of bone resorption, particularly RANKL, in the first 2 weeks after burn, suggesting that the decreased bone mass after burn injury results from increased resorption and decreased bone formation.[199]

Glucocorticoids have potent effects on bone formation and resorption, resulting in loss of bone mass. Weinstein and coworkers[200] investigated the long-term (equivalent to 3–4 human years) effects of glucocorticoids on bone metabolism in an animal model and reported a reduction in osteoclastogenesis and osteoblastogenesis leading to reduced bone turnover and reduced bone formation, respectively. Enhanced osteoclast and osteoblast apoptosis was observed in mice subjected to long-term glucocorticoid administration, as well as in patients with glucocorticoid-induced osteoporosis.[200] In addition, glucocorticoids directly downregulate expression of type I collagen and upregulate expression of collagenase-3 in chondrocytes.[201] On the other hand, IGF-1 enhances expression of type I collagen and suppresses the expression of collagenase-3.[202] Thus the massive increase in glucocorticoids and the corresponding decrease in IGF-1 in burn injury have the ability to profoundly alter bone and cartilage formation.

The mechanisms by which glucocorticoids mediate bone resorption are unclear. Glucocorticoids may mediate bone resorption by their dual capacity to initially inhibit osteoclast synthesis and later stimulate osteoclast synthesis, coupled with an increase in bone resorption.[203] Another mechanism by which cortisol may influence bone resorption is by suppression of IGF-1 or GH-induced chondrocyte proliferation.[204] The antiproliferative effect of glucocorticoids may be mediated through downregulation of the GH receptor and binding affinity, as well as suppression of the local production of IGF-1 by these cells.

Supplementation with exogenous recombinant human GH (rhGH) was studied by Herndon et al.[180,205,206] and was found to have a profound anabolic effect on the muscle and skin. Breederveld et al. reviewed trials of GH in burn patients, noting more rapid healing of burn wounds and donor sites as well as reduction of hospital stay without increasing mortality or scarring.[205] IGF-I supplementation was also examined and had an even greater anabolic effect but with less resultant hypoglycemia or hyperglycemia.[206] However Takala et al.[207] ascertained increased morbidity and mortality in trauma patients, and the use and further study of these hormones has since been restricted.[208] In a subsequent study, Herndon and Voigt employed a combination treatment of oxandrolone and propranolol that significantly ameliorated growth arrest in pediatric burn patients without the risks associated with IGF-1 treatment.[209] Rojas et al. reviewed the current pharmacotherapy for hypermetabolism in burn patients and cover these issues in detail.[210]

Glucocorticoids on Immune Suppression

Severely burned patients are susceptible to opportunistic infections, and sepsis is a major cause of death associated with burns. Burn injury leaves the patient vulnerable to opportunistic infections via skin, GI, respiratory, and urinary tracts.[211] The glucocorticoid response to thermal injury appears to play an important role in immune dysfunction, with impairment of both specific and nonspecific defenses. Corticosteroids reduce lymphocyte, eosinophil, and basophil numbers; alter lymphocyte subpopulations; depress immunoglobulin production by B cells; and suppress neutrophil and monocyte/macrophage activity.

Acute thymic involution[212,213] and a reduction of the total T-cell population occur soon after burn injury.[212–215] During initial thymic involution in an animal model, there is marked depression of $CD4^{+/}CD8^{+}$ lymphocytes. Thymic involution is a common response to various types of stress and trauma.[216] In humans, the depression of T lymphocytes is reflected by the reduction of both $CD4^{+}$ and $CD8^{+}$ cell numbers.[214] In an animal model,[212] $CD4^{+}CD8^{-}$ cells are reported to be more sensitive to the effects of thermal injury than are $CD4^{-}CD8^{+}$ cells. Unsurprisingly $CD4^{+}CD8^{-}$ cell numbers remain suppressed during the initial 2-week period following burn injury.

Thymic changes following exogenous administration of glucocorticoids are similar to those seen in burn,[217,218] in that both noninjury exogenous hypercortisolism states and burn injury are associated with decreased $CD4^{+}CD8^{+}$ and increased $CD4^{+}CD8^{-}$ thymocytes.[213] The reduction in $CD4^{+}CD8^{+}$ cell numbers during the first 24 h after burn is due to glucocorticoid-mediated apoptosis because burn-induced thymocyte apoptosis is suppressed by adrenalectomy or the administration of a glucocorticoid antagonist.[213] Other factors contributing to lymphocyte dysfunction and immunosuppression resulting from elevated corticosteroid levels may include direct inhibition of T-cell proliferation, IL-2 production,[219,220] apoptosis,[221] and altered lymphocyte membrane fluidity.[222]

Apart from these effects on lymphocytes, glucocorticoids also enhance susceptibility to infections by modifying monocyte and neutrophil function. Movement of circulating inflammatory cells to the site of infection is suppressed by the ability of glucocorticoids to reduce the cellular response to chemotactic stimuli,[223–225] diminish neutrophil adherence,[226] and induce a shift from marginal to circulating cells.[223] Glucocorticoids also suppress the bactericidal activity of monocytes[227] and neutrophils,[228] perhaps through impairment of lysosomal function.[229]

Although severe burns are associated with alterations in B-cell production and function, there is considerable inconsistency in the literature.[230–235] For example, in rats subjected to 30% burn injury, splenic lymphocytes respond poorly to LPS, and immunoglobulin synthesis is reduced in comparison to control animals.[236] Others have found an increase in circulating B cells early after burn injury.[232] Administration of methylprednisolone to normal volunteers for 2–4 weeks also reduces serum immunoglobulin levels.[237]

This review provides a glimpse of how the catecholamine and hormonal responses to thermal injury support compensatory cardiovascular, metabolic, and immunologic changes. Although adrenergic mechanisms are important for their ability to influence intracellular signaling pathways, their roles as modulators of gene expression are still being explored. While alteration of gene expressions by glucocorticoids is well described, less is known about the interplay of glucocorticoids with the complex post-injury signaling milieu seen with severe thermal injury or other forms of trauma.

Complete references available online at www.expertconsult.inkling.com

Further Reading

Atiyeh BS, Gunn SW, Dibo SA. Metabolic implications of severe burn injuries and their management: a systematic review of the literature. *World J Surg*. 2008;32(8):1857-1869.

Cuthbertson D. Post-shock metabolic response. *Lancet*. 1942;1:433-436.

Goodall M, Stone C, Haynes BW. Urinary output of adrenaline and noradrenaline in severe thermal burns. *Ann Surg*. 1957;145(4):479-487.

Norbury WB, Herndon DN, Branski LK, et al. Urinary cortisol and catecholamine excretion after burn injury in children. *J Clin Endocrinol Metab*. 2008;93(4):1270-1275.

Seyle H. A syndrome produced by diverse nocuous agents. *Nature*. 1936;138:32-33.

Wilmore DW, Aulick LH, Mason AD, et al. Influence of the burn wound on local and systemic responses to injury. *Ann Surg*. 1977;186(4):444-458.

References

1. Birke G, Duner H, Liljedahl SO, et al. Histamine, catechol amines and adrenocortical steroids in burns. *Acta Chir Scand*. 1957;114:87-98.
2. Goodall M, Stone C, Haynes BW. Urinary output of adrenaline and noradrenaline in severe thernal burns. *Ann Surg*. 1957;145(4):479-487.
3. Kulp GA, Herndon DN, Lee JO, Suman OE, Jeschke MG. Extent and magnitude of catecholamine surge in pediatric burned patients. *Shock*. 2010;33(4):369-374.
4. Norbury WB, Herndon DN, Branski LK, Chinkes DL, Jeschke MG. Urinary cortisol and catecholamine excretion after burn injury in children. *J Clin Endocrinol Metab*. 2008;93(4):1270-1275.
5. Jeschke MG, Gauglitz GG, Kulp GA, et al. Long-term persistance of the pathophysiologic response to severe burn injury. *PLoS ONE*. 2011;6(7):e21245.
6. Guillory AN, Clayton RP, Herndon DN, Finnerty CC. Cardiovascular dysfunction following burn injury: what we have learned from rat and mouse models. *Int J Mol Sci*. 2016;17(1).
7. O'Halloran E, Shah A, Dembo L, et al. The impact of non-severe burn injury on cardiac function and long-term cardiovascular pathology. *Sci Rep*. 2016;6:34650.
8. Carvajal HF, Reinhart JA, Traber DL. Renal and cardivascular functional response to thermal injury in dogs subjected to sympathetic blockade. *Circ Shock*. 1976;3:287-298.
9. Crum RL, Dominic W, Hansbrough JF, Shackford SR, Brown MR. Cardiovascular and neurohumoral responses following burn injury. *Arch Surg*. 1990;125(8):1065-1069.
10. Westfall TC, Macarthur H, Byku M, Yang CL, Murray J. Interactions of neuropeptide y, catecholamines, and angiotensin at the vascular neuroeffector junction. *Adv Pharmacol*. 2013;68:115-139.
11. Boyle WA, Segel LD. Direct cardiac effects of vasopressin and their reversal by a vascular antagonist. *Am J Physiol*. 1986;251(4 Pt 2):H734-H741.
12. Dunser MW, Hasibeder WR. Sympathetic overstimulation during critical illness: adverse effects of adrenergic stress. *J Intensive Care Med*. 2009;24(5):293-316.
13. Wilmore DW, Goodwin CW, Aulick LH, et al. Effect of injury and infection on visceral metabolism and circulation. *Ann Surg*. 1980;192(4):491-504.
14. Chruscinski AJ, Rohrer DK, Schauble E, et al. Targeted disruption of the beta2 adrenergic receptor gene. *J Biol Chem*. 1999;274(24):16694-16700.
15. Jacob G, Costa F, Shannon J, Robertson D, Biaggioni I. Dissociation between neural and vascular responses to sympathetic stimulation: contribution of local adrenergic receptor function. *Hypertension*. 2000;35(1 Pt 1):76-81.
16. Aulick LH, Wilmore DW, Mason AD Jr, Pruitt BA Jr. Influence of the burn wound on peripheral circulation in thermally injured patients. *Am J Physiol*. 1977;233(4):H520-H526.
17. Sheperd J. Circulation to skeletal muscle. In: Geiger S, Sheperd J, Abboud F, eds. *Handbook of physiology*. Section 2: the cardiovascular system. III: Peripheral circulation and organ blood flow. Baltimore: American Physiological Society; 1983:319-370.
18. Kilbourn RG, Traber DL, Szabo C. Nitric oxide and shock. *Dis Mon*. 1997;43(5):277-348.
19. Keck M, Herndon DH, Kamolz LP, Frey M, Jeschke MG. Pathophysiology of burns. *Wien Med Wochenschr*. 2009;159(13-14):327-336.
20. Zhang Z, Chen K. Vasoactive agents for the treatment of sepsis. *Ann Transl Med*. 2016;4(17):333.
21. Macarthur H, Westfall TC, Riley DP, Misko TP, Salvemini D. Inactivation of catecholamines by superoxide gives new insights on the pathogenesis of septic shock. *Proc Natl Acad Sci USA*. 2000;97(17):9753-9758.
22. Macarthur H, Couri DM, Wilken GH, et al. Modulation of serum cytokine levels by a novel superoxide dismutase mimetic, M40401, in an Escherichia coli model of septic shock: correlation with preserved circulating catecholamines. *Crit Care Med*. 2003;31(1):237-245.
23. Kolo LL, Westfall TC, Macarthur H. Nitric oxide decreases the biological activity of norepinephrine resulting in altered vascular tone in the rat mesenteric arterial bed. *Am J Physiol Heart Circ Physiol*. 2004;286(1):H296-H303.
24. Case AJ, Roessner CT, Tian J, Zimmerman MC. Mitochondrial superoxide signaling contributes to norepinephrine-mediated T-lymphocyte cytokine profiles. *PLoS ONE*. 2016;11(10):e0164609.
25. Wilmore DW, Long JM, Mason AD Jr, Skreen RW, Pruitt BA Jr. Catecholamines: mediator of the hypermetabolic response to thermal injury. *Ann Surg*. 1974;180(4):653-669.
26. Herndon DN, Wilmore DW, Mason AD Jr, Pruitt BA Jr. Humoral mediators of nontemperature-dependent hypermetabolism in 50% burned adult rats. *Surg Forum*. 1977;28:37-39.
27. Wilmore DW, Mason AD Jr, Johnson DW, Pruitt BA Jr. Effect of ambient temperature on heat production and heat loss in burn patients. *J Appl Physiol*. 1975;38(4):593-597.
28. Kraft R, Kulp GA, Herndon DN, et al. Is there a difference in clinical outcomes, inflammation, and hypermetabolism between scald and flame burn? *Pediatr Crit Care Med*. 2011;12(6):e275-e281.
29. Wolfe RR, Durkot MJ. Evaluation of the role of the sympathetic nervous system in the response of substrate kinetics and oxidation to burn injury. *Circ Shock*. 1982;9(4):395-406.
30. Herndon DN, Nguyen TT, Wolfe RR, et al. Lipolysis in burned patients is stimulated by the beta 2-receptor for catecholamines. *Arch Surg*. 1994;129(12):1301-1304, discussion 1304-1305.
31. Wolfe RR, Herndon DN, Jahoor F, Miyoshi H, Wolfe M. Effect of severe burn injury on substrate cycling by glucose and fatty acids. *N Engl J Med*. 1987;317(7):403-408.
32. Wolfe RR, Herndon DN, Peters EJ, et al. Regulation of lipolysis in severely burned children. *Ann Surg*. 1987;206(2):214-221.
33. Qi P, Abdullahi A, Stanojcic M, Patsouris D, Jeschke MG. Lipidomic analysis enables prediction of clinical outcomes in burn patients. *Sci Rep*. 2016;6:38707.
34. Elijah IE, Borsheim E, Maybauer DM, et al. Role of the PPAR-alpha agonist fenofibrate in severe pediatric burn. *Burns*. 2012;38(4):481-486.
35. Caldwell FT Jr. Energy metabolism following thermal burns. *Arch Surg*. 1976;111(2):181-185.
36. Chance WT, Nelson JL, Foley-Nelson T, Kim MW, Fischer JE. The relationship of burn-induced hypermetabolism to central and peripheral catecholamines. *J Trauma*. 1989;29(3):306-312.
37. Caldwell FT Jr, Graves DB, Wallace BH, Moore DB, Crabtree JH. Alteration in temperature regulation induced by burn injury in the rat. *J Burn Care Rehabil*. 1989;10(6):486-493.
38. Neely WA, Petro AB, Holloman GH Jr, et al. Researches on the cause of burn hypermetabolism. *Ann Surg*. 1974;179(3):291-294.
39. Herndon DN, Barrow RE, Rutan TC, et al. Effect of propranolol administration on hemodynamic and metabolic responses of burned pediatric patients. *Ann Surg*. 1988;208(4):484-492.
40. Baron PW, Barrow RE, Pierre EJ, Herndon DN. Prolonged use of propranolol safely decreases cardiac work in burned children. *J Burn Care Rehabil*. 1997;18(3):223-227.
41. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR. Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med*. 2001;345(17):1223-1229.
42. Aarsland A, Chinkes D, Wolfe RR, et al. Beta-blockade lowers peripheral lipolysis in burn patients receiving growth hormone. Rate of hepatic very low density lipoprotein triglyceride secretion remains unchanged. *Ann Surg*. 1996;223(6):777-787, discussion 787-789.
43. Finnerty CC, Herndon DN. Is propranolol of benefit in pediatric burn patients? *Adv Surg*. 2013;47:177-197.
44. Herndon DN, Rodriguez NA, Diaz EC, et al. Long-term propranolol use in severely burned pediatric patients: a randomized controlled study. *Ann Surg*. 2012;256(3):402-411.
45. Bortolin JA, Quintana HT, Tome Tde C, et al. Burn injury induces histopathological changes and cell proliferation in liver of rats. *World J Hepatol*. 2016;8(6):322-330.
46. Herndon DN, Dasu MR, Wolfe RR, Barrow RE. Gene expression profiles and protein balance in skeletal muscle of burned children after beta-adrenergic blockade. *Am J Physiol Endocrinol Metab*. 2003;285(4):E783-E789.
47. Ali A, Herndon DN, Mamachen A, et al. Propranolol attenuates hemorrhage and accelerates wound healing in severely burned adults. *Crit Care*. 2015;19:217.
48. Zhang XJ, Wang L, Tuvdendorj D, et al. Acute hyperinsulinemia and reduced plasma free fatty acid levels decrease intramuscular triglyceride synthesis. *Metabolism*. 2013;62(1):44-51.
49. Chacko CJ, Gopal S. Systematic review of use of beta-blockers in sepsis. *J Anaesthesiol Clin Pharmacol*. 2015;31(4):460-465.
50. Duan EH, Oczkowski SJ, Belley-Cote E, et al. beta-Blockers in sepsis: protocol for a systematic review and meta-analysis of randomised control trials. *BMJ Open*. 2016;6(6):e012466.

51. Padro CJ, Sanders VM. Neuroendocrine regulation of inflammation. *Semin Immunol*. 2014;26(5):357-368.
52. Calvo W. The innervation of the bone marrow in laboratory animals. *Am J Anat*. 1968;123:315-328.
53. Felten SY, Felten DL, Bellinger DL, et al. Noradrenergic sympathetic innervation of lymphoid organs. *Prog Allergy*. 1988;43:14-36.
54. Van Oosterhout AJ, Nijkamp FP. Anterior hypothalamic lesions prevent the endotoxin-induced reduction of beta-adrenoceptor number in guinea pig lung. *Brain Res*. 1984;302(2):277-280.
55. Williams JM, Felten DL. Sympathetic innervation of murine thymus and spleen: a comparative histofluorescence study. *Anat Rec*. 1981;199(4):531-542.
56. Felten DL, Ackerman KD, Wiegand SJ, Felten SY. Noradrenergic sympathetic innervation of the spleen: I. Nerve fibers associate with lymphocytes and macrophages in specific compartments of the splenic white pulp. *J Neurosci Res*. 1987;18(1):28-36.
57. Felten DL, Felten SY, Carlson SL, Olschowka JA, Livnat S. Noradrenergic and peptidergic innervation of lymphoid tissue. *J Immunol*. 1985;135(2 suppl):755s-765s.
58. Ackerman KD, Felten SY, Bellinger DL, Felten DL. Noradrenergic sympathetic innervation of the spleen: III. Development of innervation in the rat spleen. *J Neurosci Res*. 1987;18(1):49-54.
59. Livnat S, Felten SY, Carlson SL, Bellinger DL, Felten DL. Involvement of peripheral and central catecholamine systems in neural-immune interactions. *J Neuroimmunol*. 1985;10(1):5-30.
60. Felten SY, Olschowka J. Noradrenergic sympathetic innervation of the spleen: II. Tyrosine hydroxylase (TH)-positive nerve terminals form synapticlike contacts on lymphocytes in the splenic white pulp. *J Neurosci Res*. 1987;18(1):37-48.
61. Sanders VM. The beta2-adrenergic receptor on T and B lymphocytes: do we understand it yet? *Brain Behav Immun*. 2012;26(2):195-200.
62. Kohm AP, Sanders VM. Suppression of antigen-specific Th2 cell-dependent IgM and IgG1 production following norepinephrine depletion in vivo. *J Immunol*. 1999;162(9):5299-5308.
63. Ramer-Quinn DS, Baker RA, Sanders VM. Activated T helper 1 and T helper 2 cells differentially express the beta-2-adrenergic receptor: a mechanism for selective modulation of T helper 1 cell cytokine production. *J Immunol*. 1997;159(10):4857-4867.
64. Sanders VM, Baker RA, Ramer-Quinn DS, et al. Differential expression of the beta2-adrenergic receptor by Th1 and Th2 clones: implications for cytokine production and B cell help. *J Immunol*. 1997;158(9):4200-4210.
65. Swanson MA, Lee WT, Sanders VM. IFN-gamma production by Th1 cells generated from naive CD4+ T cells exposed to norepinephrine. *J Immunol*. 2001;166(1):232-240.
66. Estrada LD, Agac D, Farrar JD. Sympathetic neural signaling via the beta2-adrenergic receptor suppresses T-cell receptor-mediated human and mouse CD8(+) T-cell effector function. *Eur J Immunol*. 2016;46(8):1948-1958.
67. Kasprowicz DJ, Kohm AP, Berton MT, et al. Stimulation of the B cell receptor, CD86 (B7–2), and the beta 2-adrenergic receptor intrinsically modulates the level of IgG1 and IgE produced per B cell. *J Immunol*. 2000;165(2):680-690.
68. Kohm AP, Tang Y, Sanders VM, Jones SB. Activation of antigen-specific CD4+ Th2 cells and B cells in vivo increases norepinephrine release in the spleen and bone marrow. *J Immunol*. 2000;165(2):725-733.
69. Jeschke MG, Norbury WB, Finnerty CC, Branski LK, Herndon DN. Propranolol does not increase inflammation, sepsis, or infectious episodes in severely burned children. *J Trauma*. 2007;62(3):676-681.
70. Rosas-Ballina M, Olofsson PS, Ochani M, et al. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. *Science*. 2011;334(6052):98-101.
71. Muthu K, He LK, Szilagyi A, et al. Propranolol restores the tumor necrosis factor-alpha response of circulating inflammatory monocytes and granulocytes after burn injury and sepsis. *J Burn Care Res*. 2009;30(1):8-18.
72. Chou RC, Stinson MW, Noble BK, Spengler RN. Beta-adrenergic receptor regulation of macrophage-derived tumor necrosis factor-alpha production from rats with experimental arthritis. *J Neuroimmunol*. 1996;67(1):7-16.
73. Hu XX, Goldmuntz EA, Brosnan CF. The effect of norepinephrine on endotoxin-mediated macrophage activation. *J Neuroimmunol*. 1991;31(1):35-42.
74. Ignatowski TA, Spengler RN. Regulation of macrophage-derived tumor necrosis factor production by modification of adrenergic receptor sensitivity. *J Neuroimmunol*. 1995;61(1):61-70.
75. Liao J, Keiser JA, Scales WE, Kunkel SL, Kluger MJ. Role of epinephrine in TNF and IL-6 production from isolated perfused rat liver. *Am J Physiol*. 1995;268(4 Pt 2):R896-R901.
76. Bissonnette EY, Befus AD. Anti-inflammatory effect of beta 2-agonists: inhibition of TNF-alpha release from human mast cells. *J Allergy Clin Immunol*. 1997;100(6 Pt 1):825-831.
77. Hetier E, Ayala J, Bousseau A, Prochiantz A. Modulation of interleukin-1 and tumor necrosis factor expression by beta-adrenergic agonists in mouse ameboid microglial cells. *Exp Brain Res*. 1991;86(2):407-413.
78. Nakamura A, Johns EJ, Imaizumi A, Abe T, Kohsaka T. Regulation of tumour necrosis factor and interleukin-6 gene transcription by beta2-adrenoceptor in the rat astrocytes. *J Neuroimmunol*. 1998;88(1-2):144-153.
79. Kalinichenko VV, Mokyr MB, Graf LH Jr, Cohen RL, Chambers DA. Norepinephrine-mediated inhibition of antitumor cytotoxic T lymphocyte generation involves a beta-adrenergic receptor mechanism and decreased TNF-alpha gene expression. *J Immunol*. 1999;163(5):2492-2499.
80. Abadie C, Foucart S, Page P, Nadeau R. Interleukin-1 beta and tumor necrosis factor-alpha inhibit the release of [3H]-noradrenaline from isolated human atrial appendages. *Naunyn Schmiedebergs Arch Pharmacol*. 1997;355(3):384-389.
81. Foucart S, Abadie C. Interleukin-1 beta and tumor necrosis factor-alpha inhibit the release of [3H]-noradrenaline from mice isolated atria. *Naunyn Schmiedebergs Arch Pharmacol*. 1996;354(1):1-6.
82. Hurst SM, Collins SM. Mechanism underlying tumor necrosis factor-alpha suppression of norepinephrine release from rat myenteric plexus. *Am J Physiol*. 1994;266(6 Pt 1):G1123-G1129.
83. Ignatowski TA, Noble BK, Wright JR, et al. Neuronal-associated tumor necrosis factor (TNF alpha): its role in noradrenergic functioning and modification of its expression following antidepressant drug administration. *J Neuroimmunol*. 1997;79(1):84-90.
84. Bergmann M, Gornikiewicz A, Sautner T, et al. Attenuation of catecholamine-induced immunosuppression in whole blood from patients with sepsis. *Shock*. 1999;12(6):421-427.
85. Platzer C, Docke W, Volk H, Prosch S. Catecholamines trigger IL-10 release in acute systemic stress reaction by direct stimulation of its promoter/enhancer activity in monocytic cells. *J Neuroimmunol*. 2000;105(1):31-38.
86. Siegmund B, Eigler A, Hartmann G, Hacker U, Endres S. Adrenaline enhances LPS-induced IL-10 synthesis: evidence for protein kinase A-mediated pathway. *Int J Immunopharmacol*. 1998;20(1-3):57-69.
87. Szabo C, Hasko G, Zingarelli B, et al. Isoproterenol regulates tumour necrosis factor, interleukin-10, interleukin-6 and nitric oxide production and protects against the development of vascular hyporeactivity in endotoxaemia. *Immunology*. 1997;90(1):95-100.
88. van der Poll T, Coyle SM, Barbosa K, Braxton CC, Lowry SF. Epinephrine inhibits tumor necrosis factor-alpha and potentiates interleukin 10 production during human endotoxemia. *J Clin Invest*. 1996;97(3):713-719.
89. Takenaka MC, Araujo LP, Maricato JT, et al. Norepinephrine controls effector T cell differentiation through beta2-adrenergic receptor-mediated inhibition of NF-kappaB and AP-1 in dendritic cells. *J Immunol*. 2016;196(2):637-644.
90. Woiciechowsky C, Asadullah K, Nestler D, et al. Sympathetic activation triggers systemic interleukin-10 release in immunodepression induced by brain injury [see comments]. *Nat Med*. 1998;4(7):808-813.
91. Jones SB, Romano FD. Dose- and time-dependent changes in plasma catecholamines in response to endotoxin in conscious rats. *Circ Shock*. 1989;28(1):59-68.
92. Norbury WB, Jeschke MG, Herndon DN. Metabolism modulators in sepsis: propranolol. *Crit Care Med*. 2007;35(9 suppl):S616-S620.
93. Loftus TJ, Efron PA, Moldawer LL, Mohr AM. Beta-blockade use for traumatic injuries and immunomodulation: a review of proposed mechanisms and clinical evidence. *Shock*. 2016;46(4):341-351.
94. Jones SB, Kovarik MF, Romano FD. Cardiac and splenic norepinephrine turnover during septic peritonitis. *Am J Physiol*. 1986;250(5 Pt 2):R892-R897.
95. Kovarik MF, Jones SB, Romano FD. Plasma catecholamines following cecal ligation and puncture in the rat. *Circ Shock*. 1987;22(4):281-290.
96. Becker RA, Wilmore DW, Goodwin CW, et al. Free T4, free T3, and reverse T3 in critically ill, thermally injured patients. *J Trauma*. 1980;20(9):713-721.

97. Becker RA, Vaughan GM, Ziegler MG, et al. Hypermetabolic low triiodothyronine syndrome of burn injury. *Crit Care Med*. 1982;10(12):870-875.
98. Smeds S, Kagedal B, Lieden G, Liljedahl SO. Thyroid function after thermal trauma. *Scand J Plast Reconstr Surg*. 1981;15(2): 141-148.
99. Senel E, Kizilgun M, Akbiyik F, et al. The evaluation of the adrenal and thyroid axes and glucose metabolism after burn injury in children. *J Pediatr Endocrinol Metab*. 2010;23(5):481-489.
100. Parker CR Jr, Baxter CR. Divergence in adrenal steroid secretory pattern after thermal injury in adult patients. *J Trauma*. 1985;25(6):508-510.
101. Lephart ED, Baxter CR, Parker CR Jr. Effect of burn trauma on adrenal and testicular steroid hormone production. *J Clin Endocrinol Metab*. 1987;64(4):842-848.
102. Doerr P, Pirke KM. Cortisol-induced suppression of plasma testosterone in normal adult males. *J Clin Endocrinol Metab*. 1976;43(3):622-629.
103. Welsh TH Jr, Bambino TH, Hsueh AJ. Mechanism of glucocorticoid-induced suppression of testicular androgen biosynthesis in vitro. *Biol Reprod*. 1982;27(5):1138-1146.
104. Wilmore DW, Long JM, Mason AD, Pruitt BA Jr. Stress in surgical patients as a neurophysiologic reflex response. *Surg Gynecol Obstet*. 1976;142(2):257-269.
105. Plymate SR, Vaughan GM, Mason AD, Pruitt BA. Central hypogonadism in burned men. *Horm Res*. 1987;27(3):152-158.
106. Araneo BA, Shelby J, Li GZ, Ku W, Daynes RA. Administration of dehydroepiandrosterone to burned mice preserves normal immunologic competence. *Arch Surg*. 1993;128(3):318-325.
107. Blauer KL, Poth M, Rogers WM, Bernton EW. Dehydroepiandrosterone antagonizes the suppressive effects of dexamethasone on lymphocyte proliferation. *Endocrinology*. 1991;129(6):3174-3179.
108. Daynes RA, Meikle AW, Araneo BA. Locally active steroid hormones may facilitate compartmentalization of immunity by regulating the types of lymphokines produced by helper T cells. *Res Immunol*. 1991;142(1):40-45.
109. Suzuki T, Suzuki N, Daynes RA, Engleman EG. Dehydroepiandrosterone enhances IL2 production and cytotoxic effector function of human T cells. *Clin Immunol Immunopathol*. 1991;61(2 Pt 1):202-211.
110. Van Loon GR, Schwartz L, Sole MJ. Plasma dopamine responses to standing and exercise in man. *Life Sci*. 1979;24(24):2273-2277.
111. Viquerat CE, Daly P, Swedberg K, et al. Endogenous catecholamine levels in chronic heart failure. Relation to the severity of hemodynamic abnormalities. *Am J Med*. 1985;78(3):455-460.
112. Povoa P, Carneiro AH. Adrenergic support in septic shock: a critical review. *Hosp Pract (1995)*. 2010;38(1):62-73.
113. Devins SS, Miller A, Herndon BL, O'Toole L, Reisz G. Effects of dopamine on T-lymphocyte proliferative responses and serum prolactin concentrations in critically ill patients. *Crit Care Med*. 1992;20(12):1644-1649.
114. Van den Berghe G, de Zegher F, Wouters P, et al. Dehydroepiandrosterone sulphate in critical illness: effect of dopamine. *Clin Endocrinol (Oxf)*. 1995;43(4):457-463.
115. Higuchi K, Nawata H, Maki T, et al. Prolactin has a direct effect on adrenal androgen secretion. *J Clin Endocrinol Metab*. 1984;59(4):714-718.
116. Reeves PT, Herndon DN, Tanksley JD, et al. Five-year outcomes after long-term oxandrolone administration in severely burned children: a randomized clinical trial. *Shock*. 2016;45(4):367-374.
117. Cassidy RA, Vaughan GM, Pruitt BA Jr, Mason AD Jr. Xenoestrogens: do they lower survival after thermal injury? *Arch Environ Health*. 2003;58(9):597-604.
118. Vaughan GM, Becker RA, Allen JP, et al. Cortisol and corticotrophin in burned patients. *J Trauma*. 1982;22(4):263-273.
119. Cortes-Puch I, Hicks CW, Sun J, et al. Hypothalamic-pituitary-adrenal axis in lethal canine *Staphylococcus aureus* pneumonia. *Am J Physiol Endocrinol Metab*. 2014;307(11):E994-E1008.
120. Boonen E, Van den Berghe G. Cortisol metabolism in critical illness: implications for clinical care. *Curr Opin Endocrinol Diabetes Obes*. 2014;21(3):185-192.
121. Jeschke MG, Williams FN, Finnerty CC, et al. The effect of ketoconazole on post-burn inflammation, hypermetabolism and clinical outcomes. *PLoS ONE*. 2012;7(5):e35465.
122. Manji RA, Kumar A. Determining relevant cortisol concentrations in critically ill patients. *Crit Care*. 2010;14(1):113.
123. Vassiliadi DA, Ilias I, Tzanela M, et al. Interstitial cortisol obtained by microdialysis in mechanically ventilated septic patients: correlations with total and free serum cortisol. *J Crit Care*. 2013;28(2): 158-165.
124. Wise L, Margraf HW, Ballinger WF. Adrenal cortical function in severe burns. *Arch Surg*. 1972;105(2):213-220.
125. Mortensen RF, Johnson AA, Eurenius K. Serum corticosteroid binding following thermal injury. *Proc Soc Exp Biol Med*. 1972;139 (3):877-882.
126. Pugeat M, Bonneton A, Perrot D, et al. Decreased immunoreactivity and binding activity of corticosteroid-binding globulin in serum in septic shock. *Clin Chem*. 1989;35(8):1675-1679.
127. Garrel DR. Corticosteroid-binding globulin during inflammation and burn injury: nutritional modulation and clinical implications. *Horm Res*. 1996;45(3-5):245-251.
128. Garrel DR, Zhang L, Zhao XF, Hammond GL. Effect of burn injury on corticosteroid-binding globulin levels in plasma and wound fluid. *Wound Repair Regen*. 1993;1:10-14.
129. Jeschke MG, Mlcak RP, Finnerty CC, et al. Burn size determines the inflammatory and hypermetabolic response. *Crit Care*. 2007;11(4):R90.
130. Feldman D, Mondon CE, Horner JA, Weiser JN. Glucocorticoid and estrogen regulation of corticosteroid-binding globulin production by rat liver. *Am J Physiol*. 1979;237(6):E493-E499.
131. Frairia R, Agrimonti F, Fortunati N, et al. Influence of naturally occurring and synthetic glucocorticoids on corticosteroid-binding globulin-steroid interaction in human peripheral plasma. *Ann N Y Acad Sci*. 1988;538:287-303.
132. Smith CL, Hammond GL. Hormonal regulation of corticosteroid-binding globulin biosynthesis in the male rat. *Endocrinology*. 1992;130 (4):2245-2251.
133. Emptoz-Bonneton A, Crave JC, LeJeune H, Brebant C, Pugeat M. Corticosteroid-binding globulin synthesis regulation by cytokines and glucocorticoids in human hepatoblastoma-derived (HepG2) cells [see comments]. *J Clin Endocrinol Metab*. 1997;82(11): 3758-3762.
134. Vermes I, Beishuizen A, Hampsink RM, Haanen C. Dissociation of plasma adrenocorticotropin and cortisol levels in critically ill patients: possible role of endothelin and atrial natriuretic hormone [see comments]. *J Clin Endocrinol Metab*. 1995;80(4):1238-1242.
135. Macarthur H, Wilken GH, Westfall TC, Kolo LL. Neuronal and non-neuronal modulation of sympathetic neurovascular transmission. *Acta Physiol (Oxf)*. 2011;203(1):37-45.
136. Kellner M, Wiedemann K, Holsboer F. Atrial natriuretic factor inhibits the CRH-stimulated secretion of ACTH and cortisol in man. *Life Sci*. 1992;50(24):1835-1842.
137. Hinson JP, Vinson GP, Kapas S, Teja R. The role of endothelin in the control of adrenocortical function: stimulation of endothelin release by ACTH and the effects of endothelin-1 and endothelin-3 on steroidogenesis in rat and human adrenocortical cells. *J Endocrinol*. 1991;128(2):275-280.
138. Hirai M, Miyabo S, Ooya E, et al. Endothelin-3 stimulates the hypothalamic-pituitary-adrenal axis. *Life Sci*. 1991;48(24):2359-2363.
139. Vierhapper H, Hollenstein U, Roden M, Nowotny P. Effect of endothelin-1 in man–impact on basal and stimulated concentrations of luteinizing hormone, follicle-stimulating hormone, thyrotropin, growth hormone, corticotropin, and prolactin. *Metabolism*. 1993;42 (7):902-906.
140. Cohen J, Deans R, Dalley A, et al. Measurement of tissue cortisol levels in patients with severe burns: a preliminary investigation. *Crit Care*. 2009;13(6):R189.
141. Brown NJ, Kimble RM, Rodger S, et al. Biological markers of stress in pediatric acute burn injury. *Burns*. 2014;40(5):887-895.
142. Wallace BH, Caldwell FT Jr, Cone JB. The interrelationships between wound management, thermal stress, energy metabolism, and temperature profiles of patients with burns. *J Burn Care Rehabil*. 1994;15(6):499-508.
143. Jahoor F, Herndon DN, Wolfe RR. Role of insulin and glucagon in the response of glucose and alanine kinetics in burn-injured patients. *J Clin Invest*. 1986;78(3):807-814.
144. Wolfe RR, Shaw JH, Jahoor F, Herndon DN, Wolfe MH. Response to glucose infusion in humans: role of changes in insulin concentration. *Am J Physiol*. 1986;250(3 Pt 1):E306-E311.
145. Vaughan GM, Becker RA, Unger RH, et al. Nonthyroidal control of metabolism after burn injury: possible role of glucagon. *Metabolism*. 1985;34(7):637-641.

146. Long JM, Wilmore DW, Mason AD Jr, Pruitt BA Jr. Fat-carbohydrate interaction: effects on nitrogen-sparing in total intravenous feeding. *Surg Forum*. 1974;25(0):61-63.
147. Long MJ 3rd, Wilmore DW, Mason AD Jr, Pruitt BA Jr. Comparison of carbohydrate and fat as caloric sources. *Surg Forum*. 1975;26:108-110.
148. Long JM 3rd, Wilmore DW, Mason AD Jr, Pruitt BA Jr. Effect of carbohydrate and fat intake on nitrogen excretion during total intravenous feeding. *Ann Surg*. 1977;185(4):417-422.
149. Bane JW, McCaa RE, McCaa CS, et al. The pattern of aldosterone and cortisone blood levels in thermal burn patients. *J Trauma*. 1974;14(7):605-611.
150. Hume DM, Nelson DH, Miller DW. Blood and urinary 17-hydroxycorticosteroids in patients with severe burns. *Ann Surg*. 1956;143(3):316-329.
151. Allison SP, Hinton P, Chamberlain MJ. Intravenous glucose-tolerance, insulin, and free-fatty-acid levels in burned patients. *Lancet*. 1968;2(7578):1113-1116.
152. Khorram-Sefat R, Behrendt W, Heiden A, Hettich R. Long-term measurements of energy expenditure in severe burn injury. *World J Surg*. 1999;23(2):115-122.
153. Plager JE, Matsui N. An in vitro demonstration of the anti-insulin action of cortisol on glucose metabolism. *Endocrinology*. 1966;78:1154-1158.
154. Wolfe RR, Durkot MJ, Allsop JR, Burke JF. Glucose metabolism in severely burned patients. *Metabolism*. 1979;28(10):1031-1039.
155. Wolfe RR, Miller HI, Spitzer JJ. Glucose and lactate kinetics in burn shock. *Am J Physiol*. 1977;232(4):E415-E418.
156. Yarmush DM, MacDonald AD, Foy BD, et al. Cutaneous burn injury alters relative tricarboxylic acid cycle fluxes in rat liver. *J Burn Care Rehabil*. 1999;20(4):292-302.
157. Shuck JM, Eaton P, Shuck LW, Wachtel TL, Schade DS. Dynamics of insulin and glucagon secretions in severely burned patients. *J Trauma*. 1977;17(9):706-713.
158. Marco J, Calle C, Roman D, et al. Hyperglucagonism induced by glucocorticoid treatment in man. *N Engl J Med*. 1973;288(3):128-131.
159. Cuthbertson DP. Observations on disturbance of metabolism produced by injury to the limbs. *QJM*. 1932;25:233-246.
160. Darmaun D, Matthews DE, Bier DM. Physiological hypercortisolemia increases proteolysis, glutamine, and alanine production. *Am J Physiol*. 1988;255(3 Pt 1):E366-E373.
161. Kayali AG, Young VR, Goodman MN. Sensitivity of myofibrillar proteins to glucocorticoid-induced muscle proteolysis. *Am J Physiol*. 1987;252(5 Pt 1):E621-E626.
162. Fang CH, James HJ, Ogle C, Fischer JE, Hasselgren PO. Influence of burn injury on protein metabolism in different types of skeletal muscle and the role of glucocorticoids. *J Am Coll Surg*. 1995;180(1):33-42.
163. May RC, Kelly RA, Mitch WE. Metabolic acidosis stimulates protein degradation in rat muscle by a glucocorticoid-dependent mechanism. *J Clin Invest*. 1986;77(2):614-621.
164. Price SR, England BK, Bailey JL, Van Vreede K, Mitch WE. Acidosis and glucocorticoids concomitantly increase ubiquitin and proteasome subunit mRNAs in rat muscle. *Am J Physiol*. 1994;267(4 Pt 1):C955-C960.
165. Isozaki U, Mitch WE, England BK, Price SR. Protein degradation and increased mRNAs encoding proteins of the ubiquitin-proteasome proteolytic pathway in BC3H1 myocytes require an interaction between glucocorticoids and acidification. *Proc Natl Acad Sci USA*. 1996;93(5):1967-1971.
166. Ding X, Price SR, Bailey JL, Mitch WE. Cellular mechanisms controlling protein degradation in catabolic states. *Miner Electrolyte Metab*. 1997;23(3-6):194-197.
167. Bailey JL, Wang X, England BK, et al. The acidosis of chronic renal failure activates muscle proteolysis in rats by augmenting transcription of genes encoding proteins of the ATP-dependent ubiquitin-proteasome pathway. *J Clin Invest*. 1996;97(6):1447-1453.
168. Medina R, Wing SS, Goldberg AL. Increase in levels of polyubiquitin and proteasome mRNA in skeletal muscle during starvation and denervation atrophy. *Biochem J*. 1995;307(Pt 3):631-637.
169. Mitch WE, Medina R, Grieber S, et al. Metabolic acidosis stimulates muscle protein degradation by activating the adenosine triphosphate-dependent pathway involving ubiquitin and proteasomes. *J Clin Invest*. 1994;93(5):2127-2133.
170. Price SR, Bailey JL, Wang X, et al. Muscle wasting in insulinopenic rats results from activation of the ATP-dependent, ubiquitin-proteasome proteolytic pathway by a mechanism including gene transcription. *J Clin Invest*. 1996;98(8):1703-1708.
171. Wing SS, Goldberg AL. Glucocorticoids activate the ATP-ubiquitin-dependent proteolytic system in skeletal muscle during fasting. *Am J Physiol*. 1993;264(4 Pt 1):E668-E676.
172. Aulick LH, Wilmore DW. Increased peripheral amino acid release following burn injury. *Surgery*. 1979;85(5):560-565.
173. Liu F, Huang ZG, Peng YZ, et al. [Clinical randomized controlled trial on the feasibility and validity of continuous blood purification during the early stage of severe burn]. *Zhonghua Shao Shang Za Zhi*. 2016;32(3):133-139.
174. Abcouwer SF, Lohmann R, Bode BP, Lustig RJ, Souba WW. Induction of glutamine synthetase expression after major burn injury is tissue specific and temporally variable. *J Trauma*. 1997;42(3):421-427, discussion 7-8.
175. Abcouwer SF, Bode BP, Souba WW. Glucocorticoids regulate rat glutamine synthetase expression in a tissue-specific manner. *J Surg Res*. 1995;59(1):59-65.
176. Cunningham JJ, Hegarty MT, Meara PA, Burke JF. Measured and predicted calorie requirements of adults during recovery from severe burn trauma. *Am J Clin Nutr*. 1989;49(3):404-408.
177. Hart DW, Wolf SE, Mlcak R, et al. Persistence of muscle catabolism after severe burn. *Surgery*. 2000;128(2):312-319.
178. Milner EA, Cioffi WG, Mason AD, McManus WF, Pruitt BA Jr. A longitudinal study of resting energy expenditure in thermally injured patients. *J Trauma*. 1994;37(2):167-170.
179. Soroff HS, Pearson E, Artz C. An estimation of nitrogen requirements for equilibrium in burned patientsq. *Surg Gynecol Obstet*. 1961;2:159.
180. Diaz EC, Herndon DN, Porter C, et al. Effects of pharmacological interventions on muscle protein synthesis and breakdown in recovery from burns. *Burns*. 2015;41(4):649-657.
181. Casanueva FF. Physiology of growth hormone secretion and action. *Endocrinol Metab Clin North Am*. 1992;21(3):483-517.
182. Rosen CJ, Pollak M. Circulating IGF-1: new perspectives for a new century. *Trends Endocrinol Metab*. 1999;10(4):136-141.
183. Abribat T, Brazeau P, Davignon I, Garrel DR. Insulin-like growth factor-I blood levels in severely burned patients: effects of time post injury, age of patient and severity of burn. *Clin Endocrinol (Oxf)*. 1993;39(5):583-589.
184. Bereket A, Wilson TA, Blethen SL, et al. Regulation of the acid-labile subunit of the insulin-like growth factor ternary complex in patients with insulin-dependent diabetes mellitus and severe burns. *Clin Endocrinol (Oxf)*. 1996;44(5):525-532.
185. Davies SC, Wass JA, Ross RJ, et al. The induction of a specific protease for insulin-like growth factor binding protein-3 in the circulation during severe illness. *J Endocrinol*. 1991;130(3):469-473.
186. Ghahary A, Fu S, Shen YJ, Shankowsky HA, Tredget EE. Differential effects of thermal injury on circulating insulin-like growth factor binding proteins in burn patients. *Mol Cell Biochem*. 1994;135(2):171-180.
187. Moller S, Jensen M, Svensson P, Skakkebaek NE. Insulin-like growth factor 1 (IGF-1) in burn patients. *Burns*. 1991;17(4):279-281.
188. Dai J, Baxter RC. Regulation in vivo of the acid-labile subunit of the rat serum insulin-like growth factor-binding protein complex. *Endocrinology*. 1994;135(6):2335-2341.
189. Dai J, Scott CD, Baxter RC. Regulation of the acid-labile subunit of the insulin-like growth factor complex in cultured rat hepatocytes. *Endocrinology*. 1994;135(3):1066-1072.
190. Al Shamma GA, Goll CC, Baird TB, et al. Changes in body composition after thermal injury in the rat. *Br J Nutr*. 1979;42(3):267-275.
191. Fain SN, Scow RO, Chernick SS. Effects of glucocorticoids onmetabolism of adipose tissue in vitro. *J Biol Chem*. 1963;238:54-58.
192. Galster AD, Bier DM, Cryer PE, Monafo WW. Plasma palmitate turnover in subjects with thermal injury. *J Trauma*. 1984;24(11):938-945.
193. Harris RL, Frenkel RA, Cottam GL, Baxter CR. Lipid mobilization and metabolism after thermal trauma. *J Trauma*. 1982;22(3):194-198.
194. Klein GL, Herndon DN, Rutan TC, et al. Bone disease in burn patients. *J Bone Miner Res*. 1993;8(3):337-345.
195. Schaffler MB, Li XJ, Jee WS, Ho SW, Stern PJ. Skeletal tissue responses to thermal injury: an experimental study. *Bone*. 1988;9(6):397-406.

196. Klein GL, Herndon DN, Langman CB, et al. Long-term reduction in bone mass after severe burn injury in children. *J Pediatr*. 1995;126(2):252-256.
197. Rutan RL, Herndon DN. Growth delay in postburn pediatric patients. *Arch Surg*. 1990;125(3):392-395.
198. Klein GL, Wolf SE, Goodman WG, Phillips WA, Herndon DN. The management of acute bone loss in severe catabolism due to burn injury. *Horm Res*. 1997;48(suppl 5):83-87.
199. Hoscheit M, Conner G, Roemer J, et al. Burn injury has skeletal site-specific effects on bone integrity and markers of bone remodeling. *J Burn Care Res*. 2016;37(6):367-378.
200. Weinstein RS, Jilka RL, Parfitt AM, Manolagas SC. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts and osteocytes by glucocorticoids. Potential mechanisms of their deleterious effects on bone. *J Clin Invest*. 1998;102(2):274-282.
201. Canalis E. Clinical review 83: mechanisms of glucocorticoid action in bone: implications to glucocorticoid-induced osteoporosis. *J Clin Endocrinol Metab*. 1996;81(10):3441-3447.
202. Canalis E, Rydziel S, Delany AM, Varghese S, Jeffrey JJ. Insulin-like growth factors inhibit interstitial collagenase synthesis in bone cell cultures. *Endocrinology*. 1995;136(4):1348-1354.
203. Manelli I, Giustina I. Glucocorticoid-induced osteoporosis. *Trends Endocrinol Metab*. 2000;11(3):79-85.
204. Jux C, Leiber K, Hugel U, et al. Dexamethasone impairs growth hormone (GH)-stimulated growth by suppression of local insulin-like growth factor (IGF)-I production and expression of GH- and IGF-I-receptor in cultured rat chondrocytes [see comments]. *Endocrinology*. 1998;139(7):3296-3305.
205. Breederveld RS, Tuinebreijer WE. Recombinant human growth hormone for treating burns and donor sites. *Cochrane Database Syst Rev*. 2014;(9):CD008990.
206. Elijah IE, Branski LK, Finnerty CC, Herndon DN. The GH/IGF-1 system in critical illness. *Best Pract Res Clin Endocrinol Metab*. 2011;25(5):759-767.
207. Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med*. 1999;341(11):785-792.
208. Jeschke MG. Postburn hypermetabolism: past, present, and future. *J Burn Care Res*. 2016;37(2):86-96.
209. Herndon DN, Voigt CD, Capek KD, et al. Reversal of growth arrest with the combined administration of oxandrolone and propranolol in severely burned children. *Ann Surg*. 2016;264(3):421-428.
210. Rojas Y, Finnerty CC, Radhakrishnan RS, Herndon DN. Burns: an update on current pharmacotherapy. *Expert Opin Pharmacother*. 2012;13(17):2485-2494.
211. Herndon DN, Zeigler ST. Bacterial translocation after thermal injury. *Crit Care Med*. 1993;21(2 suppl):S50-S54.
212. Colic M, Mitrovic S, Dujic A. Thymic response to thermal injury in mice: I. Alterations of thymocyte subsets studied by flow cytometry and immunohistochemistry. *Burns*. 1989;15(3):155-161.
213. Nakanishi T, Nishi Y, Sato EF, et al. Thermal injury induces thymocyte apoptosis in the rat. *J Trauma*. 1998;44(1):143-148.
214. Maldonado MD, Venturoli A, Franco A, Nunez-Roldan A. Specific changes in peripheral blood lymphocyte phenotype from burn patients. Probable origin of the thermal injury-related lymphocytopenia. *Burns*. 1991;17(3):188-192.
215. Organ BC, Antonacci AC, Chiao J, et al. Changes in lymphocyte number and phenotype in seven lymphoid compartments after thermal injury. *Ann Surg*. 1989;210(1):78-89.
216. Selye H. Thymus and adrenals in the response of organism to injuries and intoxications. *Br J Exp Pathol*. 1936;17(234).
217. Blomgren H, Andersson B. Characteristics of the immunocompetant cells in the mouse thymus: cell population changes during cortisone-induced atrophy and subsequent regeneration. *J Immunol*. 1971;1:545-560.
218. Cowan WK, Sorenson DG. Electron microscopic observations of acute thymic involution produced by hydrocortisone. *Lab Invest*. 1964;13:353-370.
219. Gillis S, Crabtree GR, Smith KA. Glucocorticoid-induced inhibition of T cell growth factor production. I. The effect on mitogen-induced lymphocyte proliferation. *J Immunol*. 1979;123(4):1624-1631.
220. Taniguchi T. Regulation of cytokine gene expression. *Annu Rev Immunol*. 1988;6:439-464.
221. Wirth T, Westendorf AM, Bloemker D, et al. The sympathetic nervous system modulates CD4(+)Foxp3(+) regulatory T cells via noradrenaline-dependent apoptosis in a murine model of lymphoproliferative disease. *Brain Behav Immun*. 2014;38:100-110.
222. Tolentino MV, Sarasua MM, Hill OA, et al. Peripheral lymphocyte membrane fluidity after thermal injury. *J Burn Care Rehabil*. 1991;12(6):498-504.
223. Dale DC, Fauci AS, Wolff SM. Alternate-day prednisone. Leukocyte kinetics and susceptibility to infections. *N Engl J Med*. 1974;291(22):1154-1158.
224. Rinehart JJ, Balcerzak SP, Sagone AL, LoBuglio AF. Effects of corticosteroids on human monocyte function. *J Clin Invest*. 1974;54(6):1337-1343.
225. Ward PA. The chemosuppression of chemotaxis. *J Exp Med*. 1966;124(2):209-226.
226. MacGregor RR, Spagnuolo PJ, Lentnek AL. Inhibition of granulocyte adherence by ethanol, prednisone, and aspirin, measured with an assay system. *N Engl J Med*. 1974;291(13):642-646.
227. Rinehart JJ, Sagone AL, Balcerzak SP, Ackerman GA, LoBuglio AF. Effects of corticosteroid therapy on human monocyte function. *N Engl J Med*. 1975;292(5):236-241.
228. Mandell GL, Rubin W, Hook EW. The effect of an NADH oxidase inhibitor (hydrocortisone) on polymorphonuclear leukocyte bactericidal activity. *J Clin Invest*. 1970;49(7):1381-1388.
229. Hibbs JB Jr. Heterocytolysis by macrophages activated by bacillus Calmette-Guerin: lysosome exocytosis into tumor cells. *Science*. 1974;184(135):468-471.
230. Arturson G, Hogman CF, Johansson SG, Killander J. Changes in immunoglobulin levels in severely burned patients. *Lancet*. 1969;1(7594):546-548.
231. Bjornson AB, Altemeier WA, Bjornson HS. Changes in humoral components of host defense following burn trauma. *Ann Surg*. 1977;186(1):88-96.
232. Kagan RJ, Bratescu A, Jonasson O, Matsuda T, Teodorescu M. The relationship between the percentage of circulating B cells, corticosteroid levels, and other immunologic parameters in thermally injured patients. *J Trauma*. 1989;29(2):208-213.
233. Kawakami M, Meyer AA, deSerres S, Peterson HD. Effects of acute ethanol ingestion and burn injury on serum immunoglobulin. *J Burn Care Rehabil*. 1990;11(5):395-399.
234. Kohn J, Cort DF. Immunoglobulins in burned patients. *Lancet*. 1969;1(7599):836-837.
235. Munster AM, Hoagland HC, Pruitt BA Jr. The effect of thermal injury on serum immunoglobulins. *Ann Surg*. 1970;172(6):965-969.
236. Kawakami M, deSerres S, Meyer AA. Immunoglobulin synthesis by cultured lymphocytes from spleen and mesenteric lymph nodes after thermal injury. *J Burn Care Rehabil*. 1991;12(5):474-481.
237. Butler WT, Rossen RD. Effects of corticosteroids on immunity in man. I. Decreased serum IgG concentration caused by 3 or 5 days of high doses of methylprednisolone. *J Clin Invest*. 1973;52(10):2629-2640.
238. Breitenstein E, Chiolero RL, Jequier E, et al. Effects of beta-blockade on energy metabolism following burns. *Burns*. 1990;16(4):259-264.
239. Durkot MJ, Wolfe RR. Effects of adrenergic blockade on glucose kinetics in septic and burned guinea pigs. *Am J Physiol*. 1981;241(3):R222-R227.
240. Arturson G. Metabolic changes and nutrition in children with severe burns. *Prog Pediatr Surg*. 1981;14:81-109.
241. Tang Y, Shankar R, Gamboa M, et al. Norepinephrine modulates myelopoiesis after experimental thermal injury with sepsis. *Ann Surg*. 2001;233(2):266-275.
242. Cohen MJ, Shankar R, Stevenson J, et al. Bone marrow norepinephrine mediates development of functionally different macrophages after thermal injury and sepsis. *Ann Surg*. 2004;240(1):132-141.
243. Johnson NB, Posluszny JA, He LK, et al. Perturbed MafB/GATA1 axis after burn trauma bares the potential mechanism for immune suppression and anemia of critical illness. *J Leukoc Biol*. 2016.
244. Bessey PQ, Watters JM, Aoki TT, Wilmore DW. Combined hormonal infusion simulates the metabolic response to injury. *Ann Surg*. 1984;200(3):264-281.
245. Wilmore DW, Aulick LH, Mason AD, Pruitt BA Jr. Influence of the burn wound on local and systemic responses to injury. *Ann Surg*. 1977;186(4):444-458.
246. Batstone GF, Levick PL, Spurr E, et al. Changes in acute phase reactants and disturbances in metabolism after burn injury. *Burns Incl Therm Inj*. 1983;9(4):234-239.
247. Batstone GF, Alberti KGMM, Hinks L, Smythe P. Metabolic studies in subects following thermal injury. *Burns*. 1976;2(4):207-225.

248. Sevaljevic L, Petrovic M, Bogojevic D, Savic J, Pantelic D. Acute-phase response to scalding: changes in serum properties and acute-phase protein concentrations. *Circ Shock*. 1989;28(3):293-307.
249. Calvano SE, Albert JD, Legaspi A, et al. Comparison of numerical and phenotypic leukocyte changes during constant hydrocortisone infusion in normal humans with those in thermally injured patients. *Surg Gynecol Obstet*. 1987;164(6):509-520.
250. Webel ML, Ritts RE Jr, Taswell HF, Danadio JV Jr, Woods JE. Cellular immunity after intravenous administration of methylprednisolone. *J Lab Clin Med*. 1974;83(3):383-392.
251. Volenec FJ, Wood GW, Mani MM, Robinson DW, Humphrey LJ. Mononuclear cell analysis of peripheral blood from burn patients. *J Trauma*. 1979;19(2):86-93.
252. Wallner S, Vautrin R, Murphy J, Anderson S, Peterson V. The haematopoietic response to burning: studies in an animal model. *Burns Incl Therm Inj*. 1984;10(4):236-251.

24 The Hepatic Response to Thermal Injury

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Introduction

The extreme hypermetabolic and hypercatabolic stress responses induced by a severe burn injury are characterized by increased proteolysis, lipolysis, and production of endogenous glucose via glycogenolysis and gluconeogenesis. The critical organ controlling these processes is the liver. With major roles in metabolism, inflammation, immunity, and the acute-phase response, the liver orchestrates the basic functions that modulate survival and recovery in severely burned patients. The function of the liver following a severe burn injury has been elucidated, demonstrating that the preservation of liver function is associated with survival. The strong correlation between postburn survival and the expression of cytokines and acute-phase proteins (APPs) produced by the liver further supports this contention.

Worldwide, the World Health Organization (WHO) attributes approximately 265,000 deaths each year to burn injuries and their sequelae, with the vast majority of these injuries occurring in low- and middle-income countries.[1] In the United States alone, burns result in approximately 4000 deaths, 24,500 hospitalizations, and more than 745,000 nonhospitalized injuries per year, with an incidence rate of 280 burns (per 100,000 people).[2,3] The effects induced by burns are not limited to the injured area alone. A severe burn injury has devastating effects on the injured patient by affecting almost every organ system, resulting in greater morbidity and mortality.[4] Amplified glucose availability leads to increased protein catabolism and lipolysis, initiating the postburn hypermetabolic stress response.[4–6] Systemic inflammation, including pathophysiologic regulation of cytokines, hormones, and APPs, drives the hypermetabolic response.[7–9] Prolongation or amplification of the hypermetabolic or inflammatory responses may result in dysregulation of counterregulatory stress hormones (catecholamines, cortisol, glucagon), thereby exacerbating postburn hypercatabolism, multiorgan failure, and death.[10,11]

For more than 20 years, reductions in morbidity and mortality have resulted from research efforts focused on improving postburn resuscitation, hypermetabolism, infection control, ventilation, and wound healing.[5] Greater advances in clinical care, however, are needed to reduce morbidity and mortality even further. With a series of studies, we have concluded that the liver plays a fundamental role in the systemic response to burn.[12–16] Through the modulation of immune, inflammatory, metabolic, and acute-phase response signal transduction pathways, the liver contributes greatly to survival and recovery following a severe burn injury.[11] This chapter discusses liver function under normal conditions and following a severe insult such as a burn injury.

Anatomy and Physiology of the Liver

ANATOMY

In an average-sized adult, the liver weighs approximately 1500 g, making up almost 2% of the total body weight. Following a severe burn injury, the liver size can increase significantly to meet additional demands. The Couinaud's segmental system, the preferred anatomy classification system, divides the liver into eight independent functional units (termed segments) rather than relying on the traditional morphological description based on the external appearance of the liver. Roman numerals (I–VIII) delineate the segments based on the dual vascular inflow, biliary drainage, and lymphatic drainage within each segment.[17]

PHYSIOLOGY

A broad spectrum of biological functions is orchestrated by the liver. The interrelated physiologic-anatomic units of the liver direct the following processes:

a. *Energy homeostasis and nutrient metabolism*: the synthesis, degradation, and coupled interconversion of amino acids, carbohydrates, and lipids are closely linked to hepatic energy metabolism.
b. *Protein synthesis and amino acid metabolism*: The liver uses amino acids directly for protein synthesis and as a source of organic nitrogen for nonessential amino acid synthesis. The overall balance of amino acid synthesis, degradation, dietary supply, and body distribution is reflected by plasma amino acid levels.
c. *Carbohydrate metabolism*: The liver plays an important role in maintaining carbohydrate homeostasis, principally through glucose catabolism, production, and storage. The ability to use, store, synthesize, and release glucose gives the liver a central role in maintaining stable serum glucose levels. Compromise of this function can result in hypoglycemia or hyperglycemia.[18]
d. *Lipid metabolism*: Hepatic metabolic energy requirements are met principally through β-oxidation of free fatty acids (FFA). Fatty acids synthesized in the liver or derived from peripheral fat depots combine with glycerol in the liver to form triglycerides (TG). Through

the production of very-low-density lipoproteins (VLDL), the liver provides peripheral tissues with indirect access to the convergent metabolic processes in the hepatocyte that lead to triglyceride synthesis. Following synthesis by the liver, high-density lipoproteins (HDL) circulate in the plasma, where they scavenge free cholesterol released from aging cell membranes. The liver also produces apoprotein CII, which is required for the peripheral activation of lipoprotein lipase, and cholesterol.[19,20]

e. *Biotransformation*: Many environmental compounds (including drugs) and endogenous metabolic products are lipid soluble and nonvolatile, precluding their efficient excretion in urine or feces. Through biotransformation reactions, the liver transforms these substances into more water-soluble analogs and enhances their excretion via urine or bile.[21]
f. *Excretion*: The biliary tract is the principal excretory route for numerous exogenous and endogenous substances. Six hundred to eight hundred milliliters of bile are secreted daily, using a canalicular surface area of approximately 10 m^2. Inorganic ions account for most of the osmotic activity in bile, keeping it approximately isotonic with plasma. Organic solutes present in bile include conjugated bile acids, phospholipids (lecithin), cholesterol, bile pigments, hormones, and small amounts of protein.[22,23]
g. *Immunologic functions*: A major portion of the mononuclear phagocyte system is centered in hepatic sinusoids. Kupffer's cells use phagocytosis and pinocytosis to clear bacteria, particulate matter, and old erythrocytes from sinusoidal blood. Kupffer's cells are also the major site of lipopolysaccharide (endotoxin) detoxification. The liver also contributes to the humoral arm of body defense through uptake and secretion of IgA.[24]
h. *Vitamin metabolism*: Vitamin uptake, storage, and mobilization are additional important functions of the liver. The absorption of fat-soluble vitamins (A, D, E, and K) is dependent on bile salts. Because vitamin A is stored exclusively in the liver, excess ingestion may be associated with significant hepatic injury. Hepatic stellate cells play a role in vitamin A storage as well. The initial vitamin D activation step, conversion of vitamin D_3 to 25-hydroxycholecalciferol, occurs in the liver. Coagulation factors II, VII, IX, and X are dependent on vitamin K, which is essential for the γ-carboxylation and activation of these factors. Vitamin E has recently garnered much attention due to its potent antioxidative properties. Following a severe thermal or traumatic injury, vitamin E might reduce oxidative stress and subsequent damage.[25–27]
i. *Hormonal system*: The liver is an important site of hormonal synthesis, secretion, or interaction. Growth factors that are important for growth and development such as insulin-like growth factor-I (IGF-I) and the IGF binding proteins (IGFBPs) are made and secreted by the liver. Production and secretion into the bloodstream of angiotensinogen occurs within the liver. Synthesis of hepatocyte growth factor (HGF), a major hepatic regenerative growth factor, occurs in the liver.[28]

The Hepatic Response to a Severe Thermal Injury

LIVER DAMAGE AND MORPHOLOGICAL CHANGES

Burn-induced liver injury is variable and is typically proportional to the severity of the burn injury. Hepatomegaly, or a fatty liver, is a common postburn finding (Fig. 24.1). These changes can be reversed; however the significance of these alterations is related to the extent of fat deposition and its etiology.[29] Autopsies of deceased pediatric burn victims revealed that fatty infiltration of the liver is associated with hepatic failure and endotoxemia.[30] Increased hepatic edema, typically observed within 12 hours after burn injury, is associated with damage to the liver. Both liver and body weight significantly increase at 2–7 days postburn, as compared to nonburned liver/body weight.[13] In burned rats, total hepatic protein concentrations are reduced significantly, suggesting that the increase in liver weight is due to edema and not to increased protein levels or hepatocyte numbers. Hepatic edema may induce release of hepatic enzymes into the circulation as a result of cellular damage or by altering membrane permeability. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are typically detected only at low levels in plasma. Therefore, detection of elevated levels in the circulation indicates possible hepatocyte injury. Severe hepatic damage can also be detected by elevations in serum glutamate dehydrogenase or alkaline phosphatase (ALKP). Elevations in ALKP provide insight into the function of the extrahepatic biliary tract and are frequently elevated in hepatobiliary disease. The liver damage induced by thermal injury is secondary to edema formation, hypoperfusion, and inflammation. Following a severe burn, elevations between 50% and 200% of AST, ALT, and ALKP are observed (Fig. 24.2). These serum markers peak early during the first 24 hours after the burn injury, indicating that burn-induced liver damage is a rapid phenomenon.[14,31]

Increased hepatocyte death, both by apoptosis and necrosis, is associated with liver damage.[13] Two distinctly different pathways result in cell death: programmed cell death (apoptosis) and necrosis.[32] Cell shrinkage, uniform fragmentation of DNA, and membrane blebbing characterize apoptotic cells. Necrosis, on the other hand, is characterized by cellular swelling, fragmentation of the DNA in a random manner, activation of lysosomes, and complete breakdown of the cellular membrane enabling cellular contents to be extruded into the interstitium. These final steps induce an inflammatory response by attracting inflammatory cells, causing the release of free radicals and proinflammatory cytokines, leading to additional tissue breakdown. The morphological hallmarks unique to each process are used to differentiate between apoptotic and necrotic cells. At the time of autopsy, 10–15% of severely burned decedents had signs of liver necrosis, as determined by pathological examination.[33]

Apoptosis also occurs in the liver following a cutaneous thermal injury (Fig. 24.2).[13] The liver tries to maintain homeostasis when hepatocyte apoptosis increases by a compensatory increase in hepatocyte proliferation. Despite

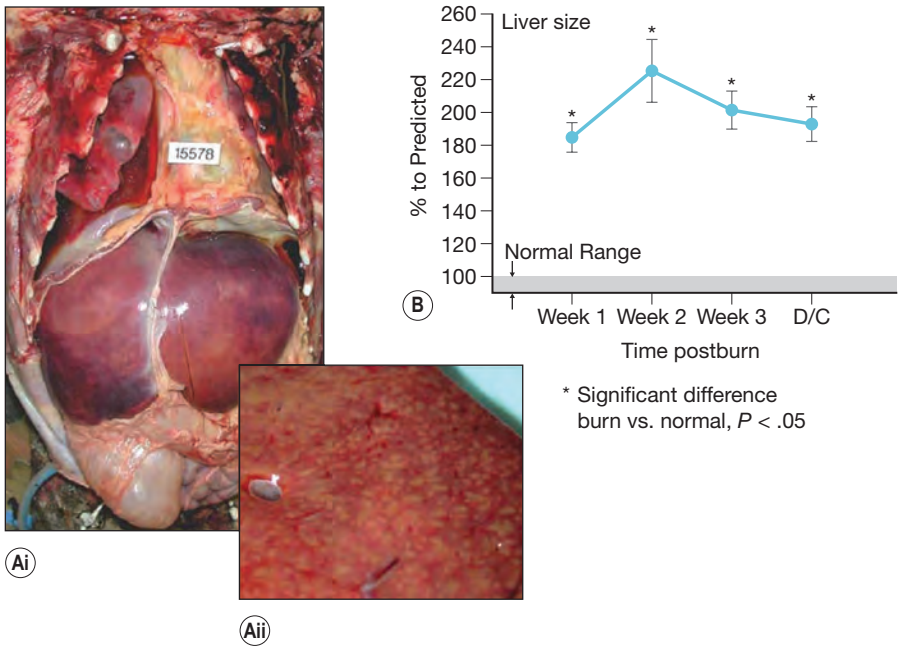

Fig. 24.1 A, Massive hepatomegaly (i) and hepatic fatty infiltration (ii) of a burn victim at autopsy. B, Liver size increased throughout acute hospitalization by over 200% in 242 surviving burn patients. (From Jeschke MG. The hepatic response to thermal injury: is the liver important for postburn outcomes? *Mol Med*. 2009;15:337–351.)

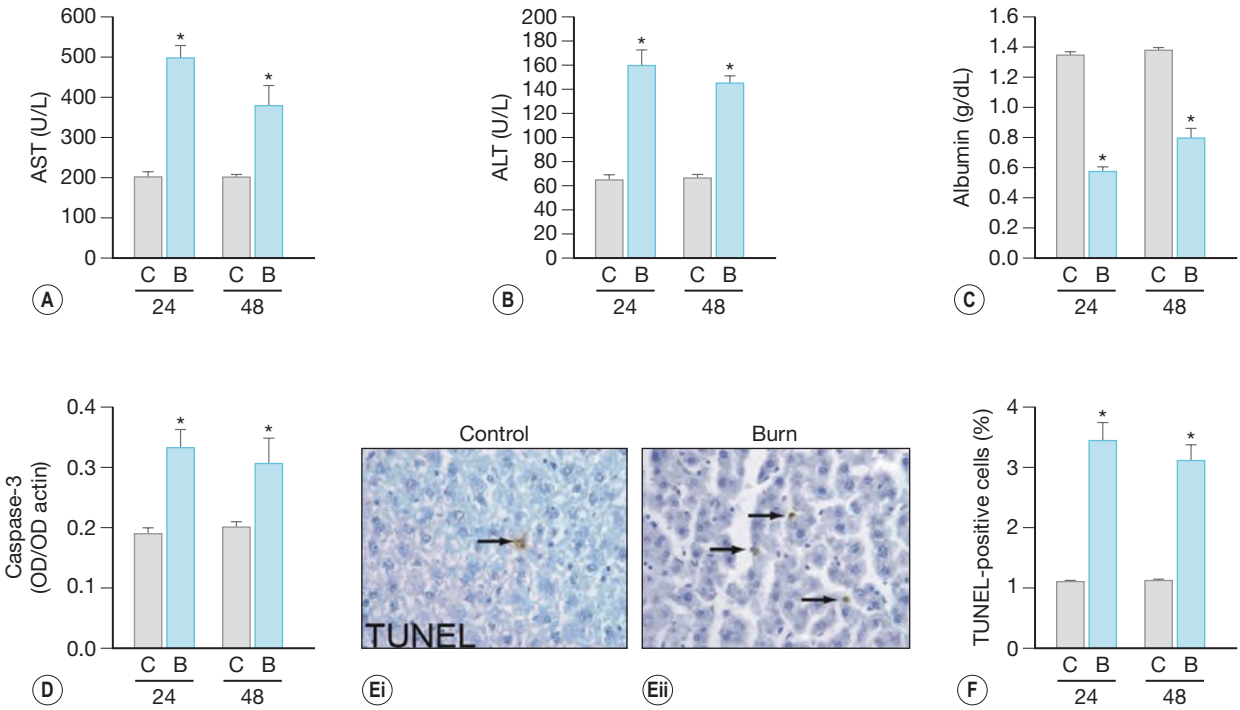

Fig. 24.2 Hepatic dysfunction of the rat burn model mimics the postburn human disease state. A, Serum aspartate amino transferase (AST) 24 and 48 hours after thermal injury. B, Serum alanine amino transferase (ALT) 24 and 48 hours after thermal injury. C, Serum albumin 24 and 48 hours after thermal injury. D, Caspase-3 activity in liver lysates as determined by successive Western blotting with active caspase-3 and actin antibodies. The data are expressed as a ratio of the two band intensities. E, TUNEL staining of a liver section before (i) and 24 hours after (ii) thermal injury. F, Quantified TUNEL-positive cells 24 and 48 hours after thermal injury. Time after injury in hours is indicated. *C,* Control; *B,* burn. Data presented are mean ± SEM. *$P < 0.05$ (Burned animals n = 8 and controls n = 4 per time point). *Significant difference between burn and control, $P < 0.05$. (From Jeschke MG. The hepatic response to thermal injury: is the liver important for postburn outcomes? *Mol Med*. 2009;15:337–351.)

the attempt to maintain homeostasis in overall hepatocyte number, the liver is unable to immediately regain mass or maintain protein concentration. The molecular mechanisms that initiate and propagate hepatocyte apoptosis following a cutaneous burn are not known.[34–37] Blood flow to the bowel is decreased by approximately 60% for up to 4 hours following a thermal injury.[38] Hepatic blood flow is likely decreased as well, and this may be one of the early events inducing programmed cell death. Apoptotic signals, including interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α), increase systemically during this same time frame.[39–42] Additional studies have revealed that the elevations of proinflammatory cytokines are not limited to the serum. Local elevations also occur after a thermal injury, as seen with increased concentrations of hepatic IL-1α, IL-1β, IL-6, and TNF-α.[43–45] Taken together, these events are probably early events in the induction of hepatocyte apoptotic signaling.

Underlying Molecular Mechanisms

The induction of hepatocyte apoptosis and dysfunction following a severe burn (Fig. 24.3), involves specific reductions in endoplasmic reticulum (ER) calcium that lead to increases in cytosolic calcium.[46] Mitochondrial damage occurs as a result of increased cytosolic calcium, leading to the release of cytochrome c, which then binds to the inositol triphosphate receptor (IP3R), causing a reduction in the amount of calcium stored in the ER. In addition, ER stress triggers apoptosis by activating c-Jun N-terminal-kinases (JNK). The serine on the insulin receptor substrate 1 (IRS-1) protein is then phosphorylated, blocking the tyrosine on the same protein from being activated by phosphorylation. At the same time, the prosurvival phosphoinositide 3-kinase (PI3K)/serine-threonine protein kinase (Akt) signaling pathway is blocked, amplifying the ER stress response by further activating the inositol triphosphate receptor (IP3R). If the unfolded protein burden can be limited through the use of chemical chaperones, this discovery may be of therapeutic significance as a method to promote hepatocyte survival.[47] Alternative pharmacologic agents are being developed to block proapoptotic ER stress signaling pathways, and, looking ahead, these alternatives may prove beneficial by improving clinical outcomes.[48,49]

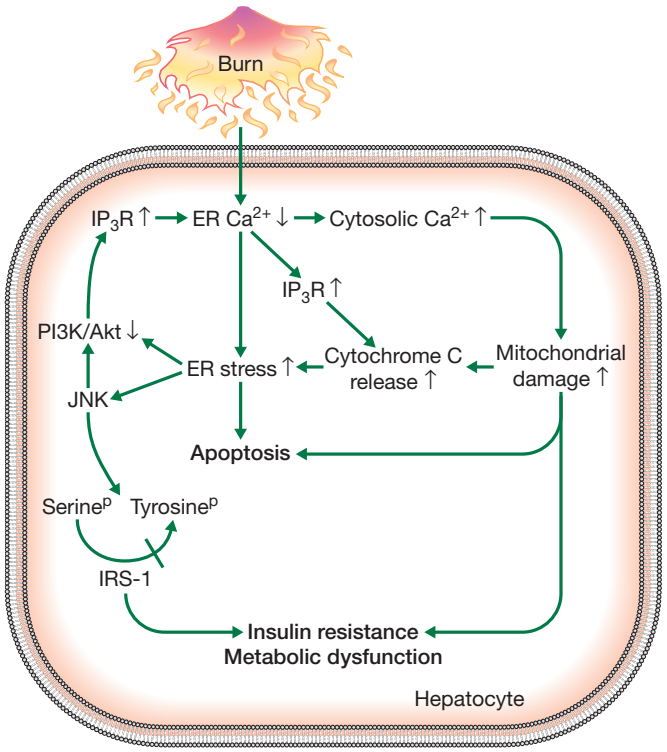

Fig. 24.3 Schematic of suggested pathways involved in the hepatic response postburn. Thermal injury leads to gross alterations in endoplasmic reticulum (ER) calcium with increased cytosolic calcium concentration. Increased cytosolic calcium induces mitochondrial damage, which releases cytochrome c. Cytochrome c increases the existing ER stress/Unfolded protein response (UPR) but also binds to the IP_3R, augmenting the depletion of ER calcium stores. ER stress/UPR leads to cell apoptosis and activation of JNK, which phosphorylates the 612 serine of IRS-1, blocking phosphorylation of tyrosine IRS-1. ER stress/UPR also impairs the prosurvival PI3K/Akt signaling, resulting in increased activation of the IP_3R, increasing ER stress/UPR. (From Jeschke MG. The hepatic response to thermal injury: is the liver important for postburn outcomes? *Mol Med.* 2009;15:337–351.)

EFFECTS ON THE BILIARY SYSTEM

Intrahepatic cholestasis frequently occurs following trauma or sepsis without demonstrable extrahepatic obstruction. Drug toxicity, total parenteral nutrition, and hypoxia are also associated with this phenomenon.[50] The occurrence of intrahepatic cholestasis is associated with impaired bile acid and organic anion transport in basolateral and canalicular hepatocytes.[51,52] Intrahepatic cholestasis occurs in approximately 26% of patients.[33]

MONONUCLEAR PHAGOCYTE SYSTEM (MPS)

The immune system is severely compromised following a major thermal injury, resulting in heightened susceptibility to infections and sepsis.[51,53,54] The phagocytic functions of the mononuclear phagocyte system (MPS) are depressed postburn,[55] although the mechanism by which this occurs is unknown. Investigations have demonstrated that MPS dysfunction may be related to hemolysis. By regulating the production of APPs and proinflammatory cytokines, the liver modulates the immune response.[43,56,57]

Glucose, Protein, and Lipid Metabolism

Hypermetabolic stress is induced by large burns covering in excess of 40% of the total body surface area (TBSA), and this response is accompanied by inflammation, the development of hyperdynamic circulation, temperature elevation, and increased glycolysis, gluconeogenesis, glycogenolysis, proteolysis, and lipolysis.[58–60] These massive alterations affecting major physiologic processes occur following traumatic injury and critical illness as well, although the duration, severity, and the magnitude of these responses are far greater in severely burned patients.[5] Exaggerated elevations in catecholamines, glucocorticoids, glucagon, and dopamine trigger the hypermetabolic response via a highly complex cascade of events.[4,31,61] Additional factors in this response, however, have been identified, including proinflammatory cytokines (IL-1 and IL-6, TNF), platelet-activating factor, endotoxin, neutrophil-adherence complexes, free radicals (reactive oxygen species and nitric oxide),

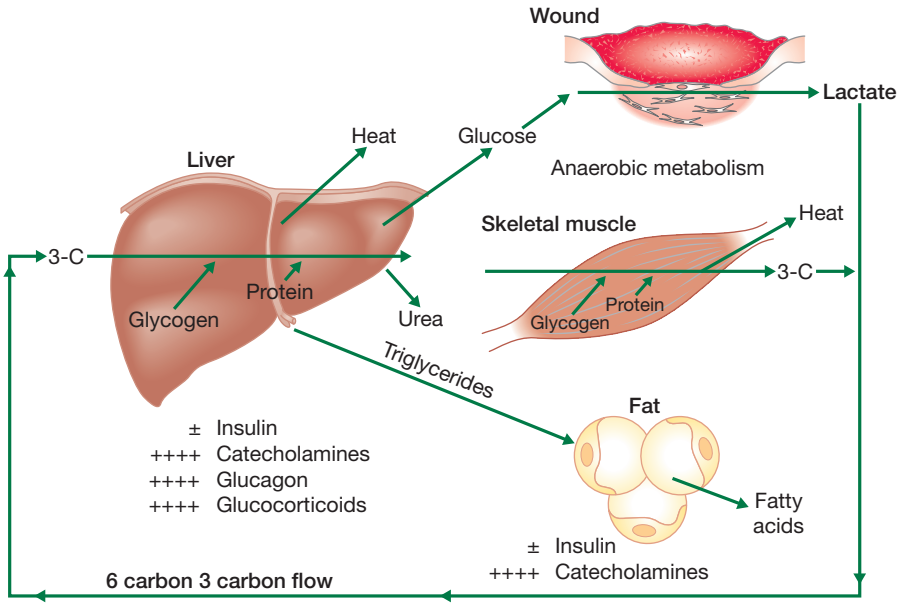

Fig. 24.4 Metabolic changes postburn with the liver playing an essential role. (From Jeschke MG. The hepatic response to thermal injury: is the liver important for postburn outcomes? *Mol Med.* 2009;15:337–351.)

and factors involved in the coagulation and complement cascades.[62] Following activation of the biological processes, these mediators and the resulting byproducts contribute to the increased metabolic rate and altered glucose metabolism that occurs following thermal injuries.[63]

The precise temporal occurrence of the modulation of these postinjury metabolic events has led to the classification of two events: the "ebb phase" and the "flow phase."[64] The first 12–14 hours following a severe burn injury are called the "ebb phase."[65,66] Events characterizing this period include decreased cardiac output, reduced oxygen consumption, attenuated metabolic rate, and hyperglycemia with impaired glucose tolerance. These metabolic processes slowly increase to a plateau over the next 5-day period, termed the "flow phase."[64] During this time, insulin release in response to glucose challenge is twice that seen in nonburned volunteers. Insulin resistance characteristically develops concurrent with elevation in plasma glucose levels during this period[67] (Fig. 24.4). Although these metabolic alterations were assumed to resolve as soon as wound closure was complete, impaired glucose metabolism has been demonstrated in approximately 12% of pediatric burn injury survivors 24–36 months after severe thermal injuries; burn size, age, lean mass, and adiposity are predictors of insulin resistance in burned children.[68]

Because the metabolic alterations that accompany critical illness have the potential to modify energy substrate utilization, glucose availability must be maintained. Stress mediator release acts in opposition to the anabolic actions of insulin by augmenting hepatic glucose production[69] to increase gluconeogenic substrates such as glycerol, alanine, and lactate by increasing lipolysis of adipose tissue and proteolysis of skeletal muscle.[70–74] The release of hepatic glucose is not suppressed by hyperglycemia, and the physiologic inhibitor property of insulin on glycogenolysis is impaired, inducing posttrauma hyperglycemia.[75,76] The hyperglycemic response to stress is further aggravated by catecholamine-induced enhancement of glycogenolysis in the liver and direct sympathetic stimulation of glycogen breakdown.[72] Peripheral insulin resistance occurs in the muscle and adipose tissue when glucose disposal is impaired by catecholamines following alterations in insulin signaling and glucose transporter type 4 (GLUT-4) translocation.[71,77] At 7 days postinjury, IRS-1 activation is impaired at the tyrosine binding site, leading to Akt inhibition in muscle from severely burned children.[67] Protein farnesylation (a posttranslational lipid modification of cysteine residues) has been identified as an additional pathophysiologic mechanism involved in the metabolic dysfunction observed after burn injury.[78] Interference with the insulin signaling pathways in liver and muscle has also been linked to a reduction in mitochondrial oxidation in both tissues and altered lipolytic rates, resulting in attenuation of insulin's action on glucose production in the liver and glucose uptake in the liver.[76,79] Glucose production via gluconeogenesis and glycogenolysis is increased by glucagon and epinephrine, which, in concert with cortisol and growth hormone (GH), act to sustain this response.[69,80] Release of the aforementioned stress hormones is initiated by the action of proinflammatory cytokines, resulting in an indirect effect of these inflammatory mediators on postburn hyperglycemia.[81–84] These same proinflammatory cytokines, including IL-6, monocyte chemotactic protein-1 (MCP-1), and TNF, have been found to directly modify the insulin signal transduction pathway, further exacerbating postburn insulin resistance in the liver and skeletal muscle.[85,86] Throughout the acute and convalescent periods following the burn injury, breakdown of lean muscle protein is prolonged by the supraphysiological expression of proinflammatory cytokines and perturbations in the metabolic pathways.[8,87,88] Thermal injury impairs the body's ability to use fat as an energy source. Significant variation in the expression of the counterregulatory hormones glucagon and cortisone occurs postburn. While burn injury decreases glucagon, there is a

marked increase in cortisone levels that lasts for at least 3 years postinjury.[61,89] Although the likelihood that perturbations of the hormonal system drive postburn hyperglycemia is low, impairment of insulin receptor signaling at the molecular level is the more probable instigator.[90]

Soon after injury, marked lean body mass wasting is driven by the increase in energy requirements, which are mainly satisfied by degradation of proteins in skeletal muscle in severely burned individuals.[5,91] Stable isotope infusion studies have confirmed that this muscle breakdown is associated with pronounced negative nitrogen balances that persist for up to 9 months postinjury.[58] Significant reductions in muscle mass probably contribute to whole-body postburn insulin resistance, as the majority of insulin-stimulated glucose uptake occurs in the skeletal muscle.[92] Stable isotope studies using leucine to monitor whole-body protein flux confirmed the relationship between hyperglycemia and muscle protein catabolism and even showed that hyperglycemia increases proteolysis.[93] Significantly elevated rates of infection and delayed wound healing are associated with reductions in lean body mass of 10–15%.[94] The growth delay in severely burned pediatric patients that lasts for up to 2 years may be accounted for by this persistent protein catabolism.[58,95–97]

During the acute response to burn, there are significant changes in the metabolism of fat, which lead to elevations in serum TGs and FFA, along with changes in body fat content and distribution.[98] This massive mobilization of fat tissue results in fatty deposits in the liver and other organs, most likely due to decreased expression of fat-transporting proteins coupled with elevations of serum TGs and FFA. Hepatomegaly with hepatic steatosis is associated with increases in septic episodes and ultimately with greater mortality,[30] further supporting the notion that impaired liver function in the severely burned patient is closely linked to survival. The hepatic accumulation of TGs occurs both in critically ill patients and in severely burned patients.[99–101] In fact, liver size is increased by more than fourfold in severely burned patients.[30,102] Despite the similar deposition of TGs in the liver following critical illness, the rate of TG accumulation in the postburn liver is far greater than that of any other pathological condition with hepatic steatosis as a sequelae. Hepatic TGs accumulate following a severe burn, resulting from lipolysis induced by β-adrenergic stimulation that releases excessive amounts of fatty acids into the circulation.[103,104] Although insulin typically suppresses lipolysis, the burn-induced insulin resistance is apparent by the diminished effectiveness of insulin in this capacity.[100] Uptake of fatty acids from the circulation by the liver is proportionate to the amount of FFAs available,[20,105] as lipolysis increases FFA delivery, hepatic uptake is increased, and the fatty acids are either oxidized or synthesized into TGs. Because oxidation is a rate-limited step, there is a marked acceleration in the rate of TG synthesis and deposition when large amounts of fat are available either due to lipolysis or diet.[106] Synthesis of hepatic TGs is considered to be a direct metabolic response to a severe burn injury. Excessive intake of glucose and consequent hyperglycemia also lead to postburn hepatic steatosis.[107] Under normal conditions, increases in VLDL-TG secretion accompany accelerated synthesis of hepatic TGs, which reduces the accumulation of TGs in the liver. However, in severely burned patients, there is a reduction in secretion of VLDL-TGs, which is not responsive to the increased synthesis of liver TGs.[104] It would therefore be expected that reducing FFA availability could minimize accumulation of TGs in the liver.

The liver is clearly a key player in the orchestration and modulation of burn-responsive metabolic processes postburn. Alterations in the metabolism of glucose, fat, and protein can result in poor outcomes, and these processes are controlled by the liver. Therefore, we propose that the liver is an essential organ in the response to severe burn injury and that liver function may determine outcomes of severely burned patients.

Acute-Phase Response

There is a shift in hepatic protein synthesis following a major trauma such as a severe burn injury. Hepatic constitutive protein production is downregulated while production is shifted to increase APPs.[11,31,57] This shift in production of APPs represents a reprioritization of liver function to meet new metabolic demands, heighten the immune and inflammatory responses, and support coagulation and wound healing.[57] Traditionally APPs have been divided into two subcategories based on whether they were mediated by IL-1-like cytokines such as IL-1 or TNF (type I APPs, e.g., haptoglobin or α1-acidglycoprotein) or IL-6-like cytokines, including IL-6 or IL-11 (type II APPs, e.g., α2-macroglobulin and fibrinogen).[11] As more evidence supports frequent communication between the type I and type II APPs, this strict division appears to be an artificial categorization that is no longer representative of function or response. While acute-phase protein synthesis is upregulated, constitutive hepatic proteins, including albumin, transthyretin, transferrin, and retinol binding protein, are downregulated.[108–111] Relative to normal levels, albumin and transferrin expression decrease by 50–70% following a severe burn. Two mechanisms downregulate the production of these proteins: the liver shifts from synthesizing constitutive proteins to APPs, coupled with extensive loss of constitutive proteins due to capillary leakage. These proteins are lost into the massive extravascular space and burn wound. The loss of these proteins following trauma, however, may negatively impact clinical outcomes. Albumin and transferrin are important transporter proteins and contribute to regulation of both osmotic pressure and plasma pH. Due to the exclusive roles that these proteins play, reduction in their synthesis has been used to monitor recovery and predict mortality.[111–113]

As noted earlier, cytokines also mediate the acute-phase response. The temporal, biphasic modulation of proinflammatory cytokine expression is highly regulated and predictable. Immediately following a burn, there is an increase in IL-1, IL-6, IL-8, and TNF expression that peaks between 2- and 10-fold above normal levels. After approximately 12 hours, there is a slight decrease in expression, followed by another increase before the overall levels begin to decline. As a testament to the extreme nature of a burn compared with other traumatic injuries, both animal and human studies have revealed that, following a traumatic injury, cytokines return to normal levels within 2 days, whereas the elevation can last for more than 2 weeks after thermal injury.[114,115] The signaling cascade modulating this response includes a multitude of pro- and antiinflammatory signal transcription

factors including nuclear factor-κ B (NF-κB), c-jun, tyrosine phosphorylation and activation of intracellular tyrosine kinases (JAKs), CCAAT/enhancer-binding proteins (C/EBPs), signal transducer and activator of transcription (STAT) 1, STAT3, STAT5, latent cytoplasmic transcription factors, and mitogen-activated protein.[56,108,109,116–119] Transcription, translation, and expression of APPs are initiated by the action of these signaling molecules. IL-6 in particular is suspected of being a major—if not the primary—mediating cytokine. Amplification of the IL-6 signal occurs by activation of glycoprotein 130 (gp 130) and the JAK-kinases (JAK-1) and propagation of the signal via translocation of STAT1 and STAT3 to the nucleus, where transcription and translation of APPs occur. This rapid initiation of the acute-phase response serves a single purpose: to protect the body from further damage. When the acute-phase response occurs in a balanced fashion, the body is protected and returns to a homeostatic existence. When there are prolonged amplifications of proinflammatory cytokines and APPs, however, hypercatabolism results, leading to increased incidence of sepsis, multiorgan failure, morbidity, and mortality.[8,10,112]

Vitamin Metabolism

Vitamins are requisite components of many biological functions including energy production and utilization, inflammation, wound healing, metabolism, and antioxidation. Vitamin deficiencies are caused by the burn-induced hypermetabolic response, so supplementation is required to maintain crucial biological functions.[120,121] Vitamin A is reduced in burn patients, perhaps related to reduced levels of its transporter—retinol binding protein. Without vitamin A, dermal wound repair is suboptimal, and supplementation with this vitamin may enhance wound healing. Vitamin E is a critical antioxidant that has profound effects in reducing lung injury.[27] Because this vitamin is also depleted in the serum and in the tissue following a burn injury, supplementation is also recommended. Vitamin D, a necessary nutrient to maintain bone health, is also reduced following a burn injury, contributing to postburn osteopenia and increasing the risk of bone fractures; vitamin D_3 supplementation after burn injury and beyond the acute period is advocated to counteract the trajectory of low vitamin D levels and associated morbidity.[122–124] Riboflavin and thiamin, also reduced by burn injury and trauma, are important participants in energy generation, protein metabolism, and wound repair. Thiamin is a key co-factor for energy generation in the Krebs cycle, for glucose oxidation, and for the formation of collagen. Riboflavin decreases postburn; due to its role as a coenzyme in oxidation-reduction reactions, this vitamin should also be supplemented.[120] Postburn reduction of folic acid negatively impacts DNA and RNA synthesis. Folate utilization is also impaired by inadequate availability of vitamin B_{12} and methionine. Folate deficiency therefore can also occur as a result of deficient levels of these two nutrients. Energy-generating and protein metabolic processes rely on the coenzymes vitamin B_6 and B_{12}. Supplementation should be in the form of a multivitamin in order to have adequate levels of these necessary components. Additional functions of these vitamins include fatty acid catabolism (vitamin B_{12}) and metabolism of amino acids (vitamin B_6). The antioxidant/free radical scavenging properties of vitamin C are crucial following a burn injury. As part of the hypermetabolic response, an elevation in free radicals including superoxide, peroxide, and hydroxyl is thought to increase burn-induced vascular permeability. Administration of vitamin C may reduce microvascular permeability, which would reduce the need for fluid replacement, in turn improving patient outcomes.[125]

Coagulation and Clotting Factors

A severe burn injury alters the coagulation cascade and activates thrombotic and fibrinolytic responses. During the early shock phase following the burn, there is a decrease in most of the homeostatic markers due to dilutional effects associated with fluid resuscitation and loss or degradation of plasma proteins to the extravascular space or the wound. Once resuscitation is achieved, clotting factors typically return to normal levels. Thrombogenicity increases later during the postburn course as a result of decreases in antithrombin III, protein C, and protein S levels resulting in an increase in the risk of thrombosis. The risk for developing disseminated intravascular coagulation (DIC) is considerably heightened by this hypercoagulable state. Postmortem DIC has been discovered in 30% of all examined cases, indicating another association between liver damage and poor outcomes.[126]

Hormones

The liver is a major site for hormone synthesis and action. In vitro and in vivo studies have demonstrated that HGF accelerates hepatic regeneration, improves hepatic function, and modulates the acute-phase response.[127–129] Elevation of plasma HGF occurs within 30–60 minutes following injury, presumably signaling the hepatocytes to begin dividing in order to meet the anticipated burden. The initiating signal that stimulates plasma HGF upregulation, however, is currently unknown, although it has been hypothesized that there is either an increase in extrahepatic production of HGF by the spleen, lung, gut, or kidney or a decrease in excretion of hepatic HGF. Hepatocyte DNA synthesis is stimulated by this rapid increase in HGF.[28] HGF only has this effect under specific conditions; when administered to noninjured rats, only a small number of hepatocytes were induced to initiate DNA synthesis. This study demonstrated that priming events—such as those experienced following a burn injury—are required to enable hepatocytes to respond to mitogenic signals.[28]

IGF-I is also synthesized in the liver.[130] In the body, approximately 99% of IGF-I is bound to one of the six binding proteins, IGFBP 1–6, for transport.[131] These hormones are synthesized in the liver following GH stimulation.[132] The effects mediated by IGF-I are similar in burn and other pathological states—improvements in cell proliferation, cell repair mechanisms, increased protein expression in the muscle, and restored normal functioning of intestinal and immune cells.[133–135] In the immediate posttrauma and postburn periods, IGF-I is a key player in regenerating the liver and modulating the acute-phase response to restore hepatic homeostasis and function.[135,136] The influence of hormones on hepatic recovery and regeneration is an important consideration when trying to restore hepatic function.

Importance of the Liver for Postburn Outcomes

We have described liver function under normal and severe stress conditions. In addition, it is important to emphasize that it is not known whether liver function and integrity are essential for favorable outcomes following a severe burn. Price et al. found an association between impaired liver function and integrity, and unfavorable postburn outcomes, in a retrospective study.[137] Our group and others have conducted several studies to determine the relationship between liver function and burn outcomes. In a review of autopsies from severely burned children, Barret et al. reported the incidence of hepatomegaly, fatty liver, and sepsis. Approximately 80% of the patients had hepatic fat infiltration, whereas 100% of the patients had hepatomegaly.[30] Additionally the incidence of sepsis was greater in patients with severe fatty infiltration of the liver. In a study of 102 severely burned children, burn injury was associated with liver enlargement in all patients regardless of outcome.[14] During the first week following a burn injury, liver size was significantly increased (+185 ± 5%), peaked during the second postinjury week (+226 ± 19%), and remained significantly enlarged (+189 ± 10%) at the time of discharge. Prolonged alteration of the hepatic structure was indicated by the continued increase in predicted liver weight (+140–150%) even 6, 9, and 12 months postburn. Synthesis of hepatic proteins was impaired for at least 12 months following the burn injury. Based on this study, it was concluded that a severe burn injury induced significant enlargement of the liver concurrent with impaired hepatic protein synthesis.

Mittendorfer et al. determined the contributions of hepatomegaly and hepatic steatosis to outcomes following a severe burn in the well-established rodent model.[106] Following a burn covering 60% TBSA, nutritional manipulation was used to induce fatty liver in a subset of rats. Hepatomegaly and hepatic steatosis were induced by consumption of a high-fat diet. If both hepatomegaly and fatty liver were present, postburn mortality increased to 40% (compared with 0% in the control group). Based on these findings, we concluded that the integrity and function of the liver were crucial for survival after a severe burn injury because hepatomegaly, hepatic steatosis, and liver dysfunction were associated with increased postburn mortality. Other models have been used to demonstrate the importance of liver function for survival after critical illness.[138] In a murine sepsis model, Deutschman et al. found that IL-6 knockout mice were more likely to die as opposed to their littermates with normal IL-6 expression. Hepatic alterations were apparent in the IL-6 knockout animals following cecal ligation and puncture. Cholestasis, steatosis, and hepatocellular injury were not found in the normal mice but were apparent in the IL-6 knockout animals; liver regeneration was absent in the septic IL-6 knockout animals, while apparent in the control group. The investigators demonstrated that IL-6 is a key regulator of the pathological changes of the liver observed after sepsis. The most interesting finding, however, was the association of a three- to fourfold increase in mortality in animals with hepatic damage or dysfunction.[138] Hepatic failure and concomitant hepatocyte apoptosis have been linked to the signaling pathway involving Fas and Fas ligand (Fas/FasL).[139] Through a series of RNA interference studies, Song et al.[140] elegantly demonstrated that reduction in the expression of Fas is protective during fulminant hepatitis. Silencing Fas prevented death, leading to the conclusion that hepatic dysfunction contributes to mortality and restoration of hepatic function reduces mortality. Although investigation of the role of Fas/FasL in burns is still in its early stages, evidence supports the postburn induction of Fas/FasL[141] possibly hinting at the mechanism underlying burn-induced hepatocyte apoptosis and dysfunction.

Because animal models do not fully recapitulate the human clinical response, prospective clinical studies are necessary to determine the relationship between liver function and postburn outcomes. In a study conducted as part of the Inflammation and the Host Response to Injury Collaborative Research Program, we used discovery proteomics to compare plasma protein expression in survivors and nonsurvivors of severe burn injuries.[142] A total of 32 patients, including 16 nonsurvivors and 16 survivors were matched according to burn size and injury severity. Discovery proteomics techniques were used to determine plasma protein expression. In burn patients, 43 proteins were associated with mortality. The main activity of the associated proteins involve the complement cascade, coagulation cascade, acute-phase response pathway, and cytokine signaling suggest that the response of the liver may be crucial to survival following a burn injury.[142]

Another study involving 330 burned children determined whether proteomics could be used to augment clinical parameters as predictors of mortality in pediatric burn patients. The study showed that the combination of both clinical and proteomic variables improved the outcome prediction accuracy from 52% to 81%. The panel of 38 potential biomarkers included hormones, proteins, and cytokines, and most of these biomarkers are produced by the liver. Taken together, the data in severely burned children and adults indicate that the liver is crucial for determining survival and postburn outcomes.[143]

Conclusion

To summarize, the widespread effects of a burn injury impact almost every organ system, resulting in significant morbidity and mortality.[5] This chapter has explored the liver's central role in the response to severe thermal injury. Myriad functions of the liver are essential for survival (Fig. 24.5), and the burn injury alters all of these hepatic responses. Available data provide strong evidence that the concentrations of hepatic proteins in the circulation can serve as biomarkers predictive of postburn morbidity and mortality. We therefore interpret these findings as supporting the central role of the liver in determining patient outcome and propose that attenuation of liver damage and restoration of hepatic function will result in a reduction of postburn morbidity and mortality.

Acknowledgments

This chapter was supported by grants from the American Surgical Association Foundation, the Shriners Hospitals for Children (71008 and 84080), the NIH (P50-GM060338, T32-GM-008256, R01-GM56687, R01-GM087285, and

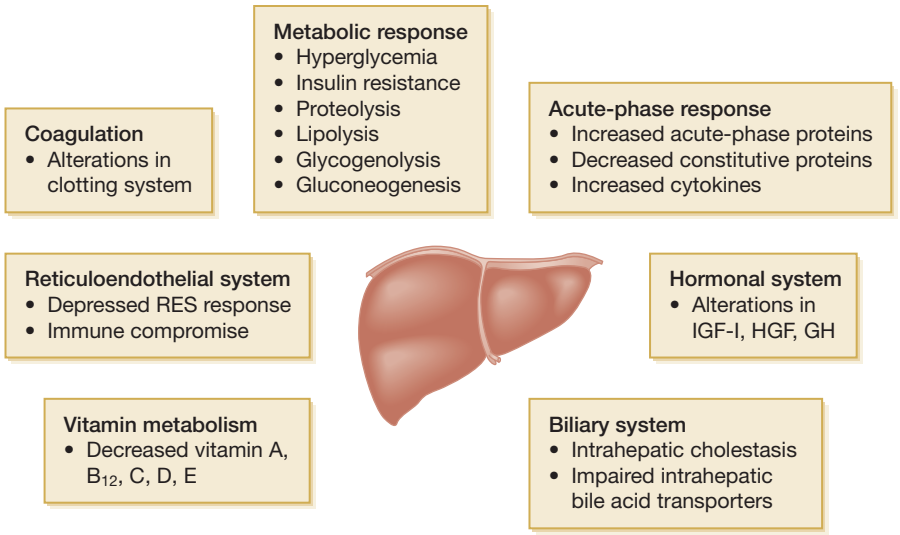

Fig. 24.5 Overview of hepatic functions and responses. (From Jeschke MG. The hepatic response to thermal injury: is the liver important for postburn outcomes? *Mol Med*. 2009;15:337–351.)

R01-GM112936), the NIH National Center for Advancing Translational Sciences the NIDILRR (KL2 TR001441), and the CFI Leaders Opportunity Fund (25407). The authors have no conflicts of interest to disclose.

Complete references available online at www.expertconsult.inkling.com

Further Reading

Chondronikola M, Meyer WJ, Sidossis LS, et al. Predictors of insulin resistance in pediatric burn injury survivors 24 to 36 months postburn. *J Burn Care Res*. 2014;35(5):409-415.

Jeschke MG, Chinkes DL, Finnerty CC, et al. Pathophysiologic response to severe burn injury. *Ann Surg*. 2008;248:387-401.

Jeschke MG, Micak RP, Finnerty CC, et al. Changes in liver function and size after a severe thermal injury. *Shock*. 2007;28:172-177.

References

1. Krug E. A WHO plan for burn prevention and care. WHO Library Cataloguing-in-Publication Data. 2015.
2. Shields BJ, Comstock RD, Fernandez S, Xiang H, Smith G. Healthcare resource utilization and epidemiology of pediatric burn-associated hospitalizations, United States, 2000. *J Burn Care Res*. 2007;28(6):811-826.
3. Corso P, Finkelstein E, Miller T, Fiebelkorn I, Zaloshnja E. Incidence and lifetime costs of injuries in the United States. *Inj Prev*. 2015;21(6):434-440.
4. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR. Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med*. 2001;345(17):1223-1229.
5. Herndon DN, Tompkins RG. Support of the metabolic response to burn injury. *Lancet*. 2004;363:1895-1902.
6. Stoecklin P, Delodder F, Pantet O, Berger MM. Moderate glycemic control safe in critically ill adult burn patients: a 15 year cohort study. *Burns*. 2016;42(1):63-70.
7. Finnerty CC, Herndon DN, Przkora R, et al. Cytokine expression profile over time in severely burned pediatric patients. *Shock*. 2006;26(1):13-19.
8. Tracey KJ, Fong Y, Hesse DG, et al. Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. *Nature*. 1987;330(6149):662-664.
9. Finnerty CC, Przkora R, Herndon DN, Jeschke MG. Cytokine expression profile over time in burned mice. *Cytokine*. 2009;45(1):20-25.
10. Tracey KJ, Lowry SF, Fahey TJ, et al. Cachectin/tumor necrosis factor induces lethal shock and stress hormone responses in the dog. *Surg Gynecol Obstet*. 1987;164(5):415-422.
11. Moshage H. Cytokines and the hepatic acute phase response. *J Pathol*. 1997;181(3):257-266.
12. Jeschke MG, Klein D, Herndon DN. Insulin treatment improves the systemic inflammatory reaction to severe trauma. *Ann Surg*. 2004;239(4):553-560.
13. Jeschke MG, Low JF, Spies M, et al. Cell proliferation, apoptosis, NF-kappaB expression, enzyme, protein, and weight changes in livers of burned rats. *Am J Physiol Gastrointest Liver Physiol*. 2001;280(6):G1314-G1320.
14. Jeschke MG, Micak RP, Finnerty CC, Herndon DN. Changes in liver function and size after a severe thermal injury. *Shock*. 2007;28(2):172-177.
15. Jeschke MG, Rensing H, Klein D, et al. Insulin prevents liver damage and preserves liver function in lipopolysaccharide-induced endotoxemic rats. *J Hepatol*. 2005;42(6):870-879.
16. Gauglitz GG, Halder S, Boehning DF, et al. Post-burn hepatic insulin resistance is associated with endoplasmic reticulum (ER) stress. *Shock*. 2010;33(3):299-305.
17. Lowe MC, D'Angelica MI. Anatomy of hepatic resectional surgery. *Surg Clin North Am*. 2016;96(2):183-195.
18. Wolfe RR, Herndon DN, Jahoor F, Miyoshi H, Wolfe M. Effect of severe burn injury on substrate cycling by glucose and fatty acids. *N Engl J Med*. 1987;317(7):403-408.
19. Corless JK, Middleton HM. Normal liver function. A basis for understanding hepatic disease. *Arch Intern Med*. 1983;143(12):2291-2294.
20. Aarsland A, Chinkes D, Wolfe RR. Contributions of de novo synthesis of fatty acids to total VLDL-triglyceride secretion during prolonged hyperglycemia/hyperinsulinemia in normal man. *J Clin Invest*. 1996;98(9):2008-2017.
21. Schwartz SI, Shires GT, Spencer FC. Liver. In: Schwartz SI, ed. *Principles of surgery*. NY: 1395-1436.
22. Gruppuso PA, Sanders JA. Regulation of liver development: implications for liver biology across the lifespan. *J Mol Endocrinol*. 2016;56(3):R115-R125.
23. Robinson MW, Harmon C, O'Farrelly C. Liver immunology and its role in inflammation and homeostasis. *Cell Mol Immunol*. 2016;13(3):267-276.
24. Kleinman RE, Harmatz PR, Walker WA. The liver: an integral part of the enteric mucosal immune system. *Hepatology*. 1982;2(3):379-384.
25. Chaves GV, Peres WAF, Goncalves JC, Ramalho A, Vitamin A. and retinol-binding protein deficiency among chronic liver disease patients. *Nutrition*. 2015;31(5):664-668.
26. Barbosa E, Faintuch J, Machado Moreira EA, et al. Supplementation of vitamin E, vitamin C, and zinc attenuates oxidative stress in burned children: a randomized, double-blind, placebo-controlled pilot study. *J Burn Care Res*. 2009;30(5):859-866.
27. Shimoda K, Nakazawa H, Traber MG, Traber DL, Nozaki M. Plasma and tissue vitamin E depletion in sheep with burn and smoke inhalation injury. *Burns*. 2008;34(8):1137-1141.
28. Gómez-Lechón MJ, Castelli J, Guillén I, et al. Effects of hepatocyte growth factor on the growth and metabolism of human hepatocytes in primary culture. *Hepatology*. 1995;21(5):1248-1254.
29. Kallinen O, Maisniemi K, Bohling T, Tukiainen E, Koljonen V. Multiple organ failure as a cause of death in patients with severe burns. *J Burn Care Res*. 2012;33(2):206-211.
30. Barret JP, Jeschke MG, Herndon DN. Fatty infiltration of the liver in severely burned pediatric patients: autopsy findings and clinical implications. *J Trauma*. 2001;51(4):736-739.
31. Jeschke MG, Chinkes DL, Finnerty CC, et al. Pathophysiologic response to severe burn injury. *Ann Surg*. 2008;248(3):387-401.
32. Steller H. Mechanisms and genes of cellular suicide. *Science*. 1995;267(5203):1445-1449.
33. Linares H, Carvajal H, Parks D. Autopsy finding in burned children. *Burn Child Chicago Year B Med*. 1991;1-25.
34. Baron P, Traber LD, Traber DL, et al. Gut failure and translocation following burn and sepsis. *J Surg Res*. 1994;57(1):197-204.
35. Baron PW, Barrow RE, Pierre EJ, Herndon DN. Prolonged use of propranolol safely decreases cardiac work in burned children. *J Burn Care Rehabil*. 1997;18(3):223-227.
36. Ikeda H, Suzuki Y, Suzuki M, et al. Apoptosis is a major mode of cell death caused by ischaemia and ischaemia/reperfusion injury to the rat intestinal epithelium. *Gut*. 1998;42(4):530-537.
37. Noda T, Iwakiri R, Fujimoto K, Matsuo S, Aw TY. Programmed cell death induced by ischemia-reperfusion in rat intestinal mucosa. *Am J Physiol*. 1998;274(2 Pt 1):G270-G276.
38. Ramzy PI, Wolf SE, Irtun O, et al. Gut epithelial apoptosis after severe burn: effects of gut hypoperfusion. *J Am Coll Surg*. 2000;190(3):281-287.
39. Bellas RE, FitzGerald MJ, Fausto N, Sonenshein GE. Inhibition of NF-kappa B activity induces apoptosis in murine hepatocytes. *Am J Pathol*. 1997;151(4):891-896.
40. Boehning D, Patterson RL, Sedaghat L, et al. Cytochrome c binds to inositol (1,4,5) trisphosphate receptors, amplifying calcium-dependent apoptosis. *Nat Cell Biol*. 2003;5(12):1051-1061.
41. Strasser A, O'Connor L, Dixit VM. Apoptosis signaling. *Annu Rev Biochem*. 2000;69:217-245.
42. Yoneda T, Imaizumi K, Oono K, et al. Activation of caspase-12, an endoplastic reticulum (ER) resident caspase, through tumor necrosis factor receptor-associated factor 2-dependent mechanism in response to the ER stress. *J Biol Chem*. 2001;276(17):13935-13940.
43. Klein D, Schubert T, Horch RE, Jauch K-W, Jeschke MG. Insulin treatment improves hepatic morphology and function through modulation of hepatic signals after severe trauma. *Ann Surg*. 2004;240(2):340-349.
44. Gauglitz GG, Song J, Herndon DN, et al. Characterization of the inflammatory response during acute and post-acute phases after severe burn. *Shock*. 2008;30(5):503-507.
45. Jeschke MG, Boehning DF, Finnerty CC, Herndon DN. Effect of insulin on the inflammatory and acute phase response after burn injury. *Crit Care Med*. 2007;35(9 suppl):S519-S523.
46. Jeschke MG, Gauglitz GG, Song J, et al. Calcium and ER stress mediate hepatic apoptosis after burn injury. *J Cell Mol Med*. 2009;13(8B):1857-1865.
47. Ozcan U, Yilmaz E, Ozcan L, et al. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. *Science*. 2006;313(5790):1137-1140.
48. Wiseman RL, Balch WE. A new pharmacology–drugging stressed folding pathways. *Trends Mol Med*. 2005;11(8):347-350.
49. Hiyama Y, Marshall AH, Kraft R, et al. Effects of metformin on burn-induced hepatic endoplasmic reticulum stress in male rats. *Mol Med*. 2013;19:1-6.
50. Cano N, Gerolami A. Intrahepatic cholestasis during total parenteral nutrition. *Lancet*. 1983;1(8331):985.
51. Knox J, Demling R, Wilmore D, Sarraf P, Santos A. Increased survival after major thermal injury: the effect of growth hormone therapy in adults. *J Trauma*. 1995;39(3):522-526.
52. Bolder U, Ton-Nu HT, Schteingart CD, Frick E, Hofmann AF. Hepatocyte transport of bile acids and organic anions in endotoxemic rats: impaired uptake and secretion. *Gastroenterology*. 1997;112(1):214-225.
53. Kobayashi M, Takahashi H, Sanford AP, et al. An increase in the susceptibility of burned patients to infectious complications due to

impaired production of macrophage inflammatory protein 1 alpha. *J Immunol*. 2002;169(8):4460-4466.
54. Kobayashi M, Tsuda Y, Yoshida T, et al. Bacterial sepsis and chemokines. *Curr Drug Targets*. 2006;7(1):119-134.
55. Trop M, Schiffrin EJ, Callahan RJ, Strauss HW, Carter EA. Effect of acute burn trauma on reticuloendothelial system phagocytic activity in rats. II: comparison of uptake of radiolabelled colloid and bacteria. *Burns*. 1990;16(4):278-280.
56. Klein D, Einspanier R, Bolder U, Jeschke MG. Differences in the hepatic signal transcription pathway and cytokine expression between thermal injury and sepsis. *Shock*. 2003;20(6):536-543.
57. Jeschke MG, Barrow RE, Herndon DN. Extended hypermetabolic response of the liver in severely burned pediatric patients. *Arch Surg*. 2004;139(6):641-647.
58. Hart DW, Wolf SE, Chinkes DL, et al. Determinants of skeletal muscle catabolism after severe burn. *Ann Surg*. 2000;232(4):455-465.
59. Reiss E, Pearson E, Artz CP. The metabolic response to burns. *J Clin Invest*. 1956;35:62-77.
60. Haze K, Yoshida H, Yanagi H, Yura T, Mori K. Mammalian transcription factor ATF6 is synthesized as a transmembrane protein and activated by proteolysis in response to endoplasmic reticulum stress. *Mol Biol Cell*. 1999;10(11):3787-3799.
61. Norbury WB, Herndon DN, Branski LK, Chinkes DL, Jeschke MG. Urinary cortisol and catecholamine excretion after burn injury in children. *J Clin Endocrinol Metab*. 2008;93(4):1270-1275.
62. Sherwood ER, Toliver-Kinsky T. Mechanisms of the inflammatory response. *Best Pract Res Clin Anaesthesiol*. 2004;18(3):385-405.
63. Pereira CT, Herndon DN. The pharmacologic modulation of the hypermetabolic response to burns. *Adv Surg*. 2005;39:245-261.
64. Wolfe RR. Review: acute versus chronic response to burn injury. *Circ Shock*. 1981;8(1):105-115.
65. Cuthbertson DP, Angeles Valero Zanuy MA, León Sanz ML. Post-shock metabolic response. 1942. *Nutr Hosp*. 2001;16(5):176.
66. Tredget EE, Yu YM. The metabolic effects of thermal injury. *World J Surg*. 1992;16(1):68-79.
67. Cree MG, Zwetsloot JJ, Herndon DN, et al. Insulin sensitivity and mitochondrial function are improved in children with burn injury during a randomized controlled trial of fenofibrate. *Ann Surg*. 2007;245(2):214-221.
68. Chondronikola M, Meyer WJ, Sidossis LS, et al. Predictors of insulin resistance in pediatric burn injury survivors 24 to 36 months post-burn. *J Burn Care Res*. 2014;35(5):409-415.
69. Khani S, Tayek JA. Cortisol increases gluconeogenesis in humans: its role in the metabolic syndrome. *Clin Sci*. 2001;101(6):739-747.
70. Wolfe RR, Herndon DN, Peters EJ, et al. Regulation of lipolysis in severely burned children. *Ann Surg*. 1987;206(2):214-221.
71. Gearhart MM, Parbhoo SK. Hyperglycemia in the critically ill patient. *AACN Clin Issues*. 2006;17(1):50-55.
72. Robinson LE, van Soeren MH. Insulin resistance and hyperglycemia in critical illness: role of insulin in glycemic control. *AACN Clin Issues*. 2004;15(1):45-62.
73. Gore DC, Jahoor F, Wolfe RR, Herndon DN. Acute response of human muscle protein to catabolic hormones. *Ann Surg*. 1993;218(5):679-684.
74. Carlson GL. Insulin resistance and glucose-induced thermogenesis in critical illness. *Proc Nutr Soc*. 2001;60(3):381-388.
75. Wolfe RR, Durkot MJ, Allsop JR, Burke JF. Glucose metabolism in severely burned patients. *Metabolism*. 1979;28(10):1031-1039.
76. Cree MG, Fram RY, Herndon DN, et al. Human mitochondrial oxidative capacity is acutely impaired after burn trauma. *Am J Surg*. 2008;196(2):234-239.
77. Hunt DG, Ivy JL. Epinephrine inhibits insulin-stimulated muscle glucose transport. *J Appl Physiol*. 2002;93(5):1638-1643.
78. Nakazawa H, Yamada M, Tanaka T, et al. Role of protein farnesylation in burn-induced metabolic derangements and insulin resistance in mouse skeletal muscle. *PLoS ONE*. 2015;10(1):e0116633.
79. Cree MG, Newcomer BR, Herndon DN, et al. PPAR-alpha agonism improves whole body and muscle mitochondrial fat oxidation, but does not alter intracellular fat concentrations in burn trauma children in a randomized controlled trial. *Nutr Metab (Lond)*. 2007;4:9.
80. Gustavson SM, Chu CA, Nishizawa M, et al. Glucagon's actions are modified by the combination of epinephrine and gluconeogenic precursor infusion. *Am J Physiol Endocrinol Metab*. 2003;285(3):E534-E544.
81. Akita S, Akino K, Ren SG, et al. Elevated circulating leukemia inhibitory factor in patients with extensive burns. *J Burn Care Res*. 2006;27(2):221-225.
82. Lang CH. Sepsis-induced insulin resistance in rats is mediated by a beta-adrenergic mechanism. *Am J Physiol*. 1992;263(4 Pt 1):E703-E711.
83. Lang CH, Dobrescu C, Bagby GJ. Tumor necrosis factor impairs insulin action on peripheral glucose disposal and hepatic glucose output. *Endocrinology*. 1992;130(1):43-52.
84. Lang CH, Frost RA, Vary TC. Regulation of muscle protein synthesis during sepsis and inflammation. *Am J Physiol Endocrinol Metab*. 2007;293(2):E453-E459.
85. Fan J, Li YH, Wojnar MM, Lang CH. Endotoxin-induced alterations in insulin-stimulated phosphorylation of insulin receptor, IRS-1, and MAP kinase in skeletal muscle. *Shock*. 1996;6(3):164-170.
86. Sell H, Dietze-Schroeder D, Kaiser U, Eckel J. Monocyte chemotactic protein-1 is a potential player in the negative cross-talk between adipose tissue and skeletal muscle. *Endocrinology*. 2006;147(5):2458-2467.
87. Jahoor F, Desai M, Herndon DN, Wolfe RR. Dynamics of the protein metabolic response to burn injury. *Metabolism*. 1988;37(4):330-337.
88. Jahoor F, Herndon DN, Wolfe RR. Role of insulin and glucagon in the response of glucose and alanine kinetics in burn-injured patients. *J Clin Invest*. 1986;78(3):807-814.
89. Gauglitz GG, Herndon DN, Kulp GA, Meyer WJ, Jeschke MG. Abnormal insulin sensitivity persists up to three years in pediatric patients post-burn. *J Clin Endocrinol Metab*. 2008;94(5):1656-1664.
90. Ikezu T, Okamoto T, Yonezawa K, Tompkins RG, Martyn JA. Analysis of thermal injury-induced insulin resistance in rodents. Implication of postreceptor mechanisms. *J Biol Chem*. 1997;272(40):25289-25295.
91. Graves C, Saffle J, Cochran A. Actual burn nutrition care practices: an update. *J Burn Care Res*. 2009;30(1):77-82. doi:10.1097/BCR.0b013e3181921f0d. PMID: 19060732.
92. DeFronzo RA, Jacot E, Jequier E, et al. The effect of insulin on the disposal of intravenous glucose. Results from indirect calorimetry and hepatic and femoral venous catheterization. *Diabetes*. 1981;30(12):1000-1007.
93. Flakoll PJ, Hill JO, Abumrad NN. Acute hyperglycemia enhances proteolysis in normal man. *Am J Physiol*. 1993;265(5 Pt 1):E715-E721.
94. Chang DW, DeSanti L, Demling RH. Anticatabolic and anabolic strategies in critical illness: a review of current treatment modalities. *Shock*. 1998;10(3):155-160.
95. Przkora R, Jeschke MG, Barrow RE, et al. Metabolic and hormonal changes of severely burned children receiving long-term oxandrolone treatment. *Ann Surg*. 2005;242(3):384-389, discussion 390-391.
96. Przkora R, Barrow RE, Jeschke MG, et al. Body composition changes with time in pediatric burn patients. *J Trauma*. 2006;60(5):968-971, discussion 971.
97. Diaz EC, Herndon DN, Porter C, et al. Effects of pharmacological interventions on muscle protein synthesis and breakdown in recovery from burns. *Burns*. 2015;41(4):649-657.
98. Patel P, Sallam HS, Ali A, et al. Changes in fat distribution in children following severe burn injury. *Metab Syndr Relat Disord*. 2014;12(10):523-526.
99. Wolfe BM, Walker BK, Shaul DB, Wong L, Ruebner BH. Effect of total parenteral nutrition on hepatic histology. *Arch Surg*. 1988;123(9):1084-1090.
100. Aarsland A, Chinkes DL, Sakurai Y, et al. Insulin therapy in burn patients does not contribute to hepatic triglyceride production. *J Clin Invest*. 1998;101(10):2233-2239.
101. Barrow RE, Mlcak R, Barrow LN, Hawkins HK. Increased liver weights in severely burned children: comparison of ultrasound and autopsy measurements. *Burns*. 2004;30(6):565-568.
102. Barrow RE, Wolfe RR, Dasu MR, Barrow LN, Herndon DN. The use of beta-adrenergic blockade in preventing trauma-induced hepatomegaly. *Ann Surg*. 2006;243(1):115-120.
103. Aarsland A, Chinkes D, Wolfe RR, et al. Beta-blockade lowers peripheral lipolysis in burn patients receiving growth hormone. Rate of hepatic very low density lipoprotein triglyceride secretion remains unchanged. *Ann Surg*. 1996;223(6):777-779.
104. Morio B, Irtun O, Herndon DN, Wolfe RR. Propranolol decreases splanchnic triacylglycerol storage in burn patients receiving a high-carbohydrate diet. *Ann Surg*. 2002;236(2):218-225.

105. Martini WZ, Irtun O, Chinkes DL, et al. Alteration of hepatic fatty acid metabolism after burn injury in pigs. *JPEN J Parenter Enteral Nutr*. 2001;25(6):310-316.
106. Mittendorfer B, Jeschke MG, Wolf SE, Sidossis LS. Nutritional hepatic steatosis and mortality after burn injury in rats. *Clin Nutr*. 1998;17(6):293-299.
107. Deng Q-G, She H, Cheng JH, et al. Steatohepatitis induced by intragastric overfeeding in mice. *Hepatology*. 2005;42(4):905-914.
108. Gilpin DA, Hsieh CC, Kuninger DT, Herndon DN, Papaconstantinou J. Effect of thermal injury on the expression of transcription factors that regulate acute phase response genes: the response of C/EBP alpha, C/EBP beta, and C/EBP delta to thermal injury. *Surgery*. 1996;119(6):674-683.
109. Gilpin DA, Hsieh CC, Kuninger DT, Herndon DN, Papaconstantinou J. Regulation of the acute phase response genes alpha 1-acid glycoprotein and alpha 1-antitrypsin correlates with sensitivity to thermal injury. *Surgery*. 1996;119(6):664-673.
110. Hiyama DT, von Allmen D, Rosenblum L, et al. Synthesis of albumin and acute-phase proteins in perfused liver after burn injury in rats. *J Burn Care Rehabil*. 1991;12(1):1-6.
111. Livingston DH, Mosenthal AC, Deitch EA. Sepsis and multiple organ dysfunction syndrome: a clinical-mechanistic overview. *New Horiz*. 1995;3(2):257-266.
112. De Maio A, Torres MB, Reeves RH. Genetic determinants influencing the response to injury, inflammation, and sepsis. *Shock*. 2005;23(1):11-17.
113. De Maio A, Mooney ML, Matesic LE, Paidas CN, Reeves RH. Genetic component in the inflammatory response induced by bacterial lipopolysaccharide. *Shock*. 1998;10(5):319-323.
114. Finnerty CC, Herndon DN, Chinkes DL, Jeschke MG. Serum cytokine differences in severely burned children with and without sepsis. *Shock*. 2007;27(1):4-9.
115. Jeschke MG, Mlcak RP, Finnerty CC, et al. Burn size determines the inflammatory and hypermetabolic response. *Crit Care*. 2007;11(4):R90.
116. Kishimoto T, Taga T, Akira S. Cytokine signal transduction. *Cell*. 1994;76(2):253-262.
117. Niehof M, Streetz K, Rakemann T, et al. Interleukin-6-induced tethering of STAT3 to the LAP/C/EBPbeta promoter suggests a new mechanism of transcriptional regulation by STAT3. *J Biol Chem*. 2001;276(12):9016-9027.
118. Janes KA, Albeck JG, Gaudet S, et al. A systems model of signaling identifies a molecular basis set for cytokine-induced apoptosis. *Science*. 2005;310(5754):1646-1653.
119. Mori K, Ma W, Gething MJ, Sambrook J. A transmembrane protein with a cdc2+/CDC28-related kinase activity is required for signaling from the ER to the nucleus. *Cell*. 1993;74(4):743-756.
120. Chan MM, Chan GM. Nutritional therapy for burns in children and adults. *Nutrition*. 2009;25(3):261-269.
121. Nguyen TT, Cox CS, Traber DL, et al. Free radical activity and loss of plasma antioxidants, vitamin E, and sulfhydryl groups in patients with burns: the 1993 Moyer Award. *J Burn Care Rehabil*. 1993;14(6):602-609.
122. Gottschlich MM, Mayes T, Khoury J, Kagan RJ. Clinical trial of vitamin d2 vs d3 supplementation in critically ill pediatric burn patients. *JPEN J Parenter Enteral Nutr*. 2017;41(3):412-421.
123. Sobouti B, Riahi A, Fallah S, et al. Serum 25-hydroxyvitamin d levels in pediatric burn patients. *Trauma Mon*. 2016;21(1):e30905.
124. Klein GL, Langman CB, Herndon DN. Vitamin D depletion following burn injury in children: a possible factor in post-burn osteopenia. *J Trauma*. 2002;52(2):346-350.
125. Matsuda T, Tanaka H, Williams S, et al. Reduced fluid volume requirement for resuscitation of third-degree burns with high-dose vitamin C. *J Burn Care Rehabil*. 1991;12(6):525-532.
126. Sherwood ER, Traber DL. The systemic inflammatory response syndrome. In: Herndon DN, ed. *Total Burn Care*. Philadelphia: WB Saunders; 2007:292-309.
127. Guillen MI, Gomez-Lechon MJ, Nakamura T. The hepatocyte growth factor regulates the synthesis of acute-phase proteins in human hepatocytes: divergent effect on interleukin-6-stimulated genes. *Hepatology*. 1996;23:1345-1352.
128. Jeschke MG, Herndon DN, Wolf SE, et al. Hepatocyte growth factor modulates the hepatic acute-phase response in thermally injured rats. *Crit Care Med*. 2000;28(2):504-510.
129. Yamashita Y, Jeschke MG, Wolf SE. Differential expression of hepatocyte growth factor in liver, kidney, lung, and spleen following burn in rats. *Cytokine*. 2000;12(9):1293-1298.
130. Humbel RE. Insulin-like growth factors I and II. *Eur J Biochem*. 1990;190(3):445-462.
131. Baxter RC. Circulating levels and molecular distribution of the acid-labile (alpha) subunit of the high molecular weight insulin-like growth factor-binding protein complex. *J Clin Endocrinol Metab*. 1990;70(5):1347-1353.
132. Jeschke MG, Chrysopoulo MT, Herndon DN, Wolf SE. Increased expression of insulin-like growth factor-I in serum and liver after recombinant human growth hormone administration in thermally injured rats. *J Surg Res*. 1999;85(1):171-177.
133. Herndon DN, Ramzy PI, DebRoy MA, et al. Muscle protein catabolism after severe burn: effects of IGF-1/IGFBP-3 treatment. *Ann Surg*. 1999;229(5):712-713.
134. Jeschke MG, Finnerty CC, Kulp GA, et al. Combination of recombinant human growth hormone and propranolol decreases hypermetabolism and inflammation in severely burned children. *Pediatr Crit Care Med*. 2008;9(2):209-216.
135. Jeschke MG, Herndon DN, Vita R, et al. IGF-I/BP-3 administration preserves hepatic homeostasis after thermal injury which is associated with increases in no and hepatic NF-kappa B. *Shock*. 2001;16(5):373-379.
136. Jeschke MG, Herndon DN, Barrow RE. Insulin-like growth factor I in combination with insulin-like growth factor binding protein 3 affects the hepatic acute phase response and hepatic morphology in thermally injured rats. *Ann Surg*. 2000;231(3):408-416.
137. Murray CJL, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2197-2223.
138. Deutschman CS, Cereda M, Ochroch EA, Raj NR. Sepsis-induced cholestasis, steatosis, hepatocellular injury, and impaired hepatocellular regeneration are enhanced in interleukin-6 -/- mice. *Crit Care Med*. 2006;34(10):2613-2620.
139. Cheng J, Zhou T, Liu C, et al. Protection from Fas-mediated apoptosis by a soluble form of the Fas molecule. *Science*. 1994;263(5154):1759-1762.
140. Song E, Lee S-K, Wang J, et al. RNA interference targeting Fas protects mice from fulminant hepatitis. *Nat Med*. 2003;9(3):347-351.
141. Jeschke MG, Bolder U, Chung DH, et al. Gut mucosal homeostasis and cellular mediators after severe thermal trauma and the effect of insulin-like growth factor-I in combination with insulin-like growth factor binding protein-3. *Endocrinology*. 2007;148(1):354-362.
142. Finnerty CC, Jeschke MG, Qian W-J, et al. Determination of burn patient outcome by large-scale quantitative discovery proteomics. *Crit Care Med*. 2013;41(6):1421-1434.
143. Finnerty CC, Ju H, Spratt H, et al. Proteomics improves the prediction of burns mortality: results from regression spline modeling. *Clin Transl Sci*. 2012;5(3):243-249.

25 Importance of Mineral and Bone Metabolism after Burn

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Metabolic Actions of Calcium, Phosphate, and Magnesium

As insoluble elements, minerals are major inorganic components of bone tissue and confer weight-bearing properties to the skeleton. Soluble calcium (Ca), phosphate (PO_4), and magnesium (Mg) play important roles in metabolic pathways, acting as cofactors and regulators of numerous biochemical systems.

CALCIUM

Calcium functions in neurotransmission, cell depolarization, impulse propagation, and muscle contractility. In intracellular pathways, after capture by Ca-binding protein or protein kinase C, Ca serves as a second messenger. In extracellular metabolism, Ca activates several factors in the coagulation cascade.[1]

PHOSPHATE

Phosphate has an integral role in the storage and transfer of energy. Inorganic phosphate groups are exchanged in multiple metabolic reactions that allow energy-demanding activities in the human body (e.g., adenosine triphosphate [ATP] metabolism). Phosphorylation reactions represent the mainstay of cellular respiration. In the form of phospholipid, PO_4 is a major structural component of cell membranes.[1]

MAGNESIUM

Magnesium is essential to the cell and mitochondria. It is a cofactor in the transfer of PO_4 groups, and it is necessary in reactions involving purine nucleotide metabolism.[1] Mg also functions in plasma membrane excitability, stabilizing conditions characterized by abnormal nerve excitation or vasospasm.

Homeostasis of Calcium, Phosphate, and Magnesium

CALCIUM

Intestinal efficiency to absorb Ca is inversely related to Ca intake, varying from 20% to 70%.[2] The regulatory mechanism is shown in Fig. 25.1. With high Ca intake, transient hypercalcemia occurs followed by suppression of parathyroid hormone (PTH) secretion and PTH-stimulated renal conversion of 25-hydroxyvitamin D to calcitriol (1,25-dihydroxyvitamin D). With low Ca intake, the opposite occurs.

These mechanisms are likely mediated by the parathyroid chief cell Ca-sensing receptor (CaR). The CaR is a membrane-bound G protein-coupled protein that may be up- or down-regulated.[3] In patients with CaR downregulation, higher circulating Ca is required to suppress PTH production and secretion, giving rise to primary hyperparathyroidism.[4] In patients with CaR upregulation, less circulating Ca is needed, leading to hypoparathyroidism.[5]

Parathyroid hormone normally increases bone resorption and renal tubular Ca reabsorption to raise serum Ca concentrations. Furthermore, it stimulates the renal enzyme 25-hydroxyvitamin D-1α hydroxylase to convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D or calcitriol. Calcitriol then binds to intestinal epithelial cells and increases transcellular Ca absorption.

Intravenous (IV) administration of Ca bypasses the intestinal control mechanism and suppresses PTH and calcitriol production.

PHOSPHATE

In contrast to Ca, the intestine plays no significant regulatory role in the absorption of PO_4. Approximately 80% of dietary PO_4 is absorbed, and the bone stores approximately 90% of the body's PO_4. Homeostatic control appears to rest primarily within the kidney.[6,7] Thus, the renal excretory rate of PO_4 primarily regulates serum PO_4 concentrations and maintains them within a normal range. Fibroblast growth factor (FGF)-23 is a key regulator of PO_4 and vitamin D metabolism in humans.[8] FGF-23 gene mutations cause autosomal dominant hypophosphatemic rickets, a phosphate-wasting disorder. FGF-23-mediated renal phosphate wasting occurs through downregulation of the type II sodium–phosphate co-transporters NPT2a and NPT2c.[8]

MAGNESIUM

Approximately 60% of the body's Mg is stored in the skeleton[1] but not at sites where matrix is calcified. Mg absorption varies with dietary intake, with about 40% of an average daily load being absorbed.[1] The relationship between Ca and Mg absorption is described as inverse, but the mechanism of this is unclear. Renal excretion is the main route of Mg elimination, and it may vary with Mg

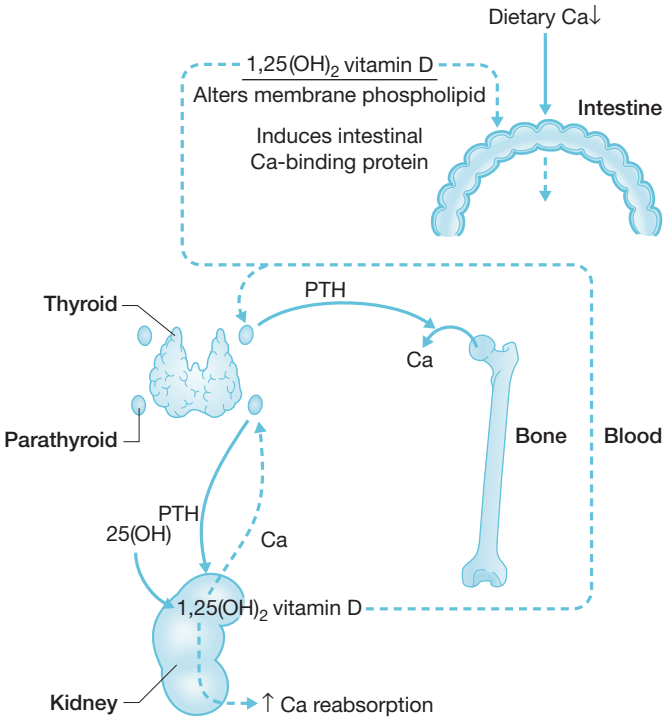

Fig. 25.1 Vitamin D and calcium metabolism. *PTH,* Parathyroid hormone.

concentration in serum. A large paracellular pathway for the intestinal absorption and secretion of Mg exists and is dependent on luminal Mg concentrations. The Mg ion channel, TRPM6, is located in intestinal brush border epithelial cells and may participate in Mg homeostasis in the gut. Mg is 70% ultrafiltrable in the serum.[1] About 70% of filtered Mg is reabsorbed along the cortical afferent limb of the loop of Henle.[1] Whereas hypermagnesemia increases urinary Mg excretion by activating the renal CaR,[9] hypomagnesemia increases loop of Henle Mg reabsorption and reduces urinary Mg excretion. Loop diuretics increase urinary Mg excretion. Because little distal tubular Mg reabsorption occurs, an IV fluid bolus decreases Mg reabsorption and increases urinary Mg excretion.[1]

Effect of Burn Injury on Calcium, Phosphate, and Magnesium Homeostasis

Significant burn injuries trigger a cascade of effects that lead to alterations in the body's metabolism of bone and minerals. These effects can be thought of in two distinct phases: the inflammatory phase and the subsequent stress response, although they occur concurrently. The inflammatory response after burn injury leads to high levels of cytokines, including interleukin (IL)-1β and IL-6, which stimulate the osteocytic and osteoblastic production of the ligand of the receptor activator of NFκB (RANKL). RANKL stimulates the differentiation of marrow stem cells into osteoclasts, stimulating bone resorption and releasing mineralized Ca into the serum.[10,11] The concomitant stress response is marked by increases in urine free cortisol, which is responsible for longer-term alterations in mineral metabolism and longer-term bone loss.[11]

Although the effects of burn injury on mineral ions are not fully understood, studies from the University of Texas Medical Branch and Shriners Hospitals for Children in Galveston describe some of the developments in this area. In children with greater than 30% total body surface area (TBSA) burns, ionized Ca is, on average, 5% below the lower normal limit.[12] In addition, serum PTH levels are too low for ionized Ca levels, indicating hypoparathyroidism. Administration of a standard amount of PTH does not increase urinary cyclic AMP and PO_4 excretion,[12] pointing to PTH resistance. Mg depletion, encountered in all the burn patients studied,[12,13] impairs hypocalcemia-induced PTH secretion and imparts resistance to PTH infusion. The prevalence of Mg depletion may result from resuscitation of patients with IV fluids lacking Mg.[12] Aggressive parenteral Mg supplementation produces repletion in 50% of patients. However, it does not improve hypoparathyroidism,[13] making the cause of postburn hypoparathyroidism unclear. Sheep studies revealed that an approximate 50% upregulation of parathyroid CaR occurs at 48 hours after burn injury,[5] associated in humans with decreased circulating Ca necessary to suppress PTH secretion.[3] The proposed mechanism underlying this phenomenon, known as a reduced set point for Ca suppression of PTH secretion, is shown in Fig. 25.2. Cytokines, especially IL-1β and IL-6, are highly produced after the systemic inflammatory response. These cytokines stimulate parathyroid cell production of CaR in vitro.[14-16]

The upregulation of parathyroid CaR decreases PTH release, lowering the blood's ionized Ca concentration.[10] This is believed to represent an effort by the body to modulate the duration and intensity of the inflammatory response after burn injury. It has been demonstrated in vitro that mononuclear cells in the peripheral blood produce chemokines in response to the medium Ca concentration. Chemokines may then attract more inflammatory cells via the production of Macrophage inflammatory protein 1 alpha (MIP-1α) and RANTES. Therefore, it appears that the inflammatory response to burn injury increases bone *re*sorption via RANKL, which in turn augments the inflammatory response, and the CaR pathway may act as a modulator of this response.[10]

In a study of 11 adult burn patients, serum concentrations of PO_4 and Mg were low, consistent with abnormalities observed in Ca homeostasis.[17] Six patients had low serum ionized Ca concentrations, three of them manifesting hypocalcemia during the first 48 hours after burn. Four had hypophosphatemia; this was most prevalent at postburn day 7. Five had hypomagnesemia, with this finding most likely to present on postburn day 3. One patient demonstrated hypercalcemia and one hyperphosphatemia. No patients had hypermagnesemia. Elevated ionized Ca or PO_4 was always transient.

Regarding alterations in bone and mineral metabolism in adults, a 2016 study of 32 adult male patients with a median TBSA of 40% found significant changes in bone turnover markers.[18] In the first 7 days after burn injury, they found increases in bone-specific alkaline phosphatase (ALP), FGF-23, and intact PTH. Serum phosphate also increased in this first week postburn. These were accompanied by decreases in 25-OH vitamin D, albumin, and ionized

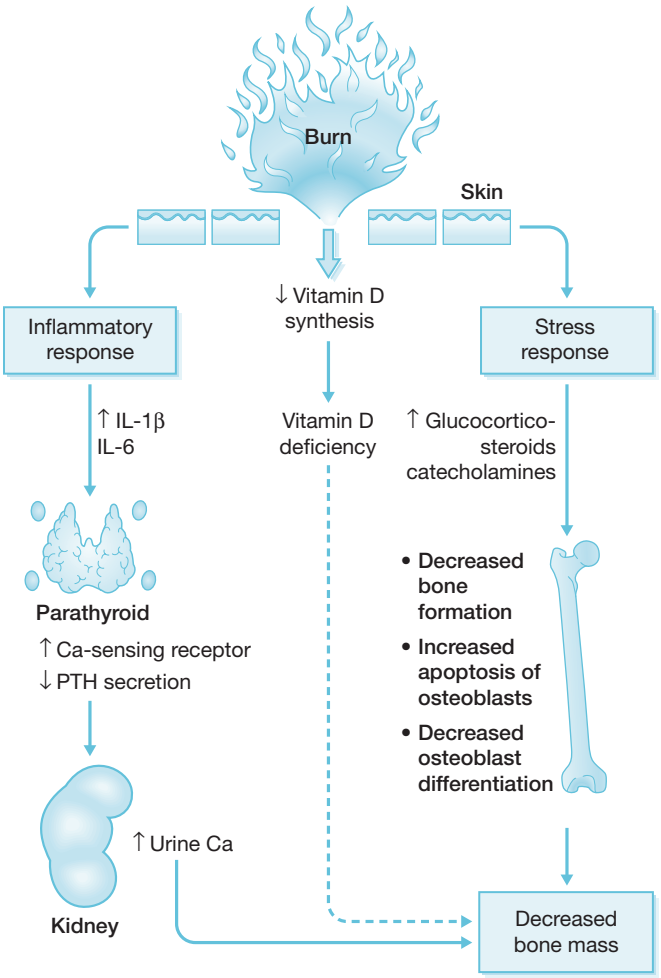

Fig. 25.2 Mechanisms of bone loss after severe burn. *IL,* Interleukin; *PTH,* parathyroid hormone

Ca. In the later phase (weeks 1–8 postburn), they found increases in Ca and ionized Ca; intact PTH, FGF-23, and phosphate all decreased in this period.[18]

Hypocalcemia cannot be diagnosed from total serum Ca concentration, owing to variability in serum albumin concentrations after burn. Blood ionized Ca concentration yields a more accurate diagnosis. Several mechanisms may underlie hypocalcemia. One is the extracellular–intracellular shift of Ca, supported by Ca accumulation seen in the erythrocytes of a burn patient.[19] Another is increased urinary Ca excretion, which occurs in burned children and is consistent with documented secondary hypoparathyroidism.[12] Ca loss in tissue exudates could also contribute to hypocalcemia. Although the amount of Ca in wound exudates is likely insufficient to account for postburn hypocalcemia,[20] few studies have measured Ca content in burn wound exudates.

Although fecal Ca losses can be high in burn patients[20] and burn-induced increases in endogenous corticosteroids may impair intestinal Ca absorption,[21] no evidence suggests that hypocalcemia is caused by corticosteroid-induced impairment of intestinal reabsorption of Ca secreted into the intestinal lumen. Other proposed mechanisms include reduced bone turnover.[17,22] However, upregulation of parathyroid CaR by inflammatory cytokines followed by a reduction in set point for Ca suppression of PTH production remains the most attractive hypothesis.[5,12]

Studies of 24 children with massive burns demonstrated a low serum concentration of 25-hydroxyvitamin D from as early as 14 months after burn[23] up to 7 years,[24] correlating with low bone density Z-scores.[24] Serum 1,25-dihydroxyvitamin D concentrations were normal 2 years after injury but were low at 7 years in 50% of patients.[24] This suggests that these patients became progressively vitamin D deficient.[24]

Possible explanations for postburn hypophosphatemia include intracellular PO_4 accumulation, inadequate intake, excessive excretion (unlikely in view of documented hypoparathyroidism), or loss into the extravascular fluid. In a review, Dolecek[20] found increased urinary PO_4 excretion only during the third and fourth weeks after burn in adults, but hypophosphatemia occurred earlier. Thus, increased urinary PO_4 excretion seen later may be more a function of increased tissue breakdown and filtered load than of inappropriate or excessive urinary PO_4 losses. There is little documentation of inadequate PO_4 intake after burns. We administer a minimum of 1.6 g PO_4 daily in enteral feedings alone.[17] What is clear is that the two major hormonal facilitators of phosphate excretion, PTH[12] and FGF23,[25] are both suppressed in burns in children during the first month postburn, suggesting a hormonal conservation of phosphate.

The cause of sustained hypomagnesemia after burn is unknown, although excessive urinary and fecal losses occur in adults,[20] and excessive losses occur in the burn wound.[26]

Rationale for Therapy

Table 25.1 describes treatments for hypocalcemia and hypophosphatemia. Hypocalcemia, especially during the resuscitation effort, can potentiate hypokalemia-induced abnormalities in cardiac muscle[27] and block responsiveness to fluid repletion in shock.[27] Parenteral Ca during resuscitation does not benefit patients without hypocalcemia[28-30] unless they have hyperkalemia, hypomagnesemia, or Ca channel blocker toxicity.[31] Similarly, although caution should be exercised during massive transfusion with citrate-containing blood, Ca therapy may not be necessary in normocalcemic patients and if hepatic and renal functions are minimally impaired. The liver will clear citrate, which may transiently chelate Ca at a rate of 1 unit of blood transfused every 5 minutes.[32] Treatment should be initiated only when clinical and electrocardiographic evidence suggests hypocalcemia. Ca infusions should be administered slowly because rapid Ca replacement can produce cardiac arrhythmias.[27,32]

Hypophosphatemia may cause tissue hypoxemia due to increased hemoglobin affinity for oxygen and decreased tissue ATP, metabolic encephalopathy, hemolysis, shortened platelet survival, myalgias, weakness, and possible impairment of myocardial contractility.[33] Hypomagnesemia, or Mg depletion with normal serum Mg, blunts the effect of PTH secreted in response to hypocalcemia on target organs and impairs secretion of PTH itself.[1] Mg deficiency

Table 25.1 Treatment Options

Disturbance	Decision Point	Recommended Treatment
Hypocalcemia	Symptomatic	Intravenous calcium: Adults 90–180 mg of elemental calcium over 5–10 minutes Infants or children: calcium chloride as 20 mg/kg dose or Ca gluconate in a 200–500 mg/kg/dose in four divided doses
	Asymptomatic	Oral calcium carbonate or intravenous calcium gluconate
Hypophosphatemia	Symptomatic	Infants or children: 5–10 mg/kg infused over 6 hours followed by 15–45 mg/kg given by infusion over 24 hours
	Asymptomatic	Oral administration of 20–25 mg/kg of elemental phosphorus in four divided doses each day.

also causes generalized convulsions, muscle tremors, and weakness.[1]

Treatments for Maintaining Mineral Homeostasis

Acute symptomatic hypocalcemia should be treated with IV Ca. Adults should receive 90–180 mg of elemental Ca over 5–10 minutes to reverse twitching. Infants and children should receive 20 mg/kg Ca chloride or 200–500 mg/kg Ca gluconate in four divided doses.[34,35] Parenteral chloride should be used carefully because it may cause phlebitis, acidosis, or both. While hypocalcemia is asymptomatic and patients can tolerate enteral feeding, milk or infant formula can provide as much as 3 g/day of bioavailable Ca.[17] Hypocalcemia can occur despite enteral provision of such large Ca quantities, making intermittent parenteral administration of Ca salts sometimes necessary. The amounts given must be determined individually and may vary significantly from patient to patient. Dosing in six of our patients with greater than 40% TBSA burns ranged between 0.9 and 15 g of 10% Ca gluconate/day over the first 5 weeks after burn. Treatments were given, on average, twice daily for 75% of the days.

Rickets secondary to PO_4 deficiency can be treated with 20–25 mg/kg elemental PO_4 in four divided oral doses per day.[35] Infants and children with symptomatic hypophosphatemia should receive 5–10 mg/kg infused over 6 hours and then 15–45 mg/kg infused over 24 hours or until serum PO_4 exceeds 2.0 mg/dL (0.6 mmol/L).[36]

Adult patients who tolerate enteral feeding and consume an average of 1.6 g/day PO_4 should have consumed enough to treat asymptomatic hypophosphatemia.[17] Prolonged hypophosphatemia has not been reported in burn patients; however, parenteral supplementation would be necessary in such cases. Patients who have signs or symptoms of Mg deficiency with serum Mg concentration less than 1.5 mEq/L (1.8 mg/dL or 0.8 mmol/L) usually require parenteral therapy.[37]

Hypercalcemia and Impaired Renal Function After Burns

Hypercalcemia with acute renal failure was reported in the May 2010 issue of *Burns*.[38] Adult patients with serum ionized Ca of 1.32 mmol or greater constituted 30% of patient admissions, and those with creatinine clearance less than 50 mL/min developing in the intensive care unit 48 hours after admission made up about 20% of admissions. Of the four hypercalcemia cases described, three responded to standard doses of bisphosphonates. The onset of hypercalcemia occurred from 6 weeks to 6 months after injury. Much remains to be learned about this complication of burn management.

Bone

Silent bone loss may occur for up to 1 year after burn. Linear growth and bone remodeling are adversely affected by burns. Linear growth at the epiphyses of the long bones usually occurs through cartilage cell proliferation with production of extracellular matrix; these chondrocytes and matrix undergo a series of biochemical changes, leading to the formation of ossification centers. As these centers expand, cartilaginous tissue is replaced by bone and a vascular system that allows the delivery of nutrients, hormones, and growth factors. Growth velocity in children is retarded for the first year after a 40% TBSA burn.[39] The underlying mechanism is unknown, but growth velocity does return to normal[39] even though long-term stunting may result.

The stress and inflammatory response contribute to bone turnover abnormalities that lead to bone loss. Urinary deoxypyridinoline excretion increases the first week after burn.[40] Deoxypyridinoline is a marker of bone resorption or one of the byproducts of bone collagen type I breakdown. Its increase in urine during the first week is because of a three- to eightfold increase in glucocorticoid production[41] and a three- to 100-fold increase in proinflammatory cytokines produced by the systemic inflammatory response.[24] In studies of sheep after a 40% TBSA burn, bone harvested 5 days postburn demonstrated an eroded surface and decreased Young's modulus consistent with bone resorption.[42] Both glucocorticoids and inflammatory cytokines stimulate bone resorption by increasing osteocyte and osteoblast RANKL production.[43] Normally, bone resorption is coupled to bone formation. In high-turnover situations (i.e., both resorption and formation are increased), bone loss occurs because after bone is laid down, it takes time for it to mineralize properly. Bone will be resorbed more quickly than it can allow the type I collagen to crystallize into hydroxyapatite with proper binding sites for Ca and PO_4.

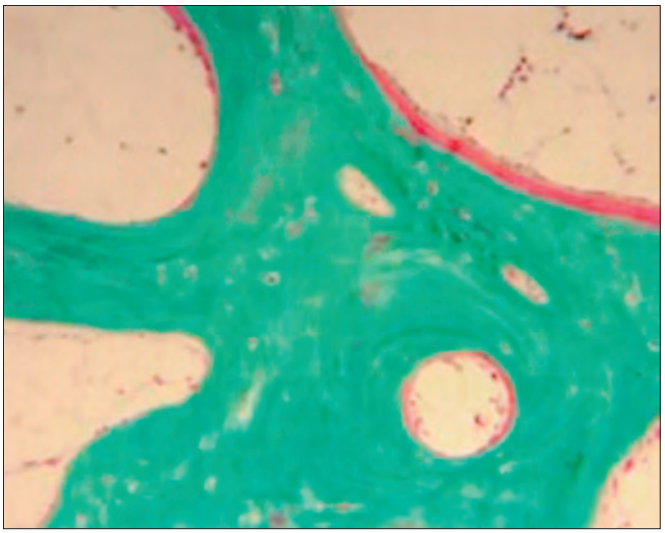

Fig. 25.3 Goldner trichrome stain of an iliac crest bone biopsy of a healthy person. The *blue-green area* represents mineralized bone. The *red area* represents unmineralized osteoid. Spindle-shaped cells from the osteoid surface are osteoblasts.

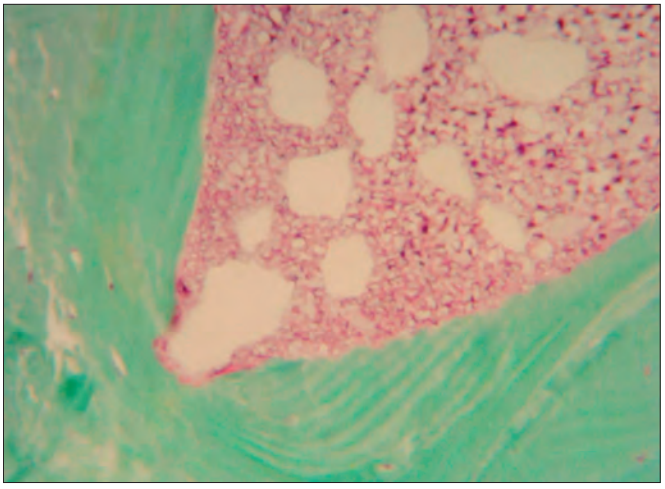

Fig. 25.4 Goldner trichrome stain of an iliac crest bone biopsy of a burned patient. The *blue-green area* represents mineralized bone. Compared with Fig. 25.3, note that osteoblasts are absent from the osteoid surface.

Osteoblasts (bone-forming cells) and osteocytes (terminally differentiated osteoblasts acting as mechanotransducers in the bone matrix) are key parts of normal coupling. They produce RANKL in response to cytokines (especially IL-1β and IL-6) and PTH. When stimulated by low serum Ca and downregulation of the parathyroid CaR, PTH increases bone resorption by binding to PTH receptors on osteoblasts. PTH also increases the number of osteoblasts on bone surfaces in humans[44] and animals.[45] However, by the second week after burn, glucocorticoids cause apoptosis of surface osteoblasts, and we even observe a loss of the ability for stromal cells to show markers of osteoblast differentiation.[11,46] This disappearance is apparent in iliac crest bone biopsies (compare normal bone in Fig. 25.3 with bone at 2 weeks after burn in Fig. 25.4). Similarly, when tetracycline is administered to children and adults before iliac crest bone biopsies, tetracycline uptake is markedly reduced, suggesting a reduction in surface osteoblasts and functioning of the surviving osteoblasts.[47] Finally, fewer markers of osteoblastic differentiation (a feature of glucocorticoid toxicity) are present in cultured marrow stromal cells from iliac crest bone of burned children than in cells from bone of age- and gender-matched control participants.[41]

Although endogenous glucocorticoids resulting from the stress response reduce osteoblast numbers and the differentiation of marrow stromal cells into osteoblasts, high circulating cytokine levels remain unabated. Therefore, cytokines would be expected to continue pushing the differentiation of marrow stem cells into osteoclasts. However, this does not occur. In fact, levels of urinary deoxypyridinoline (a bone resorption marker) remain quite low.[22] Thus, both bone formation and bone resorption fall dramatically in the second week after burn, leading to a low-turnover bone loss. This condition, known as adynamic bone, results from a lack of osteoblasts to process bone resorption stimuli.

IL-1β[14,15] and IL-6[16] stimulate upregulation of the parathyroid CaR in vitro. Moreover, both inflammation and stress produce oxidative stress, leading to a reduction in both osteoblastogenesis and osteoclastogenesis.[48] Thus, although the stress response explains the low-turnover acute bone loss after burn injury, the systemic inflammatory response explains upregulation of the parathyroid CaR in both humans and sheep. Parathyroid CaR upregulation provides continuous hypoparathyroidism after burn and renders the wasted urinary Ca unproductive in repairing demineralized bone.

In summary, 1 week after burn injury, the stress and inflammatory responses promote bone loss by increasing bone resorption and Ca wasting in the urine. By 2 weeks, osteoblasts are lost, markedly reducing bone replacement. This hypodynamic bone continues to thin, as resorption is reduced[22] and compensatory bone formation is all but shut off.

The silent events triggered by burn injury reduce bone density (Fig. 25.5) in the lumbar spine and appendicular skeleton (see radiograph in Fig. 25.6). The distribution of lumbar spine bone density Z-scores (standard deviation score) is shifted to the negative in children with greater than 40% TBSA burns (see Fig. 25.5) but not in those with less than 20% TBSA burns. Thus, more severe burns trigger the bone loss mechanisms discussed earlier. Obesity, an epidemic affecting children in the developed world, may also be implicated as a contributing factor because obese pediatric burn patients (defined as being in greater than the 85th percentile of body mass index [BMI]) had higher loss of bone mineral density (BMD) compared with their normal BMI counterparts.[49] This may be related to increased inflammation because these children also had higher C-reactive protein (CRP) levels in the months after burn injury than their normal BMI counterparts.[49]

Burn injury increases the annual extrapolated fracture incidence in boys and girls by 100% and 50%, respectively.[50] Thus, burn-induced bone loss increases the risk of fracture later on. Whereas bone remodeling recovers 1 year after burn,[51] the Z-score for at least lumbar spine BMD does not improve.[50,51] Given that peak bone mass is reached at 18 to

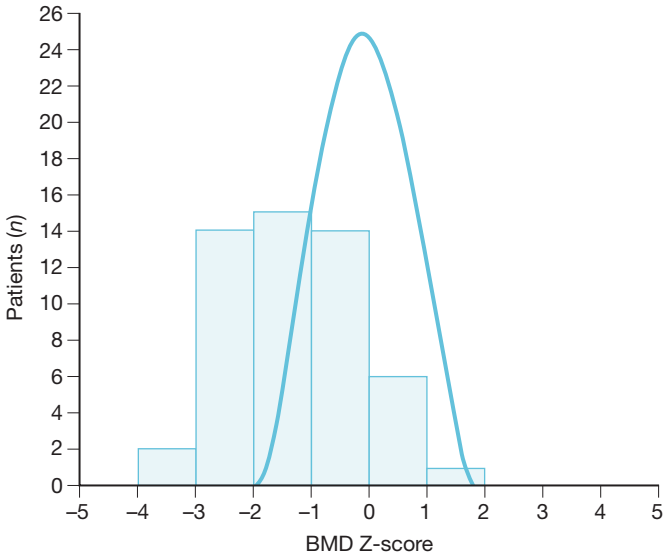

Fig. 25.5 Distribution of lumbar spine bone mineral density (BMD) Z-scores of severely burned children compared with a standard distribution curve. Note that the distribution after burn is shifted to the negative side.

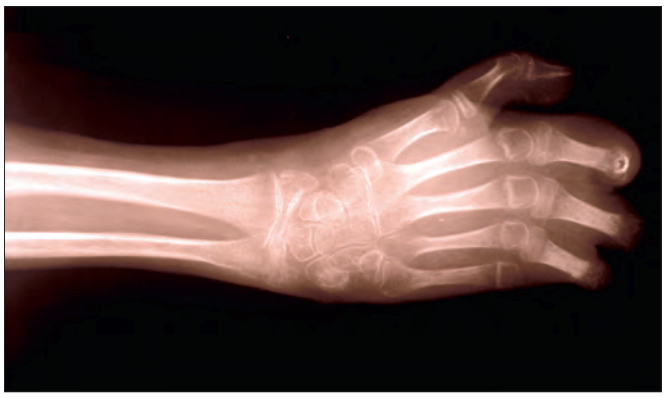

Fig. 25.6 Radiograph as an example of burn-induced osteoporosis 1 year after trauma.

30 years, failure of bone density to catch up to one's peers places burn victims at risk of entering adulthood with less than peak bone mass and may increase the risk of early-onset osteoporosis. In adults as well, we see markers of decreased BMD after prolonged follow-up. One study found that men with 30% TBSA burns, when tested at least 1 year postburn, had decreased femoral neck Z-score and femoral neck BMD, as well as bone-specific ALP, relative to non-burned control participants.[52]

Another obstacle to bone recovery is progressive vitamin D deficiency, which affects burn patients who are not discharged with vitamin D supplementation and related to a failure in skin production of vitamin D.[11] Sunlight exposure becomes limited because of heat intolerance due to sweat gland destruction, and the burn scar could become hyperpigmented. At 14 months postburn, biopsies have demonstrated that ultraviolet light converts only 25% of the normal quantity of 7-dehydrocholesterol into previtamin D_3, suggesting that skin is biochemically abnormal more than 1 year after injury.[23] Moreover, 7-dehydrocholesterol levels were significantly lower in burn scar and adjacent normal-appearing skin than normal control skin,[23] pointing to ongoing problems in cholesterol biosynthesis. In the previously discussed study of men after burn injury, they found a negative correlation between the modified Vancouver Scar Scale Score and serum vitamin D levels, suggesting that more clinically significant scars are also scars that affect vitamin D production.[52] In general, they found that burned patients had lower serum 25-OH vitamin D levels. The role of vitamin D deficiency in failed restoration of bone density is unknown. We found that 6 months after children were discharged on a vitamin D_2 (400 IU)-containing multivitamin, all but one of eight patients had vitamin D insufficiency.[53] In another study, children after burns were randomized to placebo, vitamin D_2, or vitamin D_3 supplementation and monitored for fracture; fewer fractures were observed in the vitamin D_3 group, suggesting that vitamin D_3 supplementation may decrease postburn fracture risk.[54] Thus, the vitamin D requirement for children during and after burn injury remains unknown.[53] A randomized controlled trial (RCT) of adults with severe thermal burns found that two-thirds of the patients (who were 2–5 years postburn) had vitamin D deficiencies and that more than half were osteopenic. Supplementing cholecalciferol and calcium orally improved serum vitamin D levels and quadriceps muscle strength but not BMD.[55] Thus, it remains unclear in adults as well what the optimal vitamin D supplementation regimen would be to prevent postburn bone loss.

Treatment of Bone Catabolism After Severe Burn

Several approaches have been studied to prevent, mitigate, or reverse burn-induced bone loss. Daily subcutaneous injection of 0.2 mg/kg of recombinant human growth hormone (rhGH) from admission throughout hospitalization immediately improves circulating insulin-like growth factor-1 (IGF-1) levels but does not raise serum osteocalcin levels to normal,[56] suggesting that rhGH fails to increase bone formation acutely. However, daily subcutaneous injection of 0.05 mg/kg rhGH for 1 year increases lean body mass (LBM) by 9 months after burn and increases lumbar spine bone mineral content (BMC), but not BMD, by 1 year.[57] This increased lumbar spine BMC but not bone density is notable for three reasons. First, the persistence of high glucocorticoid levels during the first year may block early efficacy of rhGH, a glucocorticoid antagonist. Next, this finding raises the question as to whether the absence of an increase in lumbar spine bone density reflects a failure of rhGH activity. Given that BMD is the quotient of BMC and bone area, an increase in BMC with no change in BMD would imply a proportional increase in bone area. Thus, a 1-year treatment with rhGH increases LBM; increases skeletal loading; and creates bigger, more biomechanically stable bone. Finally, one might ask whether the effects of rhGH on bone are only secondary, resulting from an increase in skeletal loading. This question cannot be directly answered based on available data. However, Branski et al.[58] recently showed that a 1-year treatment with 0.2 mg/kg/day rhGH (subcutaneous injection) reduces lumbar spine

BMC, increases LBM, and dramatically decreases circulating PTH. These findings suggest that high-dose rhGH directly stimulates bone resorption, with secondary suppression of serum PTH levels. Little evidence supports a direct effect at moderate rhGH doses.

The disadvantages of daily rhGH administration for at least 1 year include the high cost and the need for subcutaneous injections, which may reduce compliance. Another option is long-term use of the anabolic steroid oxandrolone. Similar to rhGH, a 0.1-mg/kg dose given orally twice daily for 1 year produced a rise in LBM succeeded by an increase in lumbar spine BMC by 3–6 months, increasing skeletal loading and bone size.[59] It is believed to work via IGF stimulation.[11] A more recent study has suggested that even longer-term treatment with oxandrolone may be even more beneficial.[60] An RCT of children with greater than 30% TBSA burns randomized participants to placebo or 24 months of oxandrolone and found that the treatment group saw increases in whole-body and spine BMC as well as lumbar spine BMD along with a greater height velocity. These improvements in bone mineralization were greater than previous studies of 1 year of oxandrolone therapy.[60] Oxandrolone is not costly and does not require subcutaneous injections, but it may produce clitoral hypertrophy. However, no premature growth plate fusion has been discovered on radiographs, and this clitoromegaly resolves when the drug is discontinued.

Another drug that has been studied is the bisphosphonate pamidronate. The current generation of nitrogen-containing bisphosphonates acts by adhering to the bone matrix, where they are taken up by osteoclasts and interfere with the cholesterol biosynthesis pathway, ultimately altering protein binding to the osteoclastic membrane and inducing apoptosis.[61] Bisphosphonates remain in bone for a prolonged period, raising concerns that they may interfere with growth or bone quality.[61] However, most bone resorption is thought to occur during the first week or two after burns, when inflammatory cytokines cause significant resorption of bone before osteoblast apoptosis. Thus, early use of bisphosphonates may prevent acute bone loss.

In a randomized, double-blind study, children with 40% TBSA or greater burns received 1.5 mg/kg of pamidronate intravenously (maximum dose, 90 mg) within 10 days of the burn and 1 week later. Pamidronate prevented the reduction in BMC in the lumbar spine and total body after 6 months of hospitalization.[62] By 2 years, BMC in the placebo group had caught up to that of the pamidronate group for the total body but not the lumbar spine.[51] This suggests that pamidronate effectively preserves the axial skeleton from bone loss and preserves the appendicular skeleton until bone replacement would otherwise "catch up." Pamidronate has glucocorticoid antagonistic properties similar to those of rhGH; however, the effects of pamidronate on bone are immediate.

Pamidronate use is not associated with hypocalcemia, growth delays, or changes in bone histomorphometry.[51,62] The next step in evaluating this drug is to determine whether the fracture rate in pamidronate-treated patients differs from that in the placebo group and from age- and gender-matched normal values.[50] Furthermore, some evidence suggests that bisphosphonates preserve muscle protein after burn, raising the question if there is some sort of communication, possibly a paracrine effect or effect in the microenvironment, between bone and muscle.[46]

Two other promising drugs bear mention. The first is recombinant human PTH (rhPTH). Daily subcutaneous injection of rhPTH for 1 year adds new bone in women with postmenopausal osteoporosis.[63] However, because rat studies have demonstrated an increase in osteogenic sarcoma,[64] the U.S. Food and Drug Administration does not allow its use in children. If this changes, rhPTH would be a potentially effective drug for adding bone mass in burned children.

Beyond pharmaceutical therapies, recent research also points to the possibility of exercise and other mechanical types of therapy playing a role in the management of post-burn bone loss. One study found that exercise, in combination with whole-body vibration therapy, helped maintain truncal BMC in children after burn injury relative to exercise alone.[65]

Heterotopic Ossification After Burn Injury

Another abnormality of bone and mineral metabolism observed after burn injury is the formation of heterotopic ossification (HO). HO is lamellar bone that forms ectopically via endochondral ossification. It is frequently seen after trauma and burns, as well as after spinal cord or traumatic brain injury and after orthopedic surgery. HO after burn injury can develop quite quickly even in the initial hospitalization. In a study of the Burn Model System National database, they found that the mean age of patients with HO by the time of discharge was 42.6, the mean TBSA was 18.5%, and the population was almost 75% male.[66] The same study found that TBSA and the need for grafting of the arm, head, neck, or trunk were risk factors for the development of HO.[66] In another study of patients from high-volume burn centers, they found that 3.5% of burn patients developed HO, almost all of whom had burns to the arms and skin grafting to the arms, with the latter translating to a 96.4 times higher odds of developing HO.[67] Patients with greater than 30% TBSA had 11.5 times higher odds of developing HO. More trips to the operating room and more days on the ventilator were also risk factors for HO development.[67] Interestingly, the prevalence of HO is low among elderly individuals. A recent website was developed to allow for further optimization of HO risk assessment (www.spauldingrehab.org/HOburncalculator)

Mouse studies suggest that the mesenchymal stem cells of younger individuals have more bone formation capacity than those of older invidiauls.[68] Additionally, younger patients are known to mount a more robust inflammatory response.

The early detection of HO is essential to its management with regards to how to manage occupational therapy. Additionally, an early diagnostic modality would allow for better directed treatment. Numerous studies have been performed to elucidate the optimal imaging modality to detect HO. Although plain radiographs and computed tomography (CT) are the mainstays of clinical HO diagnosis, mouse studies suggest that whereas near infrared imaging can detect HO as early as 5 days after burn injury, CT could

not detect it until 5 weeks after the burn.[69] Transcutaneous Raman spectroscopy can also detect HO as early as 5 days postburn injury in a mouse model.[70] Serum markers are not a reliable screening method for HO because elevated bone ALP is seen in fewer than half of patients with known hip HO, and CRP is elevated in 77% of patients with hip HO.[71] Recent studies have started to investigate the potential use of single-photon emission computed tomography (SPECT) imaging, which can detect increased pre-HO blood flow. Larger studies are needed to further validate its use. Furthermore, with increasing efficacy of high-frequency spectral ultrasound, this modality holds promise given the widespread and point of care use of ultrasonography.

The development of HO is a source of a significant amount of investigation. In one mouse study, it was noted that Adenosine Tri-Phosphate (ATP) hydrolysis as well as inhibition of the SMAD pathway both decrease HO formation, suggesting that both of these pathways play a role in the development of HO.[72] Similarly, both trauma- and burn-induced HO and genetic HO share a common pathway in hypoxia-inducible factor 1 alpha (HIF1α), and inhibiting this pathway can inhibit HO formation.[73] The early hypoxic wound is thought to stimulate HIF1α, which is a known mediator of chondrogenic differentiation, allowing for endochondral bone development. Inflammation has also been implicated in activating progenitors and stimulating osteogenic signals in the formation of HO.[74] Mouse studies also suggest that diabetic mice (i.e., leptin-deficient mice) have decreased HO formation and more HO resorption; this appears to be related to more osteoclasts noted on Tartrate-resistant acid phosphatase (TRAP) staining.[75]

The prevention and treatment of patients with HO have also been focuses of research. In patients who undergo arthroscopic surgery for femoroacetabular impingement, postoperative naproxen was exceedingly effective in preventing HO formation (4% HO incidence in the naproxen group vs 46% in the control group), so much so that they had to stop the study.[76] Another study of celecoxib found that the medication was a protective factor against the formation of HO and the development of limited Range of Motion (ROM) at 3, 6, and 9 months postoperatively.[77] Radiation is also efficacious in the prevention of HO in high-risk patients. This was demonstrated in a 1986 study of total hip arthroplasty patients.[78] Two prospective randomized trials have studied the optimal timing and dose of radiation for the development of HO; generally, pre- and postoperative radiation were both effective in preventing HO after hip surgery or arthroplasty, with either low- or medium-dose regimens that involved divided dosages of radiation.[79] Single-dose radiation therapy has also been noted to be effective in preventing HO formation after total hip arthroplasty.[80] Prospective trials studying nonsteroidal antiinflammatory drugs (NSAIDs) versus radiation in preventing HO have had mixed results, with studies showing similar efficacy or slightly more success with radiation than with NSAIDs but also noting that radiation is much more expensive and that NSAIDs have unwanted gastrointestinal side effects.[81,82]

For burn patients, bisphosphonates have also been used as early prophylaxis. However, no RCTs have been performed, and results from noncontrolled studies have had mixed results. Future treatments are currently under investigation including retinoic acid agonists, however, they should be approached with caution given their negative effect on wound healing. Additional drug development is underway to target bone morphogenetic protein receptors using kinase inhibitors because they have been shown to be effective in several animal studies. Although promising, kinase inhibitors also can have off-target effects that may impair wound healing and cause further osteopenia.

Acknowledgement

BL Supported by funding from NIH/National Institute of General Medical Sciences Grant K08GM109105-0, Plastic Surgery Foundation, the Association for Academic Surgery Roslyn Award, American Association for the Surgery of Trauma Research & Education Foundation Scholarship, American Association of Plastic Surgery Academic Scholarship, American College of Surgeons Clowes Award, AAPS/PSF Pilot Award, International FOP Association.

BL collaborates on a project unrelated to this review with Boehringer Ingelheim and has a Patent application on Rapamycin for use in heterotopic ossification which has not been licensed.

Complete references available online at
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Further Reading

Klein GL, Bi LX, Sherrard DJ, et al. Evidence supporting a role of glucocorticoids in short-term bone loss in burned children. *Osteoporos Int*. 2004;15:468-474.

Klein GL, Chen TC, Holick MF, et al. Synthesis of vitamin D in skin after burns. *Lancet*. 2004;363:291-292.

Klein GL, Herndon DN, Goodman WG, et al. Histomorphometric and biochemical characterization of bone following acute severe burns in children. *Bone*. 1995;17:455-460.

Klein GL, Herndon DN, Langman CB, et al. Long-term reduction in bone mass following severe burn injury in children. *J Pediatr*. 1995;126:252-256.

Klein GL, Nicolai M, Langman CB, et al. Dysregulation of calcium homeostasis after severe burn injury in children: possible role of magnesium depletion. *J Pediatr*. 1997;131:246-251.

Przkora R, Herndon DN, Sherrard DJ, et al. Pamidronate preserves bone mass for at least 2 years following acute administration for pediatric burn injury. *Bone*. 2007;41:297-302.

References

1. Favus MJ, Goltzmann D. Regulation of calcium and magnesium. In: Rosen CJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 7th ed. Washington, DC: American Society for Bone and Mineral Research; 2009:104-108.
2. Neer RM. Calcium and inorganic phosphate homeostasis. In: DeGroot LJ, ed. *Endocrinology*. Philadelphia: WB Saunders; 1989:927-953.
3. Brown EM. Ca 2+-sensing receptor. In: Rosen CJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 7th ed. Washington, DC: American Society for Bone and Mineral Research; 2009:134-141.
4. Silverberg SJ, Bilezikian JP. Primary hyperparathyroidism. In: Rosen CJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 7th ed. Washington, DC: American Society for Bone and Mineral Research; 2009:302-306.
5. Murphey ED, Chattopadhyay N, Bai M, et al. Up-regulation of the parathyroid calcium-sensing receptor after burn injury in sheep: a potential contributory factor to post-burn hypocalcemia. *Crit Care Med*. 2000;28:3885-3890.
6. Klein GL, Coburn JW. Parenteral nutrition: effect on bone and mineral homeostasis. *Annu Rev Nutr*. 1991;11:93-119.
7. Portale AA, Halloran BP, Murphy MM, et al. Oral intake of P can determine the serum concentration of 1,25-dihydroxyvitamin D by determining production rate in humans. *J Clin Invest*. 1986;77:7-12.
8. White KE, Econs MJ. Fibroblast growth factor-23. In: Rosen CJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 7th ed. Washington, DC: American Society for Bone and Mineral Research; 2009:112-116.
9. Hebert SC. Extracellular calcium-sensing receptor: implications for calcium and magnesium handling by the kidney. *Kidney Int*. 1996;50:2129-2139.
10. Klein GL, Castro SM, Garofalo RP. The calcium-sensing receptor as a mediator of inflammation. *Semin Cell Dev Biol*. 2016;49:52-56.
11. Klein GL. Abnormalities in bone and calcium metabolism after burns. In: *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 8th ed. Ames, Iowa, U.S.A: John Wiley & Sons, Inc; 2013:531-534.
12. Klein GL, Nicolai M, Langman CB, et al. Dysregulation of calcium homeostasis after severe burn injury: possible role of magnesium depletion. *J Pediatr*. 1997;131:246-251.
13. Klein GL, Langman CB, Herndon DN. Persistent hypoparathyroidism following magnesium repletion of burn-injured children. *Pediatr Nephrol*. 2000;14:301-304.
14. Nielsen PK, Rasmussen AK, Butters R, et al. Inhibition of PTH secretion by interleukin-1 beta in bovine parathyroid glands in vitro is associated with an up-regulation of the Ca-sensing receptor mRNA. *Biochem Biophys Res Commun*. 1997;238:880-885.
15. Toribio RE, Kohn CW, Capen CC, et al. Parathyroid hormone (PTH) secretion, PTH mRNA and calcium-sensing receptor mRNA expression in equine parathyroid cells and effects of interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha on equine parathyroid cell function. *J Mol Endocrinol*. 2003;31:609-620.
16. Canaff L, Zhou X, Hendy GN. The pro-inflammatory cytokine, interleukin-6, up-regulates calcium-sensing receptor gene transcription via Stat1/3 and Sp 1/3. *J Biol Chem*. 2008;283:13586-13600.
17. Klein GL, Herndon DN, Rutan TC, et al. Bone disease in burn patients. *J Bone Miner Res*. 1993;8:337-345.
18. MuschitzGK, et al. Early and sustained changes in bone metabolism after severe burn injury. *J Clin Endocrinol Metab*. 2016;101(4):1506-1515.
19. Baar S. The effect of thermal injury on the loss of calcium from calcium loaded cells: its relationship to red cell function and patient survival. *Clin Chim Acta*. 1982;126:25-39.
20. Dolecek R. Calcium-active hormones and post-burn low-calcium syndrome. In: Dolecek R, Brizio-Moltens L, Moltens A, eds. *Endocrinology of Thermal Trauma: Pathophysiologic Mechanisms and Clinical Interpretation*. Philadelphia: Lea and Febiger; 1990:216-237.
21. Hahn TJ, Halstead LR, Teitelbaum SI, et al. Altered mineral metabolism in glucocorticoid-induced osteopenia: effect of 25-hydroxyvitamin D administration. *J Clin Invest*. 1979;64:655-665.
22. Klein GL, Herndon DN, Goodman WG, et al. Histomorphometric and biochemical characterization of bone following acute severe burns in children. *Bone*. 1995;17:455-460.
23. Klein GL, Chen TC, Holick MF, et al. Synthesis of vitamin D in skin after burns. *Lancet*. 2004;363:291-292.
24. Klein GL, Langman CB, Herndon DN. Vitamin D depletion following burn injury in children: a possible factor in post-burn osteopenia. *J Trauma*. 2002;52:346-350.
25. Klein GL, Herndon DN, Le PT, et al. The effect of burn on serum concentrations of sclerostin and FGF23. *Burns*. 2015;41(7):1532-1535.
26. Berger MM, Rothen C, Cavadini C, et al. exudative mineral losses after serious burns: a clue to the alterations of magnesium and phosphate metabolism. *Am J Clin Nutr*. 1997;65:1473-1481.
27. British Committee for Standardization in Haematology Blood Transfusion Task Force. Guidelines for transfusion for massive blood loss. *Clin Lab Haematol*. 1988;10:265-273.
28. Stueven H, Thompson BM, Aprahamian C, et al. Use of calcium in pre-hospital cardiac arrest. *Ann Emerg Med*. 1983;12:136-139.
29. Stueven HA, Thompson BM, Aprahamian C, et al. Calcium chloride, reassessment of use in asystole. *Ann Emerg Med*. 1984;13:820-822.
30. Harrison EE, Amey BD. Use of calcium in electromechanical dissociation. *Ann Emerg Med*. 1984;13:844-845.
31. Harinan RJ, Mangiardi LM, McAllister RG, et al. Reversal of cardiovascular effects of verapamil by calcium and sodium. Differences between electrophysiologic and hemodynamic response. *Circulation*. 1979;59:797-804.
32. Dzik WH, Kirkley SA. Citrate toxicity during massive blood transfusion. *Transfus Med Rev*. 1988;2:76-94.
33. Hruska KA, Lederer E. Hyperphosphatemia and hypophosphatemia. In: Favus MJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 1999:245-253.
34. Shoback D. Hypocalcemia: definition, etiology, pathogenesis, diagnosis and management. In: Rosen CJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 7th ed. Washington, DC: American Society for Bone and Mineral Research; 2009:313-316.
35. Carpenter TO. Disorders of mineral metabolism in childhood. In: Rosen CJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 7th ed. Washington, DC: American Society for Bone and Mineral Research; 2009:349-353.
36. Lederer E. Hypophosphatemia: treatment and medication. In: eMedicine pulished on-line. http://www.emedicine.com. Updated 7 August 2009; Accessed 29 April 2010.
37. Rude RK. Magnesium depletion and hypermagnesemia. In: Rosen CJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 7th ed. Washington, DC: American Society for Bone and Mineral Research; 2009:325-328.
38. Kohut B, Rossat J, Raffoul W, et al. Hypercalcemia and acute renal failure after major burns: an under-diagnosed condition. *Burns*. 2010;36:360-366.
39. Rutan RL, Herndon DN. Growth delay in pediatric burn patients. *Arch Surg*. 1990;125:392-395.
40. Lebleblici B, Sezgin N, Ulusan SN, et al. Bone loss during the acute stage following burn injury. *J Burn Care Res*. 2008;29:763-767.
41. Klein GL, Bi LX, Sherrard DJ, et al. Evidence supporting a role of glucocorticoids in short-term bone loss in burned children. *Osteoporos Int*. 2004;15:468-474.
42. Klein GL, Xie Y, Qin YX, et al. Preliminary evidence of early bone resorption in a sheep model of acute burn injury: an observational study. *J Bone Miner Metab*. 2014;32(2):136-141.
43. Hofbauer LC, Gori F, Riggs BL, et al. Stimulation of osteoprotegerin ligand and inhibition of osteoprotegerin production by glucocorticoids in osteoblast lineage cells: potential paracrine mechanisms for glucocorticoid-induced osteoporosis. *Endocrinology*. 1999;140:4382-4389.
44. Parisien M, Charhon SA, Arlot M, et al. Evidence for a toxic effect of aluminum on osteoblasts: a histomorphometric study in hemodialysis patients with aplastic bone disease. *J Bone Miner Res*. 1988;3:259-267.
45. Rodriguez M, Felsenfeld AJ, Llach F. Aluminum administration in the rat separately affects osteoblast and bone mineralization. *J Bone Miner Res*. 1990;5:59-67.
46. Klein GL. Disruption of bone and skeletal muscle in severe burns. *Bone Res*. 2015;3:15002.
47. Parfitt AM, Drezner JK, Glorieux FH, et al. Bone histomorphometry: standardization of nomenclature, symbols and units. Report of the ASBMR Histomorphometry Nomenclature Committee. *J Bone Miner Res*. 1987;2:595-610.
48. Klein GL. The effect of glucocorticoids on bone and muscle. *Osteoporos Sarcopenia*. 2015;1(1):39-45.

49. Kraft R, Herndon DN, Williams FN, et al. The effect of obesity on adverse outcomes and metabolism in pediatric burn patients. *Int J Obes (Lond)*. 2012;36(4):485-490.
50. Klein GL, Herndon DN, Langman CB, et al. Long-term reduction in bone mass following severe burn injury in children. *J Pediatr*. 1995;126:252-256.
51. Przkora R, Herndon DN, Sherrard DJ, et al. Pamidronate preserves bone mass for at least 2 years following acute administration for pediatric burn injury. *Bone*. 2007;41:297-302.
52. Terzi R, Güven M. Bone mineral density after burn injury and its relation to the characteristics of scar tissue. *J Burn Care Res*. 2016;37(3):e263-e267.
53. Klein GL, Herndon DN, Chen TC, et al. Standard multivitamin supplementation does not improve vitamin D insufficiency after burns. *J Bone Miner Metab*. 2009;27:502-506.
54. Mayes T, Gottschlich MM, Khoury J, Kagan RJ. An investigation of bone health subsequent to vitamin D supplementation in children following burn injury. *Nutr Clin Pract*. 2015;30(6):830-837.
55. Rosseau AF, Foidart-Desalle M, Ledoux D, et al. Effects of cholecalciferol supplementation and optimized calcium intakes on vitamin D status, muscle strength and bone health: a one-year pilot randomized controlled trial in adults with severe burns. *Burns*. 2015;41(2):317-325.
56. Klein GL, Wolf SE, Langman CB, et al. Effect of therapy with recombinant human growth hormone on insulin-like growth factor system components and serum levels of biochemical markers of bone formation in children following severe burn injury. *J Clin Endocrinol Metab*. 1998;83:21-24.
57. Hart DW, Wolf SE, Klein G, et al. Attenuation of post-traumatic muscle catabolism and osteopenia by long-term growth hormone therapy. *Ann Surg*. 2001;233:827-834.
58. Branski LK, Herndon DN, Barrow RE, et al. Randomized controlled trial to determine the efficacy of long-term growth hormone treatment in severely burned children. *Ann Surg*. 2009;250(4):514-523.
59. Murphy KD, Thomas S, Mlcak RP, et al. Effects of long-term oxandrolone administration in severely burned children. *Surgery*. 2004;136:219-224.
60. Reeves PT, Herndon DN, Tanksley JD, et al. Five-year outcomes after long-term oxandrolone administration in severely burned children: a randomized clinical trial. *Shock*. 2016;45(4):367-374.
61. Russell RG. Bisphosphonates: mode of action and pharmacology. *Pediatrics*. 2007;119:S150-S162.
62. Klein GL, Wimalawansa SJ, Kulkarni G, et al. The efficacy of acute administration of pamidronate on the conservation of bone mass following severe burn injury in children: a double-blind, randomized, controlled study. *Osteoporos Int*. 2005;16:631-635.
63. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in post-menopausal women with osteoporosis. *N Engl J Med*. 2001;344:1434-1441.
64. Subbiah V, Madsen VS, Raymond AK, et al. Of mice and men: divergent risks of teriparatide-induced osteosarcoma. *Osteoporos Int*. 2010;21:1041-1045.
65. Edionwe J, Hess C, Fernandez-Rio J, et al. Effects of whole-body vibration exercise on bone mineral content and density in thermally injured children. *Burns*. 2016;42(3):605-613.
66. Schneider JC, Simko LC, Goldstein R, et al. Predicting heterotopic ossification early after burn injuries: a risk scoring system. *Ann Surg*. 2017;266(1):179-184.
67. Levi B, Jayakumar P, Giladi A, et al. Risk factors for the development of heterotopic ossification in seriously burned adults: A National Institute on Disability, Independent Living and Rehabilitation Research burn model system database analysis. *J Trauma Acute Care Surg*. 2015;79(5):870-876.
68. Peterson JR, Eboda ON, Brownley RC, et al. Effects of aging on osteogenic response and heterotopic ossification following burn injury in mice. *Stem Cells Dev*. 2014;24(32):205-213.
69. Perosky JE, Peterson JR, Eboda ON, et al. Early detection of heterotopic ossification using near-infrared optical imaging reveals dynamic turnover and progression of mineralization following Achilles tenotomy and burn injury. *J Orthop Res*. 2014;32(11):1416-1423.
70. Peterson JR, Okagbare PI, De La Rosa S, et al. Early detection of burn induced heterotopic ossification using transcutaneous Raman spectroscopy. *Bone*. 2013;54(1):28-34.
71. Citak M, Grasmücke D, Suero EM, et al. The roles of serum alkaline and bone alkaline phosphatase levels in predicting heterotopic ossification following spinal cord injury. *Spinal Cord*. 2016;54(5):368-370.
72. Peterson JR, De La Rosa S, Eboda O, et al. Treatment of heterotopic ossification through remote ATP hydrolysis. *Sci Transl Med*. 2014;6(255):255ra132-255ra132.
73. Agarwal S, Loder S, Brownley C, et al. Inhibition of Hif1α prevents both trauma-induced and genetic heterotopic ossification. *Proc Natl Acad Sci U S A*. 2016;113(3):E338-E347.
74. Kraft CT, Agarwal S, Ranganathan K, et al. Trauma-induced heterotopic bone formation and the role of the immune system: A review. *J Trauma Acute Care Surg*. 2016;80(1):156-165.
75. Agarwal S, Loder S, Li J, et al. Diminished chondrogenesis and enhanced osteoclastogenesis in leptin-deficient diabetic mice (ob/ob) impair pathologic, trauma-induced heterotopic ossification. *Stem Cells Dev*. 2015;24:2864-2872.
76. Beckmann JT, Wylie JD, Potter MQ, et al. Effect of naproxen prophylaxis on heterotopic ossification following hip arthroscopy. *J Bone Joint Surg Am*. 2015;97(24):2032-2037.
77. Sun Y, Cai J, Li F, et al. The efficacy of celecoxib in preventing heterotopic recurrence after open arthrolysis for post-traumatic elbow stiffness in adults. *J Shoulder Elbow Surg*. 2015;24(11):1735-1740.
78. Ayers DC, Evarts CM, Parkinson JR. The prevention of heterotopic ossification in high-risk patients by low-dose radiation therapy after total hip arthroplasty. *J Bone Joint Surg Am*. 1986;68(9):1423-1430.
79. Seegenschmiedt MH, Keilholz L, Martus P, et al. Prevention of heterotopic ossification about the hip: final results of two randomized trials in 410 patients using either preoperative or postoperative radiation therapy. *Int J Radiat Oncol Biol Phys*. 1997;39(1):161-171.
80. Pellegrini VD Jr, Konski AA, Gastel JA, et al. Prevention of heterotopic ossification with irradiation after total hip arthroplasty. Radiation therapy with a single dose of eight hundred centigray administered to a limited field. *J Bone Joint Surg Am*. 1992;74(2):186-200.
81. Moore DK, Katy Goss K, Anglen JO. Indomethacin versus radiation therapy for prophylaxis against heterotopic ossification in acetabular fractures. *Bone Joint J*. 1998;80(2):259-263.
82. Sell S, Willms R, Jany R, et al. The suppression of heterotopic ossifications: radiation versus NSAID therapy—a prospective study. *J Arthroplasty*. 1998;3(8):854-859.

26 Micronutrient Homeostasis

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Importance of Vitamins and Trace Elements

Essential vitamins and trace elements, which are globally known as "micronutrients," are fundamental to metabolism; they function as structures of enzymes or as their cofactors. Their requirements are influenced by the metabolic state and by increased nutritional needs after major burns.[1] The first publications about elevated vitamin requirements go back to the 1940s and of trace elements to the 1960s.[2] Their homeostasis in burn injury is summarized here.

Vitamins

Ascorbic acid (vitamin C), cholecalciferol (vitamin D), and α-tocopherol (vitamin E) have all been reported as depleted in burned patients.[3,4]

VITAMIN C

Vitamin C is not only an essential nutrient involved in many anabolic pathways and essential for would healing, but it also scavenges reactive oxygen species and improves microcirculatory flow impairment. Low plasma concentrations of vitamin C are very common in burned pediatric and adult patients.

Intravenous infusions of vitamin C have previously been shown to be beneficial in animal models. Dubick et al.[5] infused high doses of ascorbic acid in an ovine model of 40% total body surface area (TBSA) burn injury, which significantly reduced resuscitation fluid requirements of burned sheep after 48 hours. Plasma thiobarbituric acid reactive substances increased fourfold in sham-burned sheep; this was prevented by the use of the vitamin C infusion. Tanaka et al.[6] found that, using high-dose vitamin C, total tissue water content was reduced and negative interstitial fluid hydrostatic pressure was more positive in a rodent burned model when compared to unburned animals. Tanaka et al. showed in before-and-after trials that megadoses of ascorbic acid (66 mg/kg/h^{-1}) delivered during the first 24 hours after injury were associated with a significant fluid resuscitation requirement reduction and lesser weight gain,[7] suggesting a beneficial role in burn resuscitation. Randomized trials are still needed. Last, the use of vitamin C protected the seminiferous tubules and germ cell loss in burned rats compared to unburned rats,[8] but human data are not yet available.

VITAMIN D

Vitamin D is a fat-soluble micronutrient that has been implicated in a wide array of physiological systems, including skeletal muscle, bone health, cardiovascular health, immune system, and lung function. It has been shown to reduce inflammatory cytokines and reactive oxygen and nitrogen species, as well as attenuate cancer, osteoarthritis, schizophrenia, and depression. Notable risk factors for decreased vitamin D concentrations include decreased skin production, use of sunscreen, its decreased bioavailability and production, liver or kidney dysfunction, malabsorption disorders, the use of cholesterol-lowering agents, and increased glucocorticoids.[9]

Burned children develop a progressive deficiency of vitamin D as measured by circulating levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D_3. This result may be confounded by the acute reduction in serum vitamin D-binding protein[10] and albumin.[11] Fourteen months post burn, serum 25-hydroxyvitamin D levels are low[12] and remain low at 2 and 7 years post burn.[13] Whereas serum levels of 1,25-dihydroxyvitamin D_3 are normal at 2 years, about 50% of measured values are low at 7 years post burn, suggesting a progressive vitamin D deficiency.[13]

During the acute phase, the standard 200 IU/day is insufficient to maintain vitamin D status as shown in a Belgian cohort study.[14] Failure to provide vitamin D supplementation to burn patients at discharge from hospital may contribute to vitamin D deficiency. Fifteen adult burned patients were randomized into either a group that received quarterly intramuscular injections of 200,000 IU vitamin D_3 with daily oral calcium or into a placebo group.[15] After 1 year, calcidiol levels significantly increased in the vitamin D group. No change in bone health was observed between groups, but the vitamin D-treated group showed significantly improved quadriceps strength when tested at high velocity.[15]

In 2009, pediatric burned patients discharged from the Shriners Hospital for Children in Galveston received daily supplementation with a multivitamin containing 400 IU of vitamin D_2 for 6 months.[16] At that time, circulating levels of 25-hydroxyvitamin D were still in the insufficient to low range, without any improvement in lumbar spine bone density. This was further tested in pediatric burned patients at the Shriners Hospital for Children in Cincinnati with 100 IU of vitamin D_3 in a study that showed no significant differences in treated or untreated groups.[17] Thus the amount of vitamin D supplementation necessary to maintain normal circulating levels of 25-hydroxyvitamin D in pediatricburned patients is unknown. Chan and Chan cite 200–400 IU/day as required in healthy, nonburned children.[18] However there is no evidence supporting that

requirement in a burned population, and long-term vitamin D supplementation with levels exceeding 400 IU/day may be necessary to overcome the postburn deficiency.

Another major factor, however, is the profound change in skin structure and quality. Burn scar and adjacent areas of unburned skin can only convert roughly 25% of its 7-dehydrocholesterol precursor to vitamin D_3 on exposure to sunlight.[12] Moreover, the amount of 7-dehydrocholesterol substrate is significantly reduced in both burn scar and adjacent unburned skin.[12] This indicates that, after burn injury, the skin cannot synthesize normal amounts of vitamin D regardless of the amount of sun exposure received. Thus, progressive deficiency in vitamin D will result without supplementation.

VITAMIN E

It has been previously shown that adult patients with severe burns are characterized by increased free radical activity and very low levels of antioxidants; if the redox status of these patients was not restored, the patients died.[19] Vitamin E is a fat-soluble antioxidant that scavenges peroxyl radicals and prevents the radical-mediated chain reactions of polyunsaturated fatty acids. Recently, it has been shown that the tissue storage of vitamin E in burned children decreases by half as early as 3 weeks after injury.[20] Burned patients are entering the operating room with consistently low vitamin E status, and vitamin E intakes in pediatric burn patients are less than their requirements.[21,22] Furthermore, it has been shown in burned children that a combination of antioxidants (vitamin C, vitamin E, and zinc for 7 days; average of 900 IU/day, 400 IU/day, and 7 IU/day, respectively) increased circulating vitamin E and decreased malondialdehyde, which is a marker of oxidative stress.

Mechanistic studies in the ovine model of burn and smoke inhalation using deuterium-labeled vitamin E showed that the burn increased depletion of liver vitamin E, suggesting the tissue mobilization of vitamin E.[23] These studies suggested that, in addition to depletion of vitamin E from the lung and liver, other tissues were also depleted.[23] Given the hypermetabolic and hypercatabolic state and altered lipid metabolism in patients with burn injury, there is concern that depletion of adipose tissue vitamin E may reflect a significant level of oxidative stress, which then can cause secondary organ failure.[20]

The inflammatory response from excess oxidative and nitrosative stress in burn injury further impairs the healing process. Burned children who were supplemented with vitamins E, C, and zinc needed significantly fewer days to heal compared to unsupplemented children.[24] Increased wound healing using the nebulization of vitamin E in the 3-week ovine model of burn and smoke inhalation has also been demonstrated.[25] Furthermore, vitamin E has been shown to be beneficial in the treatment of wounds in a variety of models, including scar formation from acute surgical wounds[26] and in rats with skin lesions from diabetes.[27]

VITAMIN K

In a study of serum vitamin K levels in severely burned pediatric patients, Jenkins reported that 91% of children studied demonstrated low circulating levels in the first month post burn.[28] However, there was no relationship between serum vitamin K levels and prothrombin time, raising the question of clinical significance. It should be noted that osteocalcin, a gamma-carboxylated protein produced by osteoblasts, is vitamin K dependent. Osteocalcin is used as a standard index of bone formation and also has been shown to stimulate pancreatic insulin production and peripheral insulin sensitivity.[29] Circulating osteocalcin is reported to be low in the first month following burn injury.[30] Therefore, the possibility remains that low circulating vitamin K levels may contribute to the reduction in serum osteocalcin and hence to postburn insulin resistance and the reduction of bone formation.

Trace Elements

Facts about trace elements have been consolidated during the past decades. Among them, copper (Cu), iron (Fe), selenium (Se), and zinc (Zn) are involved in antioxidant and innate and adaptive immune defenses, and deficiencies largely contribute to the classical complications observed after major burns, such as persistent inflammatory state, multiorgan failure, and sepsis. Table 26.1 summarizes some of these specific alternations. Major burns differ from other trauma and critically ill patients by the magnitude of the changes and their mechanisms. Here, we address the changes affecting the blood compartment, exudative and urinary losses, their role in inflammation and antioxidant defenses, and, finally, some considerations about lesser-known and sometimes toxic trace elements.

BLOOD CONCENTRATIONS

Low blood concentrations (serum and plasma) of several trace elements in burn patients have been repeatedly reported since the 1970s[31–33] and support recommendations to determine and monitor blood levels after major burns and to orient repletion in cases of evident deficit.

Copper: Very low levels of Cu have been shown repeatedly in this category of patients. The circulating concentrations vary inversely with the size of burns.[34,35] This observation supports the diagnosis of deficiency because Cu and ceruloplasmin (Cp) usually increase during an inflammatory response, with Cp being upregulated by interleukin-1, but this increase does not occur in major burns. Further wound treatment is often carried out with silver products (silver-sulfadiazine and silver-containing hydrofiber dressings): silver penetrates in the body and antagonizes Cu, contributing to its decrease along with Cp.[36] It is important to note that Cu and Fe metabolism are tightly linked.[37]

Selenium: Blood levels of Se decrease very early after major burns due first to an inflammatory redistribution and then aggravated by large exudative losses. Se remains low for several weeks. This is associated with a nearly immediate depression of the activity of plasma glutathione peroxidase (GPX-3) (see later discussion).

Zinc: Blood Zn levels decrease within the first hours after major burns[38] and remain very low for weeks, also as the

Table 26.1 Micronutrient requirements and specific burn needs during the acute period (>10% TBSA)

	Vit A (IU)	Vit D (IU)	Vit E (IU)	Vit C (mg)	Vit K (mcg)	Folate (mcg)	Cu (mg)	Fe (mg)	Se (mcg)	Zn (mg)
AGES 0–13 YEARS										
Nonburned	1300–2000	600	6–16	15–50	2–60	65–300	0.2–0.7	0.3–8	15–40	2–8
Burned	2500–5000	NRE†	NRE†	250–500	NRE	1,000*	0.8–2.8	NRE	60–140	12.5–25
AGES ≥13 YEARS										
Nonburned	2000–3000	600	23	75–90	75–120	300–400	0.9	8–18	40–60	8–11
Burned	10,000	NRE†	NRE†	1,000	NRE	1,000*	4.0	NRE	300–500	25–40

Conversion based on the following: 1 μg of vitamin A = 3.33 IU of vitamin A; 1 μg of calciferol = 40 IU vitamin D; 1 mg of α-tocopherol = 1.5 IU of vitamin E.
NRE, no recommendations established.
*Administered Monday, Wednesday, and Friday.
†Pending Clinical Trial
Sources: Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride (1977); dietary reference intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline (1988); dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids (2000); dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc (2001); and dietary reference intakes for calcium and vitamin D (2010). These reports may be accessed at http://www.nap.edu. Berger MM, Shenkin A. *J Trace Elem Med Biol.* 2007;21(Suppl 1):44–48. Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F. *Clin Nutr.* Aug 2009;28(4): 378–386; Singer P, Berger MM, Van den Berghe G, et al. *Clin Nutr.* Aug 2009;28(4):387–400; Berger MM, Eggimann P, Heyland DK, et al. *Crit Care* 2006;10(6):R153; Berger MM, Baines M, Raffoul W, et al. *Am J Clin Nutr.* May 2007;85(5):1293–1300; Berger MM, Binnert C, Chiolero RL, et al. *Am J Clin Nutr.* May 2007;85(5):1301–1306.

result of the inflammatory redistribution associated with inflammation[39–41] and accompanying high losses.

Iron: After major burns, ferremia decreases nearly immediately and remains low for prolonged periods:[37] after the first week, other mechanisms will maintain the low ferremia, the principal being hemorrhage during surgery, but also exudative losses.[42]

Chromium: Animal studies[43] show that chromium (Cr) concentrations decrease in the liver of burned rats, becoming nondetectable after a few days and in muscle very early on and for several days. Simultaneously, urinary Cr losses increase. The changes in Cr concentrations were associated in animals with an early hyperglycemia, hyperinsulinemia, and increased secretion of stress hormones. Data from diabetic patients and patients on parenteral nutrition show that chromium deficiency contributes to insulin resistance. Preliminary human data from the Lausanne lab show that Cr is lost in exudates, along with molybdenum and manganese:[42] clinical significance must be confirmed.

Aluminum: The impact of aluminum (Al) remains debated; investigations are few but indicate potential serious consequences on bone metabolism. Large Al intakes from albumin were a problem for several years.[44] Al loading has been reported in at least one population of burned adults,[10] but no additional reports show Al uptake by either bone or liver. In pediatric patients suffering severe burns, aurin tricarboxylic staining of bone biopsies for Al accumulation at the bone surface have been negative.[11] The Al contamination of parenteral products has not been seriously addressed since the U.S. Food and Drug Administration (FDA) recommendation in 1986,[45] and because there is no real treatment in case of toxicity, suspicion should be maintained and blood levels checked in cases of neurological and bone pain, particularly in children. Preliminary data from the Lausanne Lab confirm that serum levels are above reference levels in adults and Al is detected in the exudates.[42]

EXUDATIVE AND URINARY LOSSES

In healthy subjects, trace elements are lost through urine (Se mainly) or feces (Cu, Fe, Zn), with extremely little being lost to sweat. Increased losses were suspected to occur after burns but have been difficult to measure precisely until recently.

Copper: In studies done urinary losses were shown to be above normal in the 1980s,[32,46] being particularly observed during parenteral nutrition, although excreted amounts were lesser than the infused quantities. The main losses of Cu have been shown to occur through exudates during the open wound phase after major burns: such losses occur similarly in children.[47]

Selenium: A 1984 study showed that urinary excretion of Se was decreased,[48] reflecting a deficiency status, with Se being retained. This deficit was explained by significant cutaneous losses, shown in the frame of a balance study.[49] These findings have been confirmed recently.[42]

Zinc: Urinary losses of Zn are initially above normal[50] as in other major trauma but then decrease. Significant losses occur through exudates, reaching about 10% of body content during the first week.[51]

Iron: Recently, a study investigating a large palette of trace elements showed that, in patients with 27% TBSA burns, Fe was lost in large amounts with exsudates even in the absence of active bleeding.[42]

It is important to note that, along with these four elements, other trace elements are also lost but do not seem to contribute to clinically detectable alterations. Magnesium and phosphorus losses are substantial and sufficient to explain the high requirements during the early phase of burns.[52]

ROLE OF TRACE ELEMENTS IN INFLAMMATION AND ANTIOXIDANT DEFENSES

The inflammation that starts nearly immediately after burn injury has a major impact on circulating trace elements. Already in the 1970s, in a study of rats with 20% TBSA, Van Rij et al.[39] showed that ^{65}Zn was rapidly taken up by liver, spleen, kidney, and wound, with a decrease in the brain, muscles, and bone: this type of redistribution would later be called *inflammatory-mediated redistribution of micronutrients* because it also affects Se and Fe. This type of redistribution pattern has been confirmed by several authors.[40,41]

Cu and Zn with Se are linked in cytosolic defense against reactive nitrogen and oxygen species:[53] iron adds to the complexity because it is also essential for immunity. In superoxide dismutase (SOD), Cu and Zn play major roles, enabling electron transfer. The plasma activity of SOD is decreased after major burns.[41] Furthermore, Cp plays a role as neutralizer of ferrous entities. Se is mainly active through the antioxidant family of glutathione peroxidase enzymes, which depend on Se for activity, but also through the large family of selenoproteins. Plasma GPX3 levels are the first to change, decreasing within hours after burn injury.[51] The redistribution of these trace elements to other compartments reduces their availability as first-line antioxidant defenses. Se depletion before the injury worsens the antioxidant defense, as shown in burned rats:[54] in animals made Se deficient, a nearly immediate Se supplementation did not restore their antioxidant defenses after burn.

Antioxidant and immune defenses are tightly coupled, and Cu, Se, and Zn modulate both the innate and adaptive immune response through their availability.[55] In particular, Zn deficiency will alter the activity of monocytes, polymorphonuclear, natural killer, B, and T cells: the latter are particularly susceptible to changes in Zn status.[55] Cu-dependent Cp is an acute-phase reactant protein that converts ferrous iron to its less reactive ferric form to facilitate binding to ferritin: its ferroxidase activity is important to iron handling. As recently demonstrated,[37] a low Cp favors oxidative reactions. Low Fe levels and inflammation are tightly associated, as recently shown by Dubick et al.[37] The body has developed strong defense mechanisms, including Cp, against this essential but potentially toxic trace element.[56]

TRACE ELEMENT THERAPY

In the late 1970s, combined Cu and Zn repletion was attempted in burned children by the enteral route[57] but failed to restore satisfactory blood levels due to the competition existing between Cu and Zn for absorption at the intestinal level. An animal study showed that a multi-trace element supply was required to achieve mucosal and carcass weight gains.[58] Successful treatment of deficiency requires the intravenous route, as shown by randomized studies. Low Se blood concentrations may be corrected by doses in the magnitude of 10 times RDA.[59] Intravenous therapy beginning the day of injury and combining Cu 3–4 mg/day, Se 300–400 mcg/day, and Zn 30–40 mg/day resulted in restoration of low but within-normal ranges of the three elements in 5–10 days and was associated with normalization of the activity of GPX3. The doses required in major burns are indeed higher than what can be delivered by the enteral route or that are required in parenteral nutrition. A recent study of exudates shows that there is a retention of the Cu, Se, and Zn in the body.[42] The just-listed adult doses[59,60] were adapted to children (normalized by body surface area) and also achieved restoration of blood values within reference range.[61] The clinical results of intervention trials delivering higher doses of trace elements are numerous: attenuation of oxidative stress;[24,62] improved wound healing (better graft take) probably by means of a modulation of protein metabolism;[63] improved immunity and reduced infectious complications, especially pulmonary;[64] and shortened length of stay.[59]

Conclusion

Burn injury is marked by a reduction in plasma levels of most vitamins and trace elements, which are redistributed mainly to the liver and kidney in order to maximize the antioxidant and anabolic response to injury. Antioxidant supplementation appears to have beneficial effects on both morbidity and mortality. While nutritional and antioxidant requirements of vitamins and trace elements are increased above RDA during the acute hypermetabolic phase of major burn injury, the duration and magnitude of the increased needs in the postburn state remain to be determined.

Complete references available online at
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Further Reading

Berger M. Acute copper and zinc deficiency due to exudative losses: substitution versus nutritional requirements. *Burns*. 2006;32:393.

Berger MM, Baines M, Raffoui W, et al. Trace element supplementation after major burns modulates anti-oxidant status and clinical course by way of increased tissue trace element concentrations. *Am J Clin Nutr*. 2007;85:1293-1300.

Berger MM, Chiolero RL. Anti-oxidant supplementation in sepsis and systemic inflammatory response syndrome. *Crit Care Med*. 2007;35(suppl):S584-S590.

Chan MM, Chan GM. Nutritional therapy for burns in children and adults. *Nutrition*. 2009;25:261-269.

Klein GL, Chen TC, Holick MF, et al. Synthesis of vitamin D in skin after burns. *Lancet*. 2004;363:291-292.

Voruganti VS, Klein GL, Lu HX, et al. Impaired zinc and copper status in children with burn injuries: need to reassess nutritional requirements. *Burns*. 2005;31:711-716.

References

1. Berger MM, Shenkin A. Trace element requirements in critically ill burned patients. *J Trace Elem Med Biol*. 2007;21(suppl 1):44-48.
2. Lund C, Levenson S, Green R, et al. Ascorbic acid, thiamine, riboflavin and nicotinic acid in relation to acute burns in man. *Arch Surg*. 1946;55:557-583.
3. Nguyen TT, Cox CS, Traber DL, et al. Free radical activity and loss of plasma antioxidants, vitamin E, and sulfhydryl groups in patients with burns: the 1993 Moyer Award. *J Burn Care Rehabil*. 1993;14:602-609.
4. Rock CL, Dechert RE, Khilnani R, Parker RS, Rodriguez JL. Carotenoids and antioxidant vitamins in patients after burn injury. *J Burn Care Rehabil*. 1997;18(3):269-278, discussion 268.
5. Dubick MA, Williams C, Elgjo GI, Kramer GC. High-dose vitamin C infusion reduces fluid requirements in the resuscitation of burn-injured sheep. *Shock*. 2005;24(2):139-144.
6. Tanaka H, Lund T, Wiig H, et al. High dose vitamin C counteracts the negative interstitial fluid hydrostatic pressure and early edema generation in thermally injured rats. *Burns*. 1999;25(7):569-574.
7. Tanaka H, Matsuda T, Miyagantani Y, et al. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration. *Arch Surg*. 2000;135:326-331.
8. Jewo PI, Duru FI, Fadeyibi IO, Saalu LC, Noronha CC. The protective role of ascorbic acid in burn-induced testicular damage in rats. *Burns*. 2012;38(1):113-119.
9. Patton CM, Powell AP, Patel AA. Vitamin D in orthopaedics. *J Am Acad Orthop Surg*. 2012;20(3):123-129.
10. Klein G, Herndon D, Rutan T, et al. Bone disease in burn patients. *J Bone Miner Res*. 1993;8(3):337-345.
11. Klein G, Herndon D, Goodman W, et al. Histomorphometric and biochemical characterization of bone following acute severe burns in children. *Bone*. 1995;17(5):455-460.
12. Klein GL, Chen TC, Holick MF, et al. Synthesis of vitamin D in skin after burns. *Lancet*. 2004;363(9405):291-292.
13. Klein GL, Langman CB, Herndon DN. Vitamin D depletion following burn injury in children: a possible factor in post-burn osteopenia. *J Trauma*. 2002;52(2):346-350.
14. Rousseau A, Damas P, Ledoux D, Cavalier E. Effect of cholecalciferol recommended daily allowances on vitamin D status and fibroblast growth factor-23: an observational study in acute burn patients. *Burns*. 2014;40(5):865-870.
15. Rousseau AF, Foidart-Desalle M, Ledoux D, et al. Effects of cholecalciferol supplementation and optimized calcium intakes on vitamin D status, muscle strength and bone health: a one-year pilot randomized controlled trial in adults with severe burns. *Burns*. 2015;41(2):317-325.
16. Klein GL, Herndon DN, Chen TC, Kulp G, Holick MF. Standard multivitamin supplementation does not improve vitamin D insufficiency after burns. *J Bone Miner Metab*. 2009;27(4):502-506.
17. Gottschlich MM, Mayes T, Khoury J, Kagan RJ. Clinical trial of vitamin D2 vs d3 supplementation in critically ill pediatric burn patients. *JPEN J Parenter Enteral Nutr*. 2015;2017;41:412-421.
18. Chan MM, Chan GM. Nutritional therapy for burns in children and adults. *Nutrition*. 2009;25(3):261-269.
19. Nguyen TT, Cox CS, Traber DL, et al. Free radical activity and loss of plasma antioxidants, vitamin E, and sulfhydryl groups in patients with burns: the 1993 Moyer Award. *J Burn Care Rehabil*. 1993;14(6):602-609.
20. Traber MG, Leonard SW, Traber DL, et al. (-Tocopherol adipose tissue stores are depleted after burn injury in pediatric patients. *Am J Clin Nutr*. 2010;92(6):1378-1384.
21. Circu ML, Aw TY. Reactive oxygen species, cellular redox systems, and apoptosis. *Free Radic Biol Med*. 2010;48(6):749-762.
22. Niki E. Assessment of antioxidant capacity in vitro and in vivo. *Free Radic Biol Med*. 2010;49(4):503-515.
23. Traber MG, Shimoda K, Murakami K, et al. Burn and smoke inhalation injury in sheep depletes vitamin E: kinetic studies using deuterated tocopherols. *Free Radic Biol Med*. 2007;42(9):1421-1429.
24. Barbosa E, Faintuch J, Machado Moreira E, et al. Supplementation of vitamin E, vitamin C, and zinc attenuates oxidative stress in burned children: a randomized, double-blind, placebo-controlled pilot study. *J Burn Care Res*. 2009;30(5):859-866.
25. Yamamoto Y, Sousse LE, Enkhbaatar P, et al. Gamma-tocopherol nebulization decreases oxidative stress, arginase activity, and collagen deposition after burn and smoke inhalation in the ovine model. *Shock*. 2012;38(6):671-676.
26. Havlik RJ. Vitamin E and wound healing. Plastic Surgery Educational Foundation DATA Committee. *Plast Reconstr Surg*. 1997;100(7):1901-1902.
27. Musalmah M, Fairuz AH, Gapor MT, Ngah WZ. Effect of vitamin E on plasma malondialdehyde, antioxidant enzyme levels and the rates of wound closures during wound healing in normal and diabetic rats. *Asia Pac J Clin Nutr*. 2002;11(suppl 7):S448-S451.
28. Jenkins ME, Gottschlich MM, Kopcha R, Khoury J, Warden GW. A prospective analysis of serum vitamin K in severely burned pediatric patients. *J Burn Care Rehabil*. 1998;19(1 Pt 1):75-81, discussion 73–74.
29. Ferron M, Hinoi E, Karsenty G, Ducy P. Osteocalcin differentially regulates beta cell and adipocyte gene expression and affects the development of metabolic diseases in wild-type mice. *Proc Natl Acad Sci USA*. 2008;105(13):5266-5270.
30. Klein GL, Wolf SE, Langman CB, et al. Effects of therapy with recombinant human growth hormone on insulin-like growth factor system components and serum levels of biochemical markers of bone formation in children after severe burn injury. *J Clin Endocrinol Metab*. 1998;83(1):21-24.
31. Larson D, Dobrkowsky M, Abston S, Lewis S. *Zinc concentrations in plasma, red blood cells, wound exsudate and tissues of burned children*. Bern: Huber; 1970.
32. Boosalis M, McCall J, Solem L, Ahrenholz D, McClain C. Serum copper and ceruloplasmin levels and urinary copper excretion in thermal injury. *Am J Clin Nutr*. 1986;44:899-906.
33. Shewmake K, Talbert G, Bowser-Wallace B, Cladwell F, Cone J. Alterations in plasma copper, zinc and ceruloplasmin levels in patients with thermal injury. *J Burn Care Rehabil*. 1988;9:13-17.
34. Gosling P, Rothe H, Sheehan T, Hubbard L. Serum copper and zinc concentrations in patients with burns in relation to burn surface area. *J Burn Care Rehabil*. 1995;16:481-486.
35. Cunningham J, Lydon M, Emerson R, Harmatz P. Low ceruloplasmin levels during recovery from major burns injury - Influence of open wound size and copper supplementation. *Nutrition*. 1996;12:83-88.
36. Boosalis M, Shippee R, Talwalker R, McClain C. Topical silver sulfadiazine decreases plasma copper and ceruloplasmin in a rat model of thermal injury. *J Trace Elem Exp Med*. 1994;7:119-124.
37. Dubick M, Barr J, Keen C, Atkins J. Ceruloplasmin and hypoferremia: studies in burn and non-burn trauma patients. *Antioxidants (Basel)*. 2015;4(1):153-169.
38. Khorasani G, Hosseinimehr S, Kaghazi Z. The alteration of plasma's zinc and copper levels in patients with burn injuries and the relationship to the time after burn injuries. *Singapore Med J*. 2008;49(8):627-630.
39. Van Rij A, McKenzie J, Dunckley J. Excessive urinary zinc losses and amino-aciduria during intravenous alimentation. *Proc Univ Otago Med School*. 1975;53:77-78.
40. Ding H, Zhou B, Liu L, Cheng S. Oxidative stress and metallothionein expression in the liver of rats with severe thermal injury. *Burns*. 2002;28:215-221.
41. Agay D, Anderson R, Sandre C, et al. Alterations of antioxidant trace elements (Zn, Se, Cu) and related metaloenzymes in plasma and tissues following burn injury in rats. *Burns*. 2005;31:366-371.
42. Jafari P, Augsburger M, Thomas A, et al. Kinetics of trace element losses through burn wound exudation: are burn requirements due for revision? *J Burn Care Res*. 2016;37(3 suppl).
43. Anderson R, Sandre C, Bryden N, et al. Burn-induced alterations of chromium and the glucose/insulin system in rats. *Burns*. 2006;32(1):46-51.
44. Klein G, Herndon D, Rutan T, et al. Risk of aluminum accumulation in patients with burns and ways to reduce it. *J Burn Care Rehabil*. 1994;15(4):354-358.
45. Gura K. Aluminum contamination in parenteral products. *Curr Opin Clin Nutr Metab Care*. 2014;17(6):551-557.
46. Cunningham J, Lydon M, Briggs S, DeCheke M. Zinc and copper status of severely burned children during TPN. *J Am Coll Nutr*. 1991;10:57-62.
47. Voruganti V, Klein G, Lu H, et al. Impaired zinc and copper status in children with burn injuries: need to reassess nutritional requirements. *Burns*. 2005;31(6):711-716.
48. Hunt D, Lane H, Beesinger D, et al. Selenium depletion in burn patients. *JPEN*. 1984;8:695-699.

49. Berger MM, Cavadini C, Bart A, et al. Selenium losses in 10 burned patients. *Clin Nutr*. 1992;11:75-82.
50. Selmanpakoglu A, Cetin C, Sayal A, Isimer A. Trace element (Al, Se, Zn, Cu) levels in serum, urine and tissues of burn patients. *Burns*. 1994;20:99-103.
51. Berger MM, Cavadini C, Bart A, et al. Cutaneous zinc and copper losses in burns. *Burns*. 1992;18:373-380.
52. Berger MM, Rothen C, Cavadini C, Chioléro R. Exudative mineral losses after serious burns: A clue to the alterations of magnesium and phosphate metabolism. *Am J Clin Nutr*. 1997;65:1473-1481.
53. Munoz C, Rios E, Olivos J, Brunser O, Olivares M. Iron, copper and immunocompetence. *Br J Nutr*. 2007;98(suppl 1):S24-S28.
54. Agay D, Sandre C, Ducros V, et al. Optimization of selenium status by a single intra-peritoneal injection of Se in Se deficient rat: possible application to burned patient treatment. *Free Rad Biol Med*. 2005;39(6):762-768.
55. Bonaventura P, Benedetti G, Albarede F, Miossec P. Zinc and its role in immunity and inflammation. *Autoimmun Rev*. 2015;14(4):277-285.
56. Anderson G, Wang F. Essential but toxic: controlling the flux of iron in the body. *Clin Exp Pharmacol Physiol*. 2012;39(8):719-724.
57. Pochon P. Zinc- and copper-replacement therapy – a must in burns and scalds in children? *Prog Ped Surg*. 1981;151-172.
58. Nelson J, Alexander J. Multi-trace element supplementation in enteral formulas for burned guinea pigs. *Nutrition*. 1991;7:275-279.
59. Berger MM, Baines M, Raffoul W, et al. Trace element supplements after major burns modulate antioxidant status and clinical course by way of increased tissue trace element concentration. *Am J Clin Nutr*. 2007;85:1293-1300.
60. Berger MM, Spertini F, Shenkin A, et al. Trace element supplementation modulates pulmonary infection rates after major burns: a double blind, placebo controlled trial. *Am J Clin Nutr*. 1998;68:365-371.
61. Stucki P, Perez M, Cotting J, Shenkin A, Berger M. Substitution of exudative trace elements losses in burned children. *Crit Care*. 2010;14:439.
62. Berger MM, Chiolero R. Relations between copper, zinc and selenium intakes and malondialdehyde excretion after major burns. *Burns*. 1995;21(7):507-512.
63. Berger MM, Binnert C, Chiolero R, et al. Trace element supplements after major burns increase burned skin concentrations and modulate local protein metabolism, but not whole body substrate metabolism. *Am J Clin Nutr*. 2007;85:1301-1306.
64. Berger MM, Eggimann P, Heyland D, et al. Reduction of nosocomial pneumonia after major burns by trace element supplementation: aggregation of two randomised trials. *Crit Care*. 2006;10(R153).

27 Hypophosphatemia

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Certain humoral and metabolic responses to thermal and mechanical trauma that maintain homeostasis and prevent cellular dysfunction also produce alterations in electrolyte balance. An example is renal retention of sodium during the resuscitative phase of burn injury, which alters sodium balance in the course of preserving intravascular volume. Despite the markedly increased cardiac output and renal plasma flow that occur in the subsequent flow phase, a decrease in blood volume persists and results in sustained elevation of plasma renin activity, secretion of antidiuretic hormone, and sodium retention.[1] Conversely, the severe hypophosphatemia that often follows major injury occurs concomitantly with a 50–100% increase in resting energy expenditure, leading to a possible deficiency in the high-energy phosphate compounds essential for cellular metabolism. Thermal injury induces a precipitous decrease in serum phosphate concentration that reaches its nadir between the second and fifth postburn days. This phenomenon has been recognized for quite some time[2] and was recently confirmed by the authors in a large series of burn patients.[3] Despite aggressive phosphorus supplementation, normal levels of serum phosphorus are rarely reached before the 10th postburn day (Fig. 27.1). Of 550 patients studied, 175 had serum phosphorus concentrations below 2.0 mg/dL, and of these, 49 were below 1.0 mg/dL, with the lower limit of normal serum phosphorus being 3.0 mg/dL. Such hypophosphatemia is not exclusive to thermal injury, having been described after multiple trauma,[4] head injury,[5] and elective surgery.[6] The exact mechanism by which thermal injury or severe stress induces hypophosphatemia is unknown. Several events associated with burn injury, however, affect phosphorus metabolism, and these may combine to produce hypophosphatemia.

Etiology of Postburn Hypophosphatemia

Many of the pathophysiological changes and therapeutic interventions that occur during the first postburn week influence serum phosphorus concentration (Box 27.1). Hypophosphatemia does not necessarily imply phosphorus depletion; in the case of burn injury, most patients are healthy before injury and presumably have normal phosphorus stores. Nor do simple calculations of phosphate balance explain the dramatic decrease in serum levels; simultaneous reduction of urinary phosphate excretion is observed, suggesting an extrarenal mechanism. The fractional excretion of phosphate, however, increases during the early period of diuresis after burn injury (postburn days 2–4), potentially contributing to the decline in serum levels. The pathophysiological events and therapeutic interventions discussed here are associated with hypophosphatemia in other disease states and in certain experimental animal models, but the extent of their contributions to the postburn decrease in serum phosphorus has not been critically evaluated and is, at present, undefined.

STRESS RESPONSE

In the early postburn period, the classic "fight or flight" response occurs, with elevation of plasma catecholamines, glucose, glucagon, and cortisol. Exogenous epinephrine administration has been associated with the development of hypophosphatemia, and the profound catecholamine release accompanying thermal injury may contribute to the early decrease in serum phosphorus. The mechanism by which this occurs is uncertain but may be a consequence of the accompanying hyperglycemia, resulting in a redistribution of phosphorus from the extracellular to the intracellular compartment (see the later section on metabolic support). In acute clinical states of glucagon excess, tubular reabsorption of phosphate is impaired in both the proximal and distal nephron, leading one to expect renal phosphate wastage.[7] Because urinary excretion of phosphate is usually decreased in the early postinjury period, the importance of hyperglucagonemia remains uncertain. Administration of pharmacologic doses of glucocorticoids enhances phosphorus excretion and impairs phosphate absorption by the gut and reabsorption by the kidney. Whether the adrenocortical response significantly contributes to the hypophosphatemia after burn injury is not known.

RESUSCITATION AND TOPICAL THERAPY

Administration of large doses of sodium lactate for initial burn resuscitation may decrease the serum phosphorus concentration by several mechanisms.[8] Lactate is converted to glucose in the liver, a process requiring high-energy phosphate availability. Additionally, although it does not usually occur clinically, metabolic alkalosis induced by lactate infusion may result in depression of serum phosphorus concentration. Alkalosis is associated with an increase in glycolysis that promotes transfer of phosphorus to the intracellular space. During resuscitation, alkalemia is uncommon, and patients are more likely to manifest a mild metabolic acidosis, which is compensated by hyperventilation, resulting in a normal or mildly alkaline blood pH. Acidosis markedly inhibits renal phosphate reabsorption, resulting in phosphaturia. The contribution of this mechanism to postburn hypophosphatemia is probably minor; early renal phosphate wastage is not observed, perhaps being obscured by diminished glomerular filtration early in burn injury. In addition, the *p*-carboxy metabolite of mafenide acetate strongly inhibits carbonic anhydrase. Such inhibition diminishes proximal tubular reabsorption

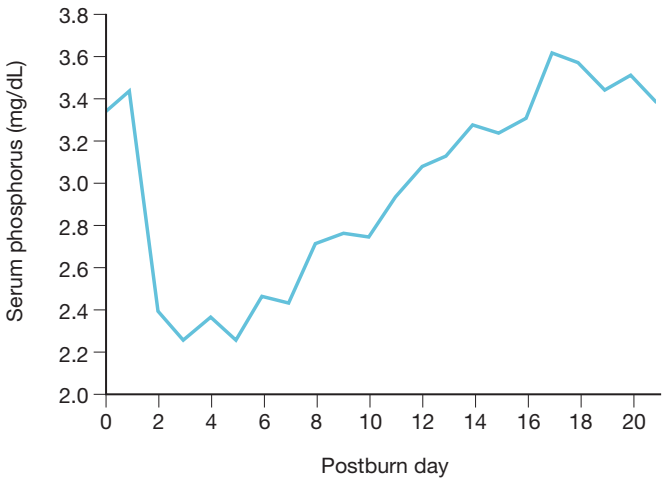

Fig. 27.1 Serum phosphorus levels abruptly decline with a nadir between postburn days 2 and 5. The data were obtained from 550 consecutive burn patients admitted to the U.S. Army Institute of Surgical Research.

Box 27.1 Possible Causes of Postburn Hypophosphatemia

Fluid resuscitation

- Volume loading
- Lactate administration

Carbohydrate administration

- Enteral alimentation
- Parenteral hyperalimentation
- 5% dextrose

Elevated catecholamines
Phosphate-binding antacids or sucralfate
Acid–base disturbance
Electrolyte imbalance

- Hypokalemia
- Hypomagnesemia
- Hypocalcemia

Carbonic anhydrase inhibition (mafenide acetate)

of phosphate and probably occurs after topical burn wound treatment with mafenide, but the magnitude of the effect is unknown.

Expansion of the extracellular fluid volume is also associated with inhibition of proximal tubular phosphate reabsorption. A tight coupling exists between sodium and phosphate transport across the renal epithelial cell. In patients with burns, mobilization and excretion of the large edema volume usually begins by the second postburn day and continues throughout the next week to 10 days. In contrast to the relative paucity of phosphate excretion during the first 24 hours after injury, when glomerular filtration is markedly reduced, a modest loss of phosphate may occur with diuresis of the edema fluid. In fact, the diuretic phase is associated with an increase in the fractional excretion of phosphate despite a concomitant reduction in the serum phosphate concentration.[9] Phosphorus excretion during the natriuretic phase of early burn injury is consistent with the tight coupling observed in other diuretic states.

ULCER PROPHYLAXIS

Effective prophylaxis against Curling's ulcers with H_2 antagonists and antacid buffering has been a mainstay of burn care for the past 2 decades. Significant degrees of hypophosphatemia and phosphate depletion occur during continuous or chronic administration of phosphate-binding agents containing magnesium, calcium, and aluminum. These agents bind not only dietary phosphate but also phosphate secreted into the intestinal lumen, often resulting in a net negative phosphate balance. The severity of such hypophosphatemia clearly depends on the dose of phosphate-binding agents, dietary phosphorus intake, and preexisting phosphate balance. To reduce alimentary scavenging of dietary and secreted phosphate, buffering with antacids containing aluminum phosphate salts (Al_2PO_4), which do not bind any additional phosphate, may be used. Sucralfate, which is also effective in preventing upper gastrointestinal stress ulceration after thermal injury, is not a buffering agent, but as a complex salt of aluminum hydroxide, is capable of binding phosphate. Its administration has also been associated with the development of hypophosphatemia in critically ill patients.[10]

HYPERVENTILATION

Respiratory alkalosis is often present during the first week postburn and may be enhanced by anxiety or pain and even by the inhibition of carbonic anhydrase induced by mafenide acetate burn cream. As fluid resuscitation progresses, the respiratory rate and tidal volume progressively increase, resulting in minute ventilation that may be twice normal. Mild hyperventilation induces only a slight decline of serum phosphorus levels; prolonged, intense hyperventilation, however, may result in serum phosphorus values less than 1.0 mg/dL.[11] During respiratory alkalosis, phosphorus virtually disappears from the urine, eliminating renal losses as the causative mechanism. Respiratory alkalosis induces a rapid movement of carbon dioxide from the intracellular to the extracellular space. Intracellular pH increases, activating glycolysis and increasing the formation of intracellular phosphorylated carbohydrate compounds. The readily diffusible inorganic phosphate pool supplies the required phosphorus, and serum phosphorus concentrations consequently fall abruptly. The extent to which this mechanism contributes to postburn hypophosphatemia is uncertain.

METABOLIC SUPPORT

Administration of carbohydrates may play a major role in the development of postburn hypophosphatemia. Infusion of glucose solutions or oral intake of carbohydrates produces mild hypophosphatemia in healthy individuals. This decrease in serum phosphate is associated with an increase of inorganic phosphate, adenosine triphosphate (ATP), and glucose 6-phosphate in muscle cells. The mechanism by which such carbohydrate administration induces hypophosphatemia is somewhat speculative. Experience with

phosphate-deficient total parenteral nutrition and subsequent development of hypophosphatemia has provided some insight into the etiology.[12,13] As carbohydrates are absorbed, insulin secretion increases, shifting phosphorus from the extracellular to the intracellular space. If phosphate reserve is low, ATP is poorly regenerated because hypophosphatemia inhibits glucose 3-phosphate dehydrogenase. Inorganic phosphates in the intracellular pool become further diminished because of incorporation, initially as newly synthesized ATP, but eventually as triose phosphates when the ATP is consumed in the hexokinase reaction. Glucose utilization by red blood cells (RBCs) requires ATP at the hexokinase and phosphofructokinase steps, but regeneration of ATP does not occur during phosphate deficiency or acute hypophosphatemia because of a block at the glucose 3-phosphate dehydrogenase step. In states of phosphate depletion, the scant phosphate that enters the RBC is incorporated into 1,3-diphosphoglycerate, but most is diverted to 2,3-diphosphoglycerate (2,3-DPG), also preventing complete glycolysis to regain the ATP consumed.

In thermally injured patients, infusion of dextrose-containing solutions usually begins 24 hours postburn, and enteral nutrition, in which most of the calories are supplied as carbohydrates, is initiated within several days of injury. These interventions are temporally correlated with the rapid descent of serum phosphorus concentrations. In other clinical states, severe hypophosphatemia after the initiation of enteral or parenteral nutrition is most commonly associated with the feeding of patients with advanced protein-calorie malnutrition. When total body phosphorus is depleted by starvation, serum phosphorus levels usually remain normal, but carbohydrate administration produces a rapid marked decline in serum phosphorus concentration. If untreated, this may result in multisystem organ dysfunction, respiratory and cardiac failure, or death. Thermally injured patients are usually well nourished before burn injury, and the clinical scenario of refeeding hypophosphatemia may not apply to them. Similar findings, however, have been described recently in previously well-nourished surgical intensive care unit patients in whom the initiation of isotonic enteral feedings resulted in a decrease of serum phosphorus from normal levels to approximately 1 mg/dL, a level that is considered to be dangerously low and to require prompt supplementation.[14,15] In addition, the authors have reported that hypophosphatemia in thermally injured patients is exacerbated by the initiation of enteral feeding and occurs regardless of the postburn day when feeding is initiated.[3] This further reduction of serum phosphorus during the first postburn week, when levels are already low, may be particularly hazardous and speaks for aggressive phosphorus supplementation before and during the initiation of enteral alimentation.

BURN WOUND PHYSIOLOGY

In patients recovering from thermal injury, the burn wound itself may act as a significant phosphorus sink. Despite the overall catabolism accompanying major injury and loss of lean body mass, healing burn wounds and skin grafts are anabolic and require phosphorus for normal repair. In addition, the continued loss of fluid and protein through the burn wound surface is a potential source of unquantified phosphorus loss and may contribute to hypophosphatemia.[16] In a comparison between burn patients and traumatically injured patients, it was shown that urinary phosphorus clearance, fractional excretion of phosphorus, and renal threshold phosphate concentrations were not different between the two groups; however, persistent hypophosphatemia persisted in the thermally injured patients. This may further implicate the wound as a source of early phosphorus loss.[17]

ACUTE-PHASE RESPONSE AND SEPSIS

Burn injury is characterized by an abrupt increase in acute-phase proteins as patients enter the hypermetabolic phase of burn injury. These same responses are similar to those observed in the sepsis syndrome. Recently, the development of hypophosphatemia has been characterized in patients with the acute-phase response syndrome.[17] Similar findings have been documented in patients with sepsis and infection, and correlation to increase in levels of cytokines such as tumor necrosis factor alpha and interleukin-6 has been made.[18] Similar findings were observed in patients with a variety of infectious diseases, and correlation of high levels of C-reactive protein and white blood cell (WBC) count was made with the magnitude of hypophosphatemia.[19] Although these reports did not include burn-injured patients, one may infer that activation of the inflammatory cascades such as occurs in major thermal injury may contribute to the development of hypophosphatemia.

OTHER ELECTROLYTES

Disorders of electrolyte balance may contribute to the development of hypophosphatemia. Experimental magnesium deficiency in animals may lead to phosphaturia and phosphorus deficiency, but intentional magnesium deficiency in man results in no change or a slight rise in serum phosphate.[20,21] In individuals with chronic alcoholism, however, hypomagnesemia and hypophosphatemia are coexistent. Hypokalemia, which is also exacerbated by magnesium deficiency, may result in phosphate wasting and hypophosphatemia. The mechanism is uncertain but may be related to coexistent metabolic alkalosis, diuretic use, or the underlying illness. Changes in calcium and phosphate homeostasis and in the regulating hormones calcitonin and parathyroid hormone (PTH) have been described after thermal injury.[22] Coincident with the early depression of serum phosphorus, the fraction of ionized calcium was shown to decrease and remain low, but within the normal range, for the 14 postburn days studied. Urinary calcium output was low, about 4.5 mmol/day, and urinary phosphate output was as high as 30 mmol/day despite a low serum phosphorus level. Serum calcitonin levels were significantly elevated for up to 2 weeks postinjury, but PTH remained within the normal range. The magnitude of the contribution of the classic regulating hormones of calcium and phosphorus homeostasis to the observed decrease in serum phosphorus after severe injury is not known with certainty. Catecholamines and glucagon are known to induce an increase in calcitonin secretion, and the administration of pharmacologic doses of calcitonin results in

phosphaturia. A direct effect of calcitonin on phosphate transport in the nephron has been demonstrated. In these burn patients, it was notable that ionized calcium decreased slightly but still within the normal range despite very high levels of calcitonin and normal PTH concentrations. A slight, although statistically significant, increase in PTH was observed around the fourth postburn day and may be related, albeit indirectly through calcium regulation, to the observed postburn decrease in serum phosphorus concentration.

SUMMARY

Clearly, multiple factors influence the serum phosphorus level after burn injury. Fluid resuscitation and subsequent mobilization of interstitial edema fluids, catecholamine excess, respiratory alkalosis, the use of phosphate-binding antacids or sucralfate, hypokalemia, hypomagnesemia, and the initiation of enteral nutrition have all been associated with hypophosphatemia in other illnesses and experimental models. All or most of these factors may be encountered in the early treatment of burn patients, and the contribution and relative importance of individual factors to the depression of serum phosphorus is difficult to analyze. Most likely, carbohydrate administration, respiratory alkalosis, and diuresis of edema fluid are the more important etiologic factors contributing to hypophosphatemia in the early postburn course.

Consequences of Hypophosphatemia

The clinical manifestations of hypophosphatemia (Box 27.2) are mainly those of organ system hypofunction. These responses have been defined through clinical observation and laboratory studies in circumstances in which hypophosphatemia occurred as a relatively isolated event. Phosphorus supplementation has been reported to reverse these abnormalities, suggesting a cause-and-effect relationship. Hypofunction of organ systems associated with phosphorus depletion has been attributed to a lack of available inorganic phosphate for synthesis of high-energy phosphorus compounds; breakdown of stored ATP occurs, and the inorganic phosphate is diverted to other intracellular pathways. Organ system dysfunction after thermal injury is characterized by early hypofunction and later hyperfunction of most organ systems. Whether hypophosphatemia contributes significantly to the early postburn depression of function that occurs in multiple organs is not known. Clearly, some of the clinical manifestations shown in Box 27.2 are commonly observed in thermally injured patients, but others are not usually associated with such injury. Most patients reported to have had complications of hypophosphatemia have also had a coexistent and severe illness. It is important to remember that prior cellular injury has been prerequisite in most instances in which hypophosphatemia has been implicated as a cause of organ system dysfunction. The following discussions of organ system abnormalities should be interpreted in light of the specific circumstances under which the observations were made.

Box 27.2 Clinical Manifestations of Hypophosphatemia

Central nervous system
- Lethargy, malaise, neuropathy, seizures, coma

Cardiovascular
- Impaired cardiovascular contractility
- Decreased response to pressor agents
- Hypotension
- Acute cardiac decompensation

Pulmonary
- Tachypnea
- Decreased vital capacity
- Respiratory failure

Gastrointestinal
- Anorexia, dysphagia

Renal
- Glycosuria, calciuria, magnesuria, renal tubular acidosis

Musculoskeletal
- Weakness, myalgia, arthralgia, rhabdomyolysis

CARDIAC DYSFUNCTION

Although the early depression of cardiac function after burn injury has been attributed to an initial decrease in circulating blood volume, the search for intrinsic myocardial depression after burn injury and for mediators of such depression continues. In experimental studies and in clinical material, a correlation between hypophosphatemia and cardiac decompensation has been reported. Cardiac output, measured by bolus thermodilution, was impaired in seven critically ill patients with hypophosphatemia and improved significantly with phosphorus supplementation.[4] In one experimental study, myocardial contractility was impaired by phosphorus deficiency and reversed by phosphorus repletion, suggesting that phosphorus deficiency may be a cause of heart failure in certain clinical conditions.[23] Hypophosphatemic cardiac depression has been described as occurring in 28.8% of surgical intensive care patients.[24] Despite these reports, there appears to be little evidence that hypophosphatemic cardiomyopathy is a frequently encountered clinical entity; most patients in whom this mechanism is invoked have already had a number of other causes for myocardial dysfunction.[25]

NEUROMUSCULAR DYSFUNCTION

Varying degrees of areflexic paralysis, paresthesias, sensory loss, weakness, and respiratory insufficiency have been reported to be associated with acute hypophosphatemia, usually induced with feeding malnourished patients.[12] A reduction in available ATP to support respiratory muscle contraction has been suggested as a mechanism for acute respiratory failure, and diaphragmatic contractility has been reported to improve with phosphorus repletion in mechanically ventilated hypophosphatemic patients.[26] Profound generalized muscle weakness associated with

isolated phosphorus depletion has been observed in both clinical and laboratory studies.[27,28] In a study of hypophosphatemia and muscle phosphate metabolism in patients with burns or mechanical trauma, no direct correlation was demonstrated between the serum phosphorus concentration and the high-energy phosphate content of muscle cells; all of these patients, however, were receiving phosphorus supplementation during the study.[29] If acute hypophosphatemia is superimposed on preexisting cellular injury, potentially reversible muscle cell dysfunction may extend to irreversible necrosis.[30] Several authors have reported severe rhabdomyolysis associated with severe hypophosphatemia after burns and major trauma.[31,32] This spectacular clinical event is rare but may occur to a lesser, subclinical, extent in critically ill patients.[30,33] Hypophosphatemia as the underlying etiology may often be dismissed because muscle cell destruction results in release of phosphate and elevation of serum phosphorus. In the absence of significant hemochromogenuria, the diagnosis may not even be suspected. Further investigation is required to determine whether this "asymptomatic" rhabdomyolysis is, in fact, an important clinical entity or merely an obligate manifestation of critical illness.

HEMATOLOGIC DYSFUNCTION

When untreated, severe hypophosphatemia may lead to RBC dysfunction by alterations in cell shape, survival, and physiological function. Lack of high-energy phosphate results in a decrease in erythrocyte 2,3-DPG and subsequent leftward shift of the dissociation curve, with a consequent risk of tissue hypoxia.[7] Clinical hypophosphatemia, with or without previous phosphate depletion, results in reduced production of 2,3-DPG, erythrocyte ATP, and other phosphorylated intermediates of RBC glycolysis. In a variety of experimental and clinical situations, including burn injury and mechanical trauma, RBC 2,3-DPG has been shown to be reduced in the presence of hypophosphatemia.[34,35] In thermally injured patients, it has been demonstrated that postburn disturbance of RBC phosphate metabolism may be prevented by administration of phosphorus in the early postburn course.[35] Hypophosphatemia has also been associated with decreased RBC survival and decreased RBC deformability, with impaired capillary transit and the potential for further deficiency of tissue oxygenation.

White blood cell dysfunction also has been observed as a result of hypophosphatemia induced by the initiation of phosphate-free parenteral nutrition and was associated with depressed chemotactic, phagocytic, and bactericidal activity of granulocytes.[35] A reduction in granulocyte ATP content was also documented and amelioration of these WBC abnormalities was coincident with phosphorus repletion. Any correlation between these observations and an increased risk of infection remains speculative for hypophosphatemic patients in general and burn patients in particular.

SUMMARY

Although it is clear that organ system dysfunction may be a manifestation of severe untreated hypophosphatemia, the relationship between these specific abnormalities and those observed in either the hypodynamic or hyperdynamic phases of burn injury remains unclear. Clinical experience dictates that even when severe hypophosphatemia is avoided, the scenario of early organ system hypofunction and later hyperfunction persists. This is not to say that the marked hypophosphatemia observed after burn injury is part and parcel of the disease process, without bearing on the postburn physiological response but that thus far, the pathophysiological milieu after thermal injury has not permitted definition of the contribution of hypophosphatemia to the overall postburn response. Until cause-and-effect relationships are defined through ongoing research, aggressive phosphorus repletion should be approached cautiously after thermal injury. Such therapy does, however, clearly ameliorate RBC 2,3-DPG depletion, which, in and of itself, supports treatment.

Prevention and Treatment of Hypophosphatemia

An unequivocal recommendation to treat hypophosphatemia in thermally injured patients should be supported by evidence that the treatment is of benefit. Such evidence is somewhat lacking in thermally injured patients, but in many analogous instances of hypophosphatemia from other causes, a direct benefit has been ascribed to repletion.

Serum phosphorus levels should be measured daily during the early phase of burn care and intravenous phosphate repletion initiated when levels drop below 2.0 mg/dL (Fig. 27.2). Most of the severe adverse effects of hypophosphatemia occur with concentrations below 1.0 mg/dL, and this replacement strategy should prevent the development of clinically significant hypophosphatemia. Correction of severe hypophosphatemia with serum phosphorus levels less than 1.0 mg/dL requires intravenous replacement, usually with solutions of sodium or potassium phosphate containing 0.16 mmol/kg body weight (5 mg/kg body weight) of elemental phosphorus over 6 hours. The dose may be halved for patients with serum phosphorus levels between 1.0 and 2.0 mg/dL.[36] After completion of the infusion, a repeat serum phosphorus determination should be obtained, and further treatment should be based on the postinfusion plasma concentration. A potential hazard associated with intravenous administration of phosphate salts is hyperphosphatemia, which may induce metastatic deposition of calcium phosphate salts and hypocalcemia. Additionally, when potassium phosphate salts are used, care must be taken to avoid excessive or too rapid administration of potassium. Phosphorus replacement should be carefully monitored; proceed with great caution in patients with impaired renal function or evidence of soft tissue injury or necrosis.

Prevention of hypophosphatemia may be facilitated by beginning oral phosphorus replacement before interventions such as the initiation of either enteral or parenteral carbohydrate administration, gastric acid neutralization with phosphate-binding antacids or sucralfate, and the administration of diuretics. The nadir of serum phosphorus

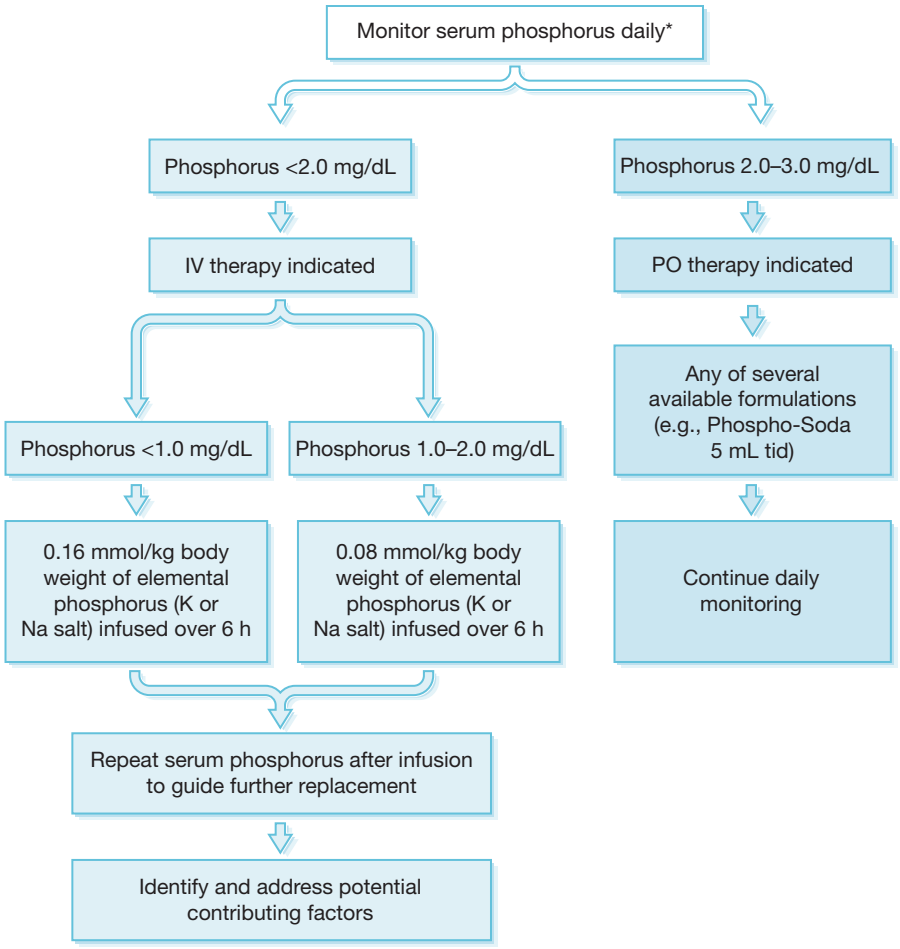

Fig. 27.2 The use of this algorithm permits prompt detection and timely correction of hypophosphatemia after burn injury. *IV,* Intravenous; *PO,* oral; *tid,* three times a day.

concentration typically occurs between 3 and 5 days postburn, during the period of edema mobilization, and the need to initiate phosphorus supplementation should be anticipated in this interval. Additionally, to temper the gastrointestinal losses caused by administration of phosphate-binding antacids, substitution of or alternation with antacids containing aluminum phosphate should be considered.

For mild asymptomatic hypophosphatemia and for prophylaxis when worsening of hypophosphatemia is expected, oral supplementation with any of several available formulations is recommended. Such oral regimens have been shown to be cost-effective.[37] Five milliliters of Phospho-Soda, containing 4.2 mmol/mL of elemental phosphorus, is commonly administered three times daily. Correction of other electrolyte abnormalities, most notably hypomagnesemia, hypocalcemia, and hypokalemia, as well as maintenance of acid–base normality, may prevent further renal phosphate losses and maintain the extracellular phosphate pool. In a recent publication by Kahn et al., continuous, preemptive repletion of phosphate by continuous infusion prevented hypophosphatemia after severe burn injury when compared with responsive repletion in historical control participants.[38] The protocol resulted in less hypophosphatemia without increasing the risk of hyperphosphatemia. Fewer cardiac and infectious complications were seen in the treatment group; however, the authors suggested that these findings needed further study.

After the 10th postburn day, the phosphorus delivered in standard liquid enteral formulas and hospital diets is usually sufficient to maintain serum phosphorus levels above 3.0 mg/dL.

SUMMARY

Thermal injury induces a precipitous decrease in serum phosphate concentration that reaches its nadir between the second and fifth postburn days. This phenomenon has been recognized for some time, but interest in the problem has been limited. The organ system dysfunctions induced by hypophosphatemia are in many ways similar to certain of the pathophysiological changes observed after burn injury. The contribution of hypophosphatemia to these manifestations remains undefined. Wound fluid losses, increased circulating catecholamines, intracellular phosphate redistribution, and increased fractional excretion of urinary phosphate, as well as iatrogenic induction of hypophosphatemia through various therapeutic interventions, have been implicated as contributing to postburn hypophosphatemia. There may be other pathways regarding phosphorus

regulation that have not been explored in this patient population. Frequent serum phosphate measurement and prompt phosphorus replacement when hypophosphatemia is recognized should minimize any sequelae of this potentially deleterious electrolyte deficiency.

Complete references available online at www.expertconsult.inkling.com

Further Reading

Berger MM, Rothen C, Cavadini C, et al. Exudative mineral losses after serious burns: a clue to the alteration of magnesium and phosphate metabolism. *Am J Clin Nutr*. 1997;65(5):1473-1481.

Cioffi WG, Vaughan GM, Heironimus JD, et al. Dissociation of blood volume and flow in regulation of salt and water balance in burn patients. *Ann Surg*. 1991;214(3):213-218.

Lennquist S, Lindell B, Nordstrom H, et al. Hypophosphatemia in severe burns: a prospective study. *Acta Chir Scand*. 1979;145:1-6.

Marik PE, Bedigian MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. A prospective study. *Arch Surg*. 1996;131(10):1043-1047.

Matthews JJ, Aleen RF, Gameli RL. Cost reduction strategies in burn nutrition services: adjustment dietary treatment of patients with hyponatremia and hypophosphatemia. *J Burn Care Rehabil*. 1999;20(1 Pt 1):80-84.

Miller JS, Simpson J. Medication-nutrient interactions: hypophosphatemia associated with sucralfate in the intensive care unit. *Nutr Clin Pract*. 1991;6:199-201.

References

1. Cioffi WG, Vaughan GM, Heironimus JD, et al. Dissociation of blood volume and flow in regulation of salt and water balance in burn patients. *Ann Surg*. 1991;214(3):213-218.
2. Nordstrom H, Lennquist S, Lindell B, et al. Hypophosphataemia in severe burns. *Acta Chir Scand*. 1977;143:395-399.
3. Mozingo DW, Cioffi WG, Mason AD Jr, et al. Initiation of continuous enteral feeding induces hypophosphatemia in thermally injured patients. *Proceedings of the 35th World Congress of Surgery/International Society of Surgery/International Surgical Week*, 22-27 August 1993.
4. O'Connor LR, Weeler WS, Bethune JE. Effects of hypophosphatemia on myocardial performance in man. *N Engl J Med*. 1977;297:901.
5. Polderman KH, Bloemers FW, Peerdeman SM, et al. Hypomagnesemia and hypophosphatemia at admission in patients with severe head injury. *Crit Care Med*. 2000;28(6):2022-2025.
6. England PC, Duari M, Tweedle DET, et al. Postoperative hypophosphatemia. *Br J Surg*. 1979;66:340.
7. Lau K. Phosphate disorders. In: Kokko JP, Tannen RL, eds. *Fluids and Electrolytes*. Philadelphia, PA: WB Saunders; 1986:398-471.
8. Knochel JP. The pathophysiology and clinical characteristics of severe hypophosphatemia. *Arch Intern Med*. 1977;137:203-220.
9. Lennquist S, Lindell B, Nordstrom H, et al. Hypophosphatemia in severe burns. A prospective study. *Acta Chir Scand*. 1979;145:1-6.
10. Miller SJ, Simpson J. Medication–nutrient interactions: hypophosphatemia associated with sucralfate in the intensive care unit. *Nutr Clin Pract*. 1991;6:199-201.
11. Mostellar ME, Tuttle EP Jr. The effects of alkylosis on plasma concentration and urinary excretion of inorganic phosphate in man. *J Clin Invest*. 1964;43:138-149.
12. Solomon SM, Kirby DF. The refeeding syndrome: a review. *JPEN J Parenter Enteral Nutr*. 1990;14(1):90-97.
13. Sheldon GF, Grzyb S. Phosphate depletion and repletion: relation to parenteral nutrition and oxygen transport. *Ann Surg*. 1975;182(6):683-689.
14. Hayek ME, Eisenberg PG. Severe hypophosphatemia following the institution of enteral feedings. *Arch Surg*. 1989;124:1325-1328.
15. Marik PE, Bedigian MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. A prospective study. *Arch Surg*. 1996;131(10):1043-1047.
16. Berger MM, Rothen C, Cavadini C, et al. Exudative mineral losses after serious burns: a clue to the alteration of magnesium and phosphate metabolism. *Am J Clin Nutr*. 1997;65(5):1473-1481.
17. Dickerson RN, Gervasio JM, Sherman JJ, et al. A comparison of renal phosphorus regulation in thermally injured and multiple trauma patients receiving specialized nutrition support. *JPEN J Parenter Enteral Nutr*. 2001;25(3):152-159.
18. da Cunah DF, dos Santos VM, Monterio JP, et al. Hypophosphatemia in acute-phase response syndrome patients. Preliminary data. *Miner Electrolyte Metab*. 1998;24(5):337-340.
19. Barak V, Schwartz A, Kalickman I, et al. Prevalence of hypophosphatemia in sepsis and infection: the role of cytokines. *Am J Med*. 1998;104(1):40-47.
20. Haglin L, Burman LA, Nilsson M. High prevalence of hypophosphatemia amongst patients with infectious diseases. A retrospective study. *J Intern Med*. 1999;246(1):45-52.
21. Whang R, Welt LG. Observations in experimental magnesium depletion. *J Clin Invest*. 1963;42:305-313.
22. Shils ME. Experimental human magnesium depletion. *Medicine (Baltimore)*. 1969;48:61-82.
23. Loven L, Nordstrom H, Lennquist S. Changes in calcium and phosphate and their regulating hormones in patients with severe burn injuries. *Scand J Plast Reconstr Surg*. 1984;18:49-53.
24. Fuller TJ, Nichols WW, Brenner BJ, et al. Reversible depression in myocardial performance in dogs with experimental phosphorus deficiency. *J Clin Invest*. 1978;62:1194-2000.
25. Zazzo JF, Troche G, Ruel P, et al. High incidence of hypophosphatemia in surgical intensive care patients: efficacy of phosphorus therapy on myocardial function. *Intensive Care Med*. 1995;21(10):826-831.
26. Knochel JP. The clinical status of hypophosphatemia. *N Engl J Med*. 1985;313(7):447-449.
27. Aubier M, Murciano D, Lecocguic Y, et al. Effect of hypophosphatemia on diaphragmatic contractility in patients with acute respiratory failure. *N Engl J Med*. 1985;313:420-424.
28. Lotz M, Nay R, Bartter FC. Osteomalacia and debility resulting from phosphorus depletion. *Trans Assoc Am Physicians*. 1964;77:281-295.
29. Lotz M, Zisman E, Bartter FC. Evidence for a phosphorus depletion syndrome in man. *N Engl J Med*. 1968;278:409.
30. Loven L, Lennquist S, Liljedahl SO. Hypophosphataemia and muscle phosphate metabolism in severely injured patients. *Acta Chir Scand*. 1983;149:743-749.
31. Knochel JP, Barcenas C, Cotton JR, et al. Hypophosphatemia and rhabdomyolysis. *J Clin Invest*. 1978;62:1240-1246.
32. Guechot J, Cynober L, Lioret N, et al. Rhabdomyolysis and acute renal failure in a patient with thermal injury. *Intensive Care Med*. 1986;12:159-160.
33. Pfeifer PM. Acute rhabdomyolysis following surgery for burns. *Anaesthesia*. 1986;41:614-669.
34. Singhal PC, Kumar A, Desroches L, et al. Prevalence and predictors of rhabdomyolysis in patients with hypophosphatemia. *Am J Med*. 1992;92:458-464.
35. Loven L, Anderson E, Larsson J, et al. Muscular high-energy phosphates and red-cell 2.3-DPG in post-traumatic hypophosphataemia. *Acta Chir Scand*. 1983;149:735-741.
36. Loven L, Larsson L, Nordstrom H, et al. Serum phosphate and 2,3-diphosphoglycerate in severely burned patients after phosphate supplementation. *J Trauma*. 1986;26(4):348-352.
37. Perreault MM, Ostrop NJ, Tierney MG. Efficacy and safety of intravenous phosphate replacement in critically ill patients. *Ann Pharmacother*. 1997;31(6):683-688.
38. Kahn SA, Bell DE, Stassen NA, Lentz CW. Prevention of hypophosphatemia after burn injury with a protocol for continuous, preemptive repletion. *J Burn Care Res*. 2014;36:e220-e225.

28 Nutritional Needs and Support for the Burned Patient

JOSHUA S. CARSON, HOUMAN KHOSROZADEH, WILLIAM B. NORBURY, and DAVID N. HERNDON

Introduction

The massive burn is as much a metabolic insult as it is a tissue injury. Clearly resultant tissue defects represent the critical factor in long-term functional complications from massive burns. In the acute phase of burn care, a persistent, overwhelming metabolic response to thermal injury compromises the functional integrity of virtually every organ system. This response compromises wound healing capacity and the integrity of the body's defense mechanisms.

The massive burn represents a metabolic "double hit," a nutritional challenge of both supply and demand for the injured patient. The burn wound creates drastically increased demand for anabolic metabolism for wound healing while simultaneously triggering a systemic catabolic state. The resulting mismatch between high anabolic demand and negative anabolic supply (catabolism) leads to a profound state of functional malnutrition which, in turn, facilitates rapid debilitation and immunosuppression that place patients at profound risk for infectious complications. Addressing these nutritional challenges is thus critical to effective care for the burn patient.

Metabolic Pathology Associated With Burn Injury

Following all forms of major trauma, inflammatory and hormonal responses are activated and greatly influence metabolic pathways and mechanisms. Nutrient intake, absorption, and substrate assimilation are all affected during the different stages of the stress response. Nutrient requirements will increase but become more difficult to predict, and enteral or parenteral feeding will often be necessary to meet vastly increased nutritional requirements.

The physiologic response to trauma leads to activation of an array of processes, many of which increase immediate energy availability as part of the evolved flight-or-flight response. It is an evolved response to stress that assists the organism in overcoming a transient stress. However there is no adaptive response to the kind of sustained stress state seen with massive burns because these injuries were not survivable prior to the development of modern medicine. By supporting patients through what would otherwise be nonsurvivable states, modern medical care has created a novel physiologic state—a state of prolonged acute injury for which there is no adapted evolutionary response. In this state, powerfully adaptive responses to immediate stress become maladaptive when sustained for a timeline well beyond those encountered in the evolutionary context (Fig. 28.1).

The hypermetabolic response to stress is particularly exaggerated in thermal injuries. The severity of the catabolic response to burn injury cannot be overemphasized. Decades of clinical and animal research have demonstrated with increasing depth and detail the ways in which burn injury profoundly alters the host organism's metabolism to upregulate catabolic processes and inhibit anabolic processes. The net result is a substantial net loss of lean body weight with a distinctly exaggerated effect on protein stores. The pathophysiology of this protein wasting is notable for a diverse array of endocrine and metabolic factors from the cellular to the organismal level (Fig. 28.2).[1–3]

Adrenal hyperactivity in burn patients was well documented more than 50 years ago, with massive surges in serum and urinary catecholamine levels seen within hours of burn. Inappropriate catecholamine and cortisol production has since been found to persist for weeks to months following massive burns, with end organ effects reaching the metabolic, cardiovascular, musculoskeletal, and immune systems.[4–8] A sustained surge of catecholamines and inflammatory cytokines, along with massive wounds and profound dysregulation of thermal homeostasis, all combine and interact to yield enormous increases in resting energy expenditure.

Distorted thermal regulation plays a significant role in the increase in resting energy expenditures seen in burn patients. Destruction of a large portion of the primary thermoregulatory organ, the skin, leads to an ongoing drain of body heat via decreased insulation and the facilitation of evaporative heat loss. The primary central hyperthermia associated with the burn response compounds this energy drain. Alterations in thalamic temperature set-point, catecholamine-induced hypermetabolism, and shunting of mitochondrial energy to heat-producing pathways all drive the hyperthermia seen within 24 h of burn injury. As Wilmore and Pruitt et al. described in 1974, "Burn patients are internally warm, not [just] externally cold." Thus, the burn patient's metabolism is taxed with the challenge of generating sufficient heat to maintain a higher body temperature with less heat-conserving resources.[8]

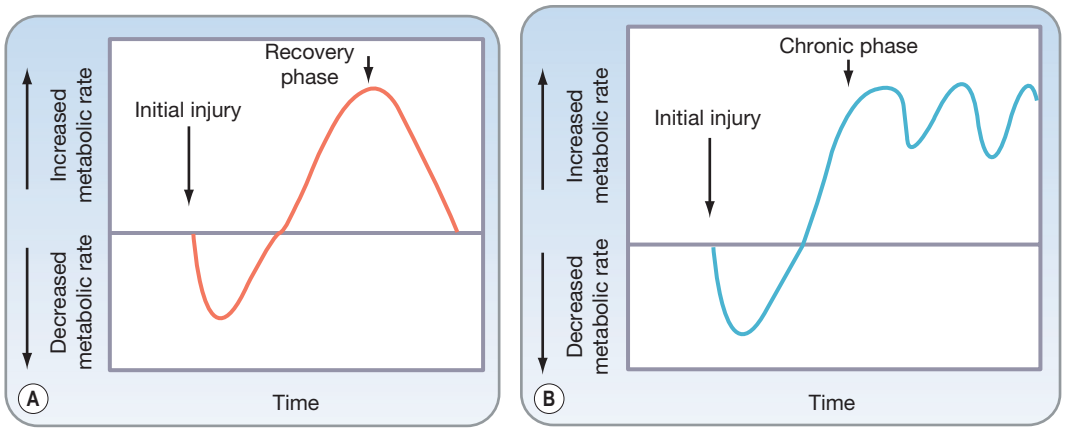

Fig. 28.1 Metabolic response to injury and trauma. Burn patients transition from the initial hypermetabolic response directly into a state of chronic hypermetabolism. (A) Classic ebb and flow phases of the acute stress response. The metabolic rate initially falls below normal and then increases to supranormal levels before returning to normal. (B) Ebb and flow revisited. In burn patients, the classic ebb and flow pattern is altered. Recurrent bouts of sepsis superimposed over a baseline of burn-induced proinflammatory stimuli result in a fluctuating metabolic demand, which remains chronically elevated. (From Ball S, Baudouin SV. Endocrine disorders in the critically ill: the endocrine response to critical illness. In Hall GM, Hunter JM, Cooper MS, editors. *Core topics in endocrinology in anaesthesia and critical care*. Cambridge: Cambridge University Press; 2010: 126–131.)

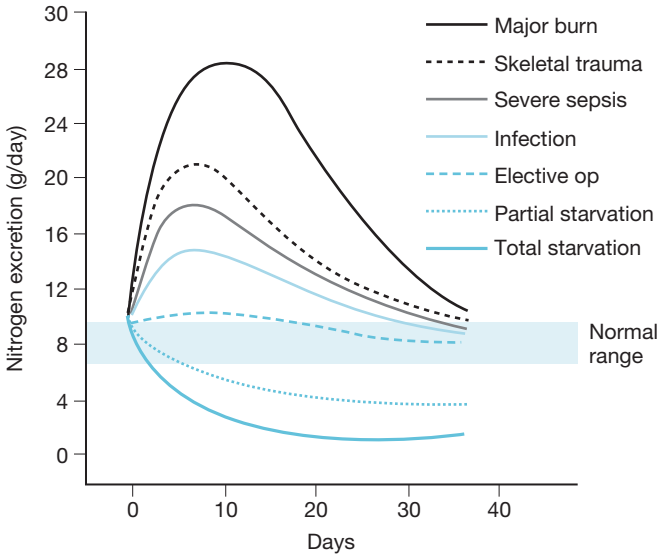

Fig. 28.2 Thermal injury induces a distinctly profound metabolic shift towards proteolysis. (From Long CL, Blakemore WS. Energy and protein requirements in the hospitalized patient. *JPEN J Parenter Enteral Nutr*. 1979 Mar–Apr;3(2):69–71.)

Nutritional Demand and Substrate Metabolism in Burn Patients

INCREASED TOTAL CALORIC DEMAND

Thermal injury triggers a marked increase in global energy expenditure, driven by a maelstrom of catecholamines, corticosteroids, and inflammatory cytokines.[2,9] In an earlier era of burn care—prior to the advent of early excision, pharmacologic interventions for hypermetabolism, and modern critical care—measurements of energy expenditure in patients with large burns were reported to range from 1.5 to 2.5 times those found in nonburn controls. While modern burn care has made significant progress in countering this hypermetabolic response, contemporary studies still report an average resting energy expenditure from 1.3 to 1.5 times those found in nonburn controls.[10–12]

SUBSTRATE-SPECIFIC REQUIREMENTS

See Fig. 28.3 for a simplified overview of the metabolic pathways involved in massive burn trauma.

Carbohydrates

The acute metabolic response to burn injury significantly alters carbohydrate metabolism and demands. Glucose/carbohydrate metabolism presents the burn physician with a rather vexing conundrum. On the one hand, failure to provide adequate carbohydrates results in additional compensatory protein catabolism.[13,14] And yet, on the other hand, the human body has a finite capacity for glucose oxidation. Multiple studies have demonstrated a limit to the amount of carbohydrate calories a burn patient can assimilate—approximately 5 g/kg per day in adult and 7 g/kg per day in children.[15,16] Providing glucose in excess of these limits will thus result in increasing hyperglycemia with resultant lactic acidosis (Fig. 28.4).

Unfortunately, with the enormous global energy expenditure of the massive burn patients, even a diet with a reasonably low percentage of carbohydrate-based calories can yield total carbohydrate loads well in excess of these limits when titrated up to meet full caloric requirements. Unfortunately administration of carbohydrates in excess of the patient's capacity for glucose oxidation will only result in increasing degrees of hyperglycemia, glucosuria, and hypertriglyceridemia. In such cases, the patient's nutritional demands simply reach a point where they exceed that patient's metabolic capacity.

Guidelines typically recommend providing 50–60% of calories as carbohydrates in the setting of trauma or burn injury.[17–19] However these same guidelines also recommend that total carbohydrate provisions not exceed 5 g/kg per

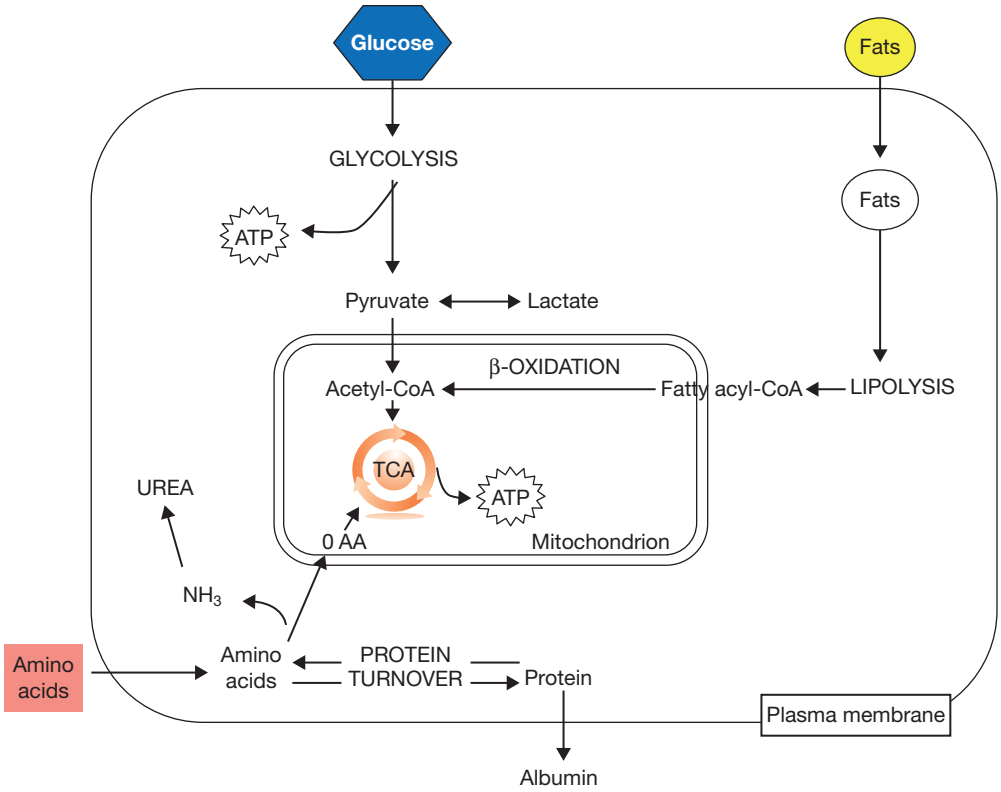

Fig. 28.3 Simplified overview of metabolic pathways.

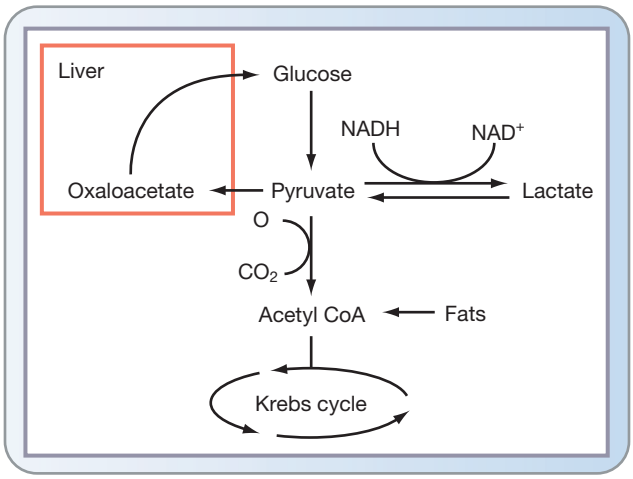

Fig. 28.4 Oxidative decarboxylation of pyruvate is a pivotal step in the overall oxidative metabolism of carbohydrates and fats. Overwhelmingly high levels of glucose may lead to lactate production, even in the presence of oxygen. (From Gore DC, Ferrando A, Barnett J, et al. Influence of glucose kinetics on plasma lactate concentration and energy expenditure in severely burned patients. *J Trauma* 2000;49:673–677.)

day (or 7 g/kg per day in children). Unfortunately providing 50–60% of calories as carbohydrate in the context of a nutritional therapy that meets the appropriately calculated total caloric needs of a burn patient will often result in doses of carbohydrates well in excess of these recommended limits.[11,12,16,18–20] There is no simple, clinically vetted solution to this challenge. A reasonable approach to this dilemma is to start by titrating enteral formula delivery up to a rate that delivers 5–7 g/kg per day of carbohydrates and then provide all further calories in the form of protein supplementation.

Fats

While lipids are unquestionably critical to effective basic homeostasis and wound healing, the amount of fat required to prevent essential fatty acid deficiency is remarkably small in patients with intact fat stores. Excess fat administration, on the other hand, can cause significant harm. The hypermetabolic response to thermal trauma upregulates lipolysis of circulating lipids. This surfeit of circulating free fatty acids is countered by increased hepatic esterification, with close to 70% of the free fatty acids accumulating in the liver. To minimize hepatic steatosis, the percentage of dietary calories from fat should be limited and carefully monitored. Multiple studies have demonstrated improved outcomes with lower fat nutrition therapy in burn patients.[21–23] Fat content should make up 3–15% of total calories. Patients receiving total parenteral nutrition (TPN) for a short period of time (e.g., less than 10–14 days) can generally be spared lipid infusion. In those requiring sustained TPN, 0.5–1 g/kg one to two times per week is sufficient. It should be noted that nondietary fat calories need to be taken into considerations as well: for example 1% propofol solution carries a proportional fat load equivalent to that found in a 10% intralipid emulsion.

It should be noted that the preceding discussion of the role of fat alimentation in nutritional therapy reflects a literature that largely predates the application of alternative

fat sources (e.g., fish oil, olive oil, borage oil, etc.). In the United States, the current standard of care for both enteral and parenteral fat administration features significant components of fats that have been shown to encourage inflammation, most notably omega-6 fatty acids. Alternative fat sources have become the standard of care in Europe and are anticipated to receive U.S. Food and Drug Administration (FDA) approval in this country shortly. While there are still insufficient data to declare these alternatives superior to the standard of care, there is certainly sufficient evidence to warrant future study. As our understanding of the unique advantages and disadvantages of different fat sources matures, a reexamination of the role of fat alimentation in burn nutrition is sure to come due.[24]

Protein

Proteolysis is the metabolic hallmark of the hypermetabolic response to thermal injury. As much as 150 g of skeletal muscle is lost per day in the absence of adequate nutritional support.[6] If not attenuated, ongoing systemic proteolysis leads to immune dysfunction and retarded wound healing. Protein requirements of 1.5–2 g/kg per day in burned adults and 2.5–4 g/kg per day in burned children is well accepted in clinical practice. Unfortunately there are limits to the rate of effective protein assimilation as well. Increasing protein intake above these values will often increase urea load and azotemia, with limited additional impact on muscle wasting.[25–27]

Amino acids alanine, arginine, and glutamine play a key role in wound healing in burn patients. Glutamine plays an important role in the function of enterocytes and lymphocytes, and low plasma glutamine concentrations have been associated with increased bowel permeability and increased rates of infection. Copious studies in animal models of trauma and shock have shown distinct roles for these particular amino acids in recovering enteral and immunologic competence.[28] Glutamine supplementation and other "immunotrition" formulas featuring these key amino acids have been associated with decreased incidents of infection, shorter hospital stays, and decreased mortality in the setting of traumatic injury.[29–31] While the appropriateness and even safety of glutamine supplementation has recently been called into question by the results of a large, international randomized controlled trial in critically ill patients, showing an increased mortality risk in patients randomized to receive high-dose parenteral glutamine supplements, how these results should be interpreted remains in question (Fig. 28.5). (See further discussion in the section on formulas.)

Nutritional Support

In the face of the metabolic storm associated with acute burn injuries, provision of effective nutritional support is critical to wound healing, avoidance of complications and, ultimately, survival. Failure to provide sufficient calories superimposes starvation over a state of hypercatabolism, resulting in devastating loss of lean body mass and depletion of the protein-energy pool available to meet the pressing needs of wound healing, mucosal integrity, and basic immunologic defenses.[30,32–34]

ENTERAL NUTRITION

Benefits of Enteral Nutrition

In addition to serving as a means for systemic delivery of nutrients, enteral nutrition (EN) performs a critical function in supporting the alimentary tract itself. Enteral feeds provide direct high-concentration nutrients (e.g., glutamine, alanine), stimulate enteric blood flow, maintain barrier function by preserving tight-junction integrity, and induce production and release of mucosal immunoglobulin and critical endogenous growth factors. These functions are not replaced with parenteral nutrition (PN).[35] After dietary ingestion, polysaccharides such as fiber and starch undergo bacterial fermentation in the colonic lumen. Bacterial fermentation provides two functions crucial to intestinal health: (1) it supports the normal flora of the gut lumen, which in turn prevents colonization and subsequent infection (e.g., *Clostridium difficile*) and (2) it produces acetoacetate, propionate, and butyrate (a short-chain fatty acid). Butyrate appears to be the preferred fuel of colonic mucosa cells and is therefore essential for mucosal integrity. Both animal and human studies show that the presence of enteral feeds (in addition to or in place of PN) is associated with increased mucosal mass, mucosal oxygenation, brush-border enzyme synthesis, and villus height when compared to PN alone.[35,36] Clinically enteral feeding has frequently been found to associate with improved clinical outcomes both in terms of gastrointestinal and total patient morbidity and mortality.

Initiation of Feeds

Early Initiation. Copious data support the safety and benefit of initiating EN early in the context of traumatic injury and in burns specifically.[37,38] In both clinical and animal studies of thermal injury and shock, early EN has consistently been shown to result in improved survival and function of the enteric mucosa and decreased bacterial translocation. Perhaps most importantly, early enteral feeding represents one of the most effective means of metabolic modulation in thermal injury, with a significant blunting of the catabolic response to thermal injury associated with early feeding protocols.[39–46]

Full feeds should not be delivered in the setting of marked hemodynamic instability and/or high-dose vasopressor requirements because this runs the risk of inducing or exacerbating nonobstructive mesenteric ischemia. However complete EN can be delivered safely to patients on low to moderate doses of vasopressors with stable or decreasing vasopressor requirements.[1,17,47]

In patients without hemodynamic compromise, feeding should be initiated rapidly. While the traditional practice has long been to gradually titrate enteric feeds up to a goal rate over time, there is reason to suspect that a more aggressive approach may be warranted. Pilot studies have suggested that restarting feeds immediately and at full-goal postoperatively (rather than titrating) is well tolerated in burn patients undergoing excision and grafting. The approach of gradually restarting feeds results in significant calorie deficits accumulating over the course of care. In patients still in the midst of resuscitation, though, foregoing the process of gradually increased feeding rates may increase the rates of gastric ileus.[48,49]

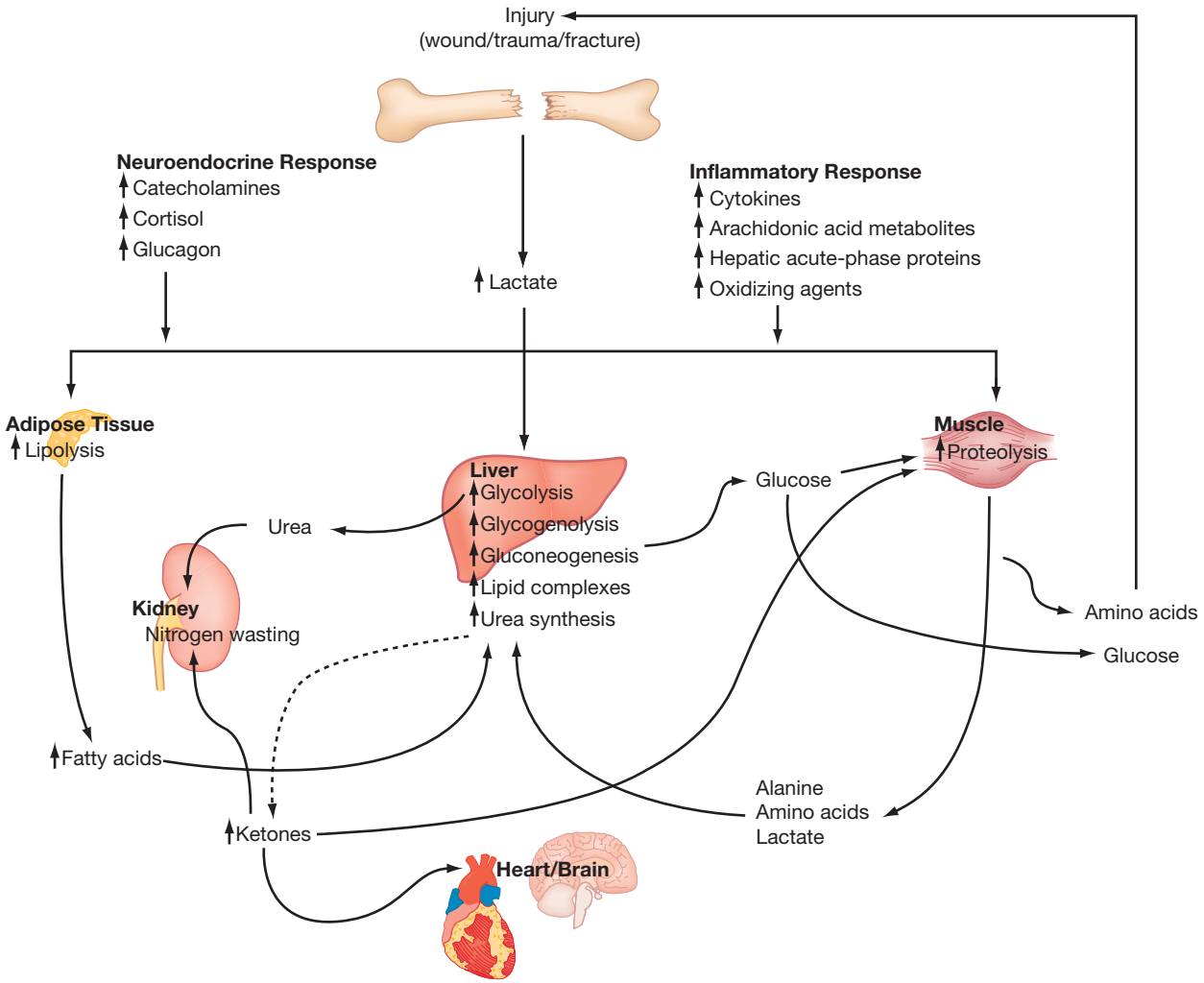

Fig. 28.5 Schematic representation of thermal-injury-induced shifts in substrate metabolism.

DELIVERING ENTERAL FEEDS

PO Feeding

For the conscious patient with an intact appetite and swallowing function, direct oral intake is the preferred feeding modality. When prescribing a patient an oral diet, it is essential that the physician continuously monitor for adequate intake. In the acute surgical setting, patients may fail to take in adequate calories due to decreased appetite, depressed mental status, pain, or any other practical obstacle to eating. Should a patient consistently fail to meet estimated caloric needs with a PO diet, consideration should be given to supplemental feeds via nasoenteric tube.

In those patients continuing to take food orally, careful monitoring should be maintained to ensure appropriate nutrition. Left unchecked, patients may frequently undereat or take in a disproportionate amount of calories as sugar or fat. A simple nutritional journal listing all foods and liquids consumed should be maintained by the nursing staff, patient, and/or family throughout the day, and dietary adjustments can be encouraged as needed. In patients attempting to meet all needs orally (and thus avoid the need for an enteric access tube), supplemental "protein shakes" can be quite helpful in boosting total protein-caloric input.

Enteral Access for Feeding

Burn victims, particularly those suffering from larger burns, frequently prove incapable of eating sufficient quantities to meet their nutritional needs. Direct enteral feeding ("tube feeding") is the route of choice to supplement or replace oral intake.

Either gastric or small-bowel access tubes can be used for delivering EN. Gastric feeding access allows for direct (trophic) feeding of the gastric mucosa. In the immediate postburn phase of resuscitation, though, gastric dysmotility can present quite early in response to burn injury and pose significant risk for aspiration and (particularly in children) vagally mediated cardiac events. As such, we recommend placement of a venting naso- or oro-gastrostomy tube for the duration of initial resuscitation.

The same dysmotility effect does not tend to manifest in the small bowel as rapidly or as profoundly as in the stomach. Feeding using a nasojejunal tube advanced past the ligament of Treitz can be initiated within 6 hours following injury and may help in preempting the onset of

starvation-associated ileus. This approach also allows continuous feeding during surgeries and physical therapy sessions. It should be noted that some authorities recommend attempting gastric feeds before resorting to postpyloric feeding, reasoning that gastric feeds may minimize the risk of gastric ileus associated with severe injury.

Nasojejunal feeding may be preferable in some settings because it does not need to be stopped prior to surgery to prevent aspiration. Contrary to the previously postulated protective effect of the pyloric sphincter, the largest randomized controlled trial and most recent meta-analysis of earlier studies indicate that nasogastric and nasojejunal feeds are associated with comparable rates of pneumonia.[50]

In the past it was thought that monitoring residual stomach volumes via gastric tubes prevented aspiration pneumonia by (1) serving as a marker of enteric feed intolerance and (2) alerting the clinician to gastric distension so that feeds can be held to avert impending reflux and/or aspiration. Recently large, multiinstitutional clinical trials have shown that larger gastric residual volumes do not actually predict aspiration, and forgoing gastric residual monitoring altogether did not increase the incidence of pneumonia.[51–53] In both studies, increasing or eliminating the gastric residual volume threshold led to significantly improved nutritional intakes.

DIET COMPOSITION AND ENTERAL FEED FORMULAS

Numerous enteral formulations are available and can be classified according to their composition. Standard formulas are sterile, nutritionally complete, and intended for patients with a normal GI tract who cannot ingest adequate nutrients and calories by regular oral diets. Modular formulas consist of a singular macronutrient as a source of calories (e.g., fiber, protein) and are generally used by mixing with standard or specialty formulas (Table 28.1).

In a subset of distinctly hypermetabolic patients, the use of high-sugar, high-protein diets consisting of 3% fat, 82% carbohydrate, and 15% protein stimulates protein synthesis, increases endogenous insulin production, and improves lean body mass accretion.[13]

Muscle protein degradation is markedly decreased with the administration of a high-carbohydrate diet compared with fat-containing diets. Endogenous insulin concentration is increased, improving the net balance of skeletal muscle protein by decreasing protein breakdown. (See the previous discussion on "substrate-specific requirements" for further discussion of the impact of augmenting various nutritional components.)

Immunonutrition

As noted earlier, immune dysfunction represents one of the most critical complications of malnutrition in burn patients. Specific nutrients, including arginine, omega-3 polyunsaturated fatty acids, glutamine, and nucleotides, have been shown to modulate the host response in animal and clinical experiments, with potential improvements in immune function. Clinically arginine supplementation is intended to support T lymphocytes and provides a substrate for the generation of nitric oxide. Inclusion of nucleotides nonspecifically enhances immune competence. Long-chain omega-3 fatty acids decrease the production of inflammatory eicosanoids, cytokines, and adhesion molecules. This occurs directly by replacing arachidonic acid as an eicosanoid substrate, inhibiting arachidonic acid metabolism, and giving rise to antiinflammatory resolvins. The indirect effect occurs through the modulation of transcription factors that regulate the expression of inflammatory genes. Omega-3 polyunsaturated fatty acids are potentially useful antiinflammatory agents and may be beneficial for patients at risk of acute and chronic inflammatory conditions (Table 28.2).[54]

Immune-enhancing formulas consist of nutritional components enriched with arginine, glutamine, nucleotides, and omega-3 fatty acids. Although most formulations are hyperosmolar at full strength, dilution by 25% to 50% to make isotonic and hypotonic formulas, respectively, is initially preferred to minimize the possibility of diarrhea from excess osmotic load and to facilitate absorption.

A myriad of clinical trials of immunoenhancing nutritional therapies over the past 5–10 years have yielded conflicting results ranging from great promise early on to disappointing and even concerning results from more recent trials. Most troublesome, the REDOX trial, which examined the impact of glutamine supplementation in a large, heterogeneous population of critically ill patients, found that patients receiving glutamine supplementation had no benefit but, rather, an actual increase in mortality as compared to those subjects treated with standard of care. Naturally this finding has greatly dampened enthusiasm for glutamine supplementation and immunonutrition in general.

While application in broader patient populations was disappointing, studies limited to major trauma and burn patients show a more consistent benefit. It is thus quite possible that glutamine supplementation and immunonutrition can still benefit certain subsets of critically injured patients, including those with massive burns.[29,55–59] Studies of serum glutamine levels in broad populations of critically ill patients suggest that not all are deficient. Thus the advantage of immunonutrient supplements may be greater in populations with a greater risk for deficiency—i.e., premorbidly malnourished patients or acutely catabolic trauma and burn patients.[60–65] Finally post-hoc analysis of the redox data suggested that the majority of the mortality risk associated with glutamine supplementation could be attributed to those patients already in multiorgan or renal failure prior to initiation of treatment. It is therefore quite possible that glutamine supplementation could prove particularly beneficial should a different set of exclusion criteria be applied. Clearly there is significant work to be done before the precise role of immunonutrient supplementation is made clear.

PARENTERAL NUTRITION

For decades, the critical-care literature has emphasized the significant morbidity and even mortality risks associated with the use of PN. This emphasis on the risks of PN has led to the widespread dogma that the beneficial impact of PN can outweigh its risks only when applied to patients who are otherwise facing prolonged total starvation. More recent reassessments of PN suggest that the risk profile of

Table 28.1 Composition of Various Enteral Nutrition Formulations

Formula	kcal/mL	CHO, g/L (% Calories)	PRO, g/L (% Calories)	FAT, g/L (% Calories)	Osmolality (mOsm/L)	Comments
			STANDARD			
Similac	0.67	72 (43)	15 (8)	36 (49)		Infant nutrition
Enfamil	0.67	73 (44)	14 (8)	35 (48)		Infant nutrition
Isomil	0.67	68 (41)	18 (10)	37 (49)		Infant nutrition, lactose-free, used in cow protein allergy
Isosource HN	1.2	160 (53)	53 (18)	39 (29)	490	High nitrogen
Ensure Plus	1.5	208 (57)	54 (15)	46 (28)	680	Concentrated calories
Pediasure Enteral	1.0	133 (53)	30 (12)	40 (35)	335	For ages 1–13 years, with fiber, not easily digestible
Jevity 1 Cal	1.06	155 (54)	44 (17)	35 (29)	300	Isotonic nutrition with fiber
Boost Kid Essential	1.0	135 (54)	30 (12)	38 (34)	550–600	Oral or tube feeding
Boost HP	1.0	137 (55)	62 (24)	25 (21)	650	Oral or tube feeding, high protein
Promote	1.0	130 (52)	62 (25)	26 (23)	340	High protein, oral or tube feeding
Promote w/Fiber	1.0	138 (50)	62 (25)	28 (25)	380	Very high protein, oral or tube feeding
Nutren 1.0	1.0	127 (51)	40 (16)	38 (33)	370	With fiber, decreases diarrhea
			IMMUNE-ENHANCING			
Crucial	1.5	89 (36)	63 (25)	45 (39)	490	With ARG, critical illness, major surgery, transitional feedings, hydrolyzed protein
Impact	1.0	130 (53)	56 (22)	28 (25)	375	With ARG, GLN, and fiber
Impact GLN	1.3	150 (46)	78 (24)	43 (30)	630	Immunonutrition, GLN, ARG, omega-3 PUFA, nucleic acids
Oxepa	1.5	105 (28)	63 (17)	94 (55)	535	ARDS, acute lung injury, sepsis; concentrated
			SPECIALTY			
Glucerna	1.0	96 (34)	42 (17)	54 (49)	355	For glucose-intolerant or diabetic patients, low CHO
Nepro	1.8	167 (34)	81 (18)	96 (48)	585	For CKD and patients on dialysis; concentrated
Osmolite1Cal	1.06	144 (54)	44 (17)	35 (29)	300	Isotonic, for use in those intolerant to hyperosmolar nutrition
Vivonex RTF	1.0	175 (70)	50 (20)	12 (10)	630	Transitional feeding, low fat, easily digestible
Vivonex TEN	1.0	210 (82%)	38 (15%)	2.8 (3%)	630	100% free amino acids, very low fat, used for severe trauma (e.g., burns) or surgery, transitional feeding
Vivonex Plus	1.0	190 (76%)	45 (18%)	6.7 (6%)	650	100% free amino acids, very low fat, used for severe trauma (e.g., burns) or surgery, transitional feeding
Elecare	0.67	72 (43%)	20 (15%)	32 (42%)	350	Prepared at 9.4 g/60 mL; amino acid-based nutrition
			MODULAR			
Resource Benefiber	0.27	66 (100%)	0%	0%	—	Prepared at 4 g/60 mL; tasteless, odorless, soluble fiber, used for constipation
Resource Beneprotein	0.83	0%	200 (100%)	0%	—	Prepared at 7 g/30 mL; whey protein, mixed in foods, protein-calorie malnutrition

From Al-Mousawi A, Branski LK, Andel HL, et al. Ernährungstherapie bei Brandverletzten. In Kamolz LP, Herndon DN, Jeschke MG, editors. Verbrennungen: diagnose, therapie und rehabilitation des thermischen traumas. German edition, New York: Springer-Verlag; 2009: 183–194.

ARDS, Acute respiratory distress syndrome; *ARG,* arginine; *CHO,* carbohydrate; *CKD,* chronic kidney disease; *GLN,* glutamine; *PRO,* protein.

[a]Data extrapolated from Nestle clinical nutrition: Enteral product reference guide. Minneapolis: Nestle, 2010; and Abbott nutrition pocket guide. Abbott Park, IL: Abbott Laboratories, 2009.

PN has declined significantly over the past 20 years in the setting of improving efficacy of contemporary critical care practices.[66–69]

Although PN undoubtedly involves significant risks and morbidity, there is reason to believe that recent advances in critical care (e.g., improved glycemic control practices, increased evidence of infection control techniques) have significantly mitigated these risks. Multiple large trials have evaluated the use of PN as a supplement to rather than replacement for EN, with variable results. Large multiinstitutional clinical trials in broader populations of critically ill patients have found that the use of PN as a supplement to EN or as a replacement for EN (i.e., TPN) no longer worsens outcomes even in patients able to tolerate EN. Perhaps most

Table 28.2 Effect of Omega-3 Polyunsaturated Fatty Acids on Eicosanoid Synthesis[a]

Metabolite	Physiologic Action	Omega-3 Effect
	AA EICOSANOID	
PGE_2	Proinflammatory, vasodilator[b]	↓
TXA_2	Potent platelet aggregation and vasoconstrictor	↓
LTB_4	Proinflammatory, neutrophil chemotaxis	↓
	EPA EICOSANOID	
TXA_3	Mild platelet aggregation	↑
PGI_3	Mild platelet disaggregation	↑
RvE1	Potent antiinflammatory	↑
	DHA DOCOSANOID	
RvD1	Potent antiinflammatory	↑
NPD1	Potent antiinflammatory, neuroprotective bioactivity	↑

AA, Arachidonic acid; *DHA*, docosahexaenoic acid; *EPA*, eicosapentaenoic acid; *LT*, leukotriene; *NP*, neuroprotectin; *PG*, prostaglandin; *PGI*, prostacyclin; *Rv*, resolvin; *TX*, thromboxane.
[a]Biochemical basis of a less inflammatory phenotype.
[b]Prostaglandin E2 has been reported to have dual activity as both a pro- and antiinflammatory. The latter effect, although weak, has been reported to be the effect of the induced production of lipoxins.

Table 28.3 Composition of Parenteral Nutrition Formulations

	Caloric Content			
Sample Nutrition[a]	g/dL	kcal/g	kcal/ mL	mOsm/ L
	2-IN-1 SOLUTIONS			
Dextrose				
DW 10%	10	3.4 (CHO)	0.34	505
DW 30%	30	3.4 (CHO)	1.02	1510
DW 70%	70	3.4 (CHO)	2.38	3530
Amino acids				
Aminosyn RF 5.2%	5.2	4 (PRO)	0.2	427
Travasol 10%	10	4 (PRO)	0.4	998
Prosol 20%	20	4 (PRO)	0.8	1835
Lipid emulsion				
Intralipid 10%	10	11 (FAT)[b]	1.1	300
Intralipid 20%	20	10 (FAT)[b]	2	350
Intralipid 30%	30	10 (FAT)[b]	3	310

CHO, Carbohydrate; *PRO*, protein.
[a]3-in-1 solutions: total nutrient admixture (TNA).
[b]Estimated at 9 kcal/g for fat plus additional calories from glycerol.

Table 28.4 Clinical Conditions Requiring Cautious Use of Parenteral Nutrition

Condition	Suggested Criteria
Hyperglycemia	Glucose >300 mg/dL
Azotemia	BUN >100 mg/dL
Hyperosmolality	Serum osmolality >350 mOsm/kg
Hypernatremia	Na >150 mEq/L
Hypokalemia	K <3 mEq/L
Hyperchloremic metabolic acidosis	Cl >115 mEq/L
Hypophosphatemia	Phosphorus <2 mg/dL
Hypochloremic metabolic alkalosis	Cl <85 mEq/L

BUN, Blood urea nitrogen.
From Mirtallo JM. In Gottschlich MM, editor. *The A.S.P.E.N. nutrition support core curriculum: a case-based approach: the adult patient.* Silver Spring, MD: American Society for Parenteral and Enteral Nutrition; 2007: 268.

convincingly, Harvey et al. randomized 2400 ICU patients to receive either EN or PN and found no indication of increased 30-day morbidity or mortality in the PN group.[70] While extremely provocative, these findings have not been tested in burn patients specifically. Such studies would be well-warranted and should be encouraged.

The utility of supplemental PN (applied liberally) remains a matter of considerable debate. It is our opinion that supplemental nutrition can be quite helpful when applied selectively, based on the clinician's assessment of the individual patient's metabolic needs and nutritional status. It is our practice to use supplemental PN in the acute phase of burn injury response in any patients unable to tolerate enteral feeds at quantities sufficient to meet (or at least approach) protein-caloric requirements. Alternatively in those patients who manifest enteral feeding intolerance in the subacute phase of their burn injury response, we typically prescribe supplemental PN only to those with evidence of preexisting malnutrition at the time of burn.[71–73]

Prior to receiving PN, patients should be hemodynamically stable and able to tolerate the fluid volume and nutrient content of parenteral formulations; PN should be used with caution in patients with congestive heart failure, pulmonary disease, diabetes mellitus, and other metabolic disorders because the significant amounts of fluid and sugar may be difficult for patients to tolerate (Table 6.9). While there has been some debate as to the optimal timing for initiating TPN in patients unable to tolerate adequate EN, results of recent large randomized controlled trials suggest that early initiation of TPN is an appropriate general strategy in such patients (Tables 28.3 and 28.4).[66,74,75]

MEETING PRESCRIBED FEEDING GOALS

Frequently failures to provide adequate nutrition result not from underprescription, but from unanticipated (and often undetected) gaps in execution. Even in the setting of a fully invested care team treating under a clearly articulated nutritional care plan, calories provided will frequently fall short of the amount prescribed because, for example, enteral feeds are held for studies or procedures or interrupted by the clamping of enteral tubes for medication administration or transport. Even PN may be interrupted for transportation or compounding delays.[76,77] The key to

Table 28.5 Complications of Enteral Feeding

Problem	Common Causes	Management
Diarrhea	Medications (e.g., antibiotics, H_2 blockers, laxatives, hyperosmotic, hypertonic solutions), feeding intolerance (osmolarity, fat), acquired lactase deficiency	Measure stool output Rule out infection (bacterial, viral, parasitic) Supply fiber Change medication or formula Check osmolarity and infusion rate Replace lost fluids as needed Administer antimotility medications (e.g., loperamide, codeine)—Note: do not administer antimotilities until *Clostridium difficile* colitis has been ruled out
Nausea and vomiting	Delayed stomach emptying, constipation, medications, odor and appearance of formulations	Administer feedings at room temperature Use isotonic formulations Use a closed system when possible Reduce doses of narcotics Use gastroprokinetic agents (metoclopramide, erythromycin) Monitor gastric residuals and stool output
Constipation, fecal impaction	Dehydration, lack or excess of fiber	Monitor fluid balance daily Rectal disimpaction Consider the use of cathartics, stool softeners, laxatives, or enemas
Aspiration pneumonitis	Long-term supine position, delayed stomach emptying, altered mental status, malpositioned feeding tube, vomiting, nonfunctional nasogastric drainage tube	Place head of bed at 45 degrees during feedings Stop EN if gastric residual volume exceeds 200 mL Use of nasoduodenal or nasojejunal tubes has not been shown to decrease aspiration risk (when compared to gastric feeding)
Hypervolemic hyponatremia (overhydration)	Excess fluid intake, refeeding syndrome, organ failure (e.g., liver, heart, kidney)	Monitor fluid balance and body weight daily Consider fluid restriction Change formula (avoid low-sodium intake) Initiate diuretic therapy
Hypernatremia	Dehydration, inadequate fluid intake	Increase free water
Dehydration	Diarrhea, inadequate fluid intake	Determine cause Increase fluid intake
Hyperglycemia	High content of carbohydrate in feedings, insulin resistance	Evaluate and adjust feeding formula Consider insulin regimen Check for dextrose-based carriers in IV medications
Hypokalemia, hypomagnesemia, hypophosphatemia	Diarrhea, refeeding syndrome	Correct electrolyte abnormalities Determine cause Reduce rate if refeeding syndrome is present and monitor patient
Hyperkalemia	Excess potassium intake, renal impairment	Change feeding formula Reduce potassium intake Consider insulin regimen

minimizing such gaps between prescribed and delivered calories is awareness, with careful monitoring of delivery. Once recognized, such gaps can be minimized by making a conscious effort to keep all feeding interruptions to a minimum and establishing some mechanism to compensate for anticipated gaps in nutrition. For example, when prescribing tube feed rates, we often increase the resting energy expenditure (REE) multiplier to 1.4 or even 1.6 to compensate for such gaps.

COMPLICATIONS OF NUTRITIONAL SUPPORT

Complications of nasogastric and enteric feeding include nausea and vomiting, epistaxis, sinusitis, nasal necrosis, aspiration leading to pneumonia, tube malpositioning, dislodgment, and feeding-associated diarrhea. Fine-bore tubes are more comfortable but can become blocked easily. Auscultation examination of gastric fluid aspirate and pH testing can be used to confirm tube position, particularly for large-bore nasal tubes, although many units prefer radiologic confirmation. Tubes can also be inserted under endoscopic or fluoroscopic guidance (Table 28.5). (See the preceding section on "delivering enteral nutrition" for a discussion of ways to minimize aspiration risk.)

Unfortunately in burn patients efforts to deliver adequate nutrition enterally are frequently complicated by the degree of feeding intolerance manifested by either diarrhea or ileus (i.e., aperistalsis). GI ileus may reflect an underlying deterioration; therefore monitoring gastric residual volumes serves as an indicator of intercurrent conditions such as sepsis. In burn patients specifically, residuals that increase above the amount of food delivered routinely every hour have been shown to correlate with the development of bacterial sepsis. A full sepsis workup should be considered in any critically ill or injured patient with a sudden increase in gastric residuals over 200 mL.[78]

Ileus is derived from mesenteric hypoperfusion prior to adequate resuscitation, and it is reversed once the patient has been resuscitated. Conversely overresuscitation leads to GI edema and should also be avoided. The initiation of

immediate enteral feeding allows the delivery of calculated caloric requirements by the third day postinjury. Early enteral feeding is associated with reduction of hypermetabolism and less intense elevations in glucagon, cortisol, and catecholamine levels.[18,20,45,60]

Diarrhea probably represents the most common complication of EN and typically presents an ongoing challenge in the management of the massively burned patient. The source of this diarrhea is multifactorial, making it fairly difficult to manage. In the setting of shock, diarrhea can represent mucosal failure from incipient intestinal ischemia. A variety of medications can contribute to this problem, most notably antacid agents and antibiotics. Infectious causes are not particularly common but nonetheless must be ruled out. *Clostridium difficile* should always be ruled out due to its potential for severe deterioration and the risk for contagion to other patients. Cytomegalovirus enterocolitis can emerge secondary to burn-associated immunosuppression. Naturally, specific pathogens endemic to the individual patient's exposure history should always be considered.

The most common source of diarrhea in burn patients treated with enteral tube feeds is likely the feeds themselves. The high osmolar concentration of these feeds, the volume of feeds required to meet the high caloric requirements of burn patients, and the gut response to stress all combine to result in a state of relative *solute overload*. Inappropriately rapid administration of hyperosmolar solutions may result in diarrhea, dehydration, electrolyte imbalance, hyperglycemia, and loss of potassium, magnesium, and other ions through diarrhea. Reducing the osmolality by decreasing formula strength while adjusting the rate is the first step in addressing this complication. If aggressive administration of hyperosmolar solute continues, pneumatosis intestinalis with bowel necrosis and perforation can result. Hyperosmolar nonketotic coma can also occur with enteral feedings. In some cases, diarrhea may persist even after converting to isoosmolar feeds, reflecting intestinal failure from shock and/or ischemic insult. In such situations, it may be necessary to convert to TPN with trophic feeds until intestinal function returns.

Support with PN offers a distinctly different profile of side effects. The potential complications associated with the attendant access requirements (i.e., central lines) must be considered, particularly given the decreasing use of central lines for nonnutritional applications in contemporary critical care. And, of course, the PN formula itself can significantly disturb metabolic and electrolyte homeostasis. Without the benefit of first-pass liver metabolism and responsive regulation of absorption by the functional intestinal mucosa, the direct infusion of nutritional elements can result in precipitous, often dangerous shifts in serum chemistry (Table 28.6).

Table 28.6 Complications of Parenteral Nutrition

Problem	Common Causes	Management
Hypoglycemia	Excess insulin administration, sudden cessation of PN infusion	Stop insulin Start 10% dextrose IV Give a 50% dextrose ampule before resuming central line feeding
Hyperglycemia	Excess dextrose concentration, stress-associated (e.g., sepsis), chromium deficiency	0.1–0.2 U insulin/g dextrose therapy, SQ or IV insulin sliding scale, limit dextrose content, consider discontinuing PN until improved blood glucose control
Hypertriglyceridemia (acceptable concentrations <400 mg/dL)	Dextrose overfeeding, rapid administration of intravenous fatty emulsion (>110 mg/kg/h)	Infusion of IVFE should be restricted to less than 30% of total calories or 1 g/kg/day, given slowly, over no less than 8 to 10 h, if administered separately
Essential fatty acid deficiency (e.g., dermatitis, alopecia, hepatomegaly, thrombocytopenia, anemia)	1- to 3-week administration of PN lacking linoleic and alpha-linolenic fatty acid emulsions	2–4% daily energy requirements should be derived from linoleic acid, 0.5% from alpha-linolenic acid[43] (500 mL of 10% IVFE over 8–10 h, twice weekly)
Electrolyte and mineral abnormalities	Inadequate monitoring Inadequate supplementation in TPN formula	Electrolytes should be checked daily and parenteral nutrition formulas should be adjusted daily until electrolytes stabilized Parenteral iron uncommonly increases risk of anaphylactic reactions
Azotemia	Dehydration, excess protein, inadequate carbohydrate calories	Free water, 5% dextrose via a peripheral vein
Metabolic bone disease (osteoporosis in 41% of those on long-term home PN)	Unclear, multifactorial (e.g., postmenopausal, long-term PN, Cushing's syndrome, Crohn's disease, malabsorption, multiple myeloma, osteogenesis imperfect, corticosteroids, heparin, immobilization)	Early screening of risk factors, DEXA, management of premorbid conditions Special PN considerations: Supplement calcium, P, Mg, Cu Minimize aluminum contamination, treat metabolic acidosis, avoid heparin
Elevated liver function parameters (increased transaminase, bilirubin, alkaline phosphatase levels)	Common following initiation; usually temporary	If persistent, usually caused by amino acid load; reduce protein delivery

DEXA, Dual-energy x-ray absorptiometry.

Refeeding syndrome is a rare but dramatic clinical entity occasionally seen when initiating nutritional support in patients with long-standing starvation. It is heralded by the development of refractory hypokalemia, hypomagnesemia, and hypophosphatemia. Electrolyte abnormalities can result in cardiac failure and dysrhythmias, respiratory failure, neurologic disturbances, and renal and hepatic dysfunction. This should not present a concern in patients treated with early initiation of nutrition postinjury and continuous nutritional support.

Nutritional Assessment and Monitoring

Goal-directed nutritional support is a cornerstone of effective burn care. Underfeeding can result in stalled wounded healing, pulmonary compromise, increased immunocompromise, and a myriad of secondary and tertiary complications. Overfeeding is detrimental as well, leading to hypercapnia and metabolic acidosis, hyperglycemia, hypertriglyceridemia, hepatic dysfunction, and azotemia. Thus an ongoing nutritional assessment is the starting point for any nutritional therapy.

TOTAL CALORIC REQUIREMENTS

Determining nutritional requirements for patients is essential to effective care because the provision of inadequate or excess calories can adversely affect outcome. Caloric requirements in patients with severe burns are particularly difficult to predict because energy expenditure varies widely both from patient to patient and over the course of any individual patient's care. Energy demand and the metabolic response shift gradually with changes in body composition and acutely with acute physiologic stresses such as operative interventions or septic episodes.

A variety of equations have been created to estimate caloric requirements in burn patients (Tables 28.7 and 28.8). Although these are useful for establishing a quick estimate of caloric needs, their accuracy is limited.[79] Because no algorithm can fully accommodate the complex interactions among surgical stress, wound burden, infectious complications, and metabolism seen in the thermally injured patient, in situ measurement of REE are particularly valuable in this population.

An evaluation of the metabolic status can be performed by indirect calorimetry using bedside metabolic carts, which measure REE using expired gas volumes; oxygen consumption (VO_2) and carbon dioxide production (VCO_2) are measured directly as follows:

$$\text{REE (kcal/day)} = 1.44\,(3.9\,VO_2\,[\text{mL/min}] + 1.1\,VCO_2\,[\text{mL/min}])$$

These steady-state measurements have been shown to predict 24-hour energy expenditure with remarkable accuracy.[79] Measurements obtained are generally reliable and reproducible over a wide range of catabolic conditions, metabolic rates, and values of Fio_2. Given the significant changes in energy expenditure occurring over the course of care, the use of bedside carts for repeated measurements is

Table 28.7 Formulas for Estimating Caloric Requirements in Adult Burn Patients

Formula	Equation	Comments
	HARRIS-BENEDICT[61]	
Men	BEE (kcal/ day) = 66.5 + (13.75 × W) + (5.00 × H) − (6.76 × A)	Multiply BEE by stress factor of 1.2–2.0 (1.2–1.5 sufficient for most burns) to estimate caloric requirement
Women	BEE (kcal/day) = 655 + (9.56 × W) + (1.85 × H) − (4.68 × A)	
	CURRERI	
Age, 16–59 years	Calories (kcal/day) = (25 × W) + (40 × % BSAB)	Specific for burns, may significantly overestimate energy requirements, maximum 50% BSAB
Age >60 years	Calories (kcal/day) = (20 ×W) + (65 × % BSAB)	

A, Age (yr); *BEE,* basal energy expenditure; *% BSAB,* percentage of total body surface area burned; *H,* height (cm); *W,* weight (kg).

Table 28.8 Formulas for Estimating Caloric Requirements in Pediatric Burn Patients

Formula	Sex/Age (Years)	Equation (Daily Requirement in kcal)
WHO	Males 0–3	(60.9 × W) − 54
	3–10	(22.7 × W) + 495
	10–18	(17.5 × W) + 651
	Females 0–3	(61.0 × W) − 51
	3–10	(22.5 × W) + 499
	10–18	(12.2 × W) + 746
RDA	0–6 months	108 × W
	6 months–1 year	98 × W
	1–3	102 × W
	4–10	90 × W
	11–14	55 × W
Curreri junior	<1	RDA + (15 × %BSAB)
	1–3	RDA + (25 × %BSAB)
	4–15	RDA + (40 × %BSAB)
Galveston infant	0–1	2,100 kcal/m^2 BSA + 1,000 kcal/m^2 BSAB
Galveston revised	1–11	1,800 kcal/m^2 BSA+ 1,300 kcal/m^2 BSAB
Galveston adolescent	12+	1,500 kcal/m^2 BSA+ 1,500 kcal/m^2 BSAB

Adapted from Al-Mousawi A, Branski LK, Andel HL, et al. Ernährungstherapie bei Brandverletzten. In Kamolz LP, Herndon DN, Jeschke MG, editors. *Verbrennungen: diagnose, therapie und rehabilitation des thermischen traumas*, German edition. New York: Springer-Verlag; 2009: 183–194.
BSA, Body surface area; *RDA,* recommended dietary allowance.

ideal for calculating optimal nutritional requirements in these extremely metabolically labile patients.

To attain a value for REE, indirect calorimetry is performed with the patient completely at rest—ideally hours removed from any acute manipulation such as medical or surgical procedure, rehabilitation therapy, and the like. To estimate the actual daily energy expenditure, this result is increased by 10–20% to allow for variability and activity.[79,80]

Indirect calorimetry also provides insight into the substrate metabolism balance via the respiratory quotient ($RQ = VCO_2/ VO_2$). An RQ in the range of 0.7 to 1.0 is seen in the normal uptake of mixed substrates. An RQ of 0.7 or less is consistent with either an increased portion of fat calories supplied (or utilized) or underfeeding. On the other hand, an RQ higher than 1.0 suggests lipogenesis from either carbohydrate-bias skewed input or overfeeding.

Traditionally nitrogen balances have been used to assess the balance between protein anabolism and catabolism in trauma patients. A negative nitrogen balance occurs when the excretion of nitrogen exceeds the daily intake (i.e., net catabolism), whereas a positive nitrogen balance is associated with muscle gain. Unfortunately the variable and often large quantities of nitrogen lost in the wound exudate of burn patients make measurement of nitrogen balance distinctly difficult in these patients.

BODY COMPOSITION

Ultimately body composition and changes therein represent the most fundamental and meaningful reflection of a patient's nutritional status and the efficacy of his or her nutritional therapy.

Total Body Weight

Although total body weight is the simplest means of following global changes in body composition, its value as a reflection of nutritional status is extremely limited. Changes in total body weight seen over the short term (i.e., days) are far more sensitive to fluid shifts than they are reflective of meaningful changes in tissue mass. Over prolonged periods of time (e.g., weeks to months), severe decline in total body weight certainly indicates malnutrition and lean body mass attrition (presuming, of course, that one corrects for amputations or massive tissue excisions). However total body weight measures are largely influenced by significant changes in body fat seen over the course of acute illness. As such, even on this longer time-scale, the quantity of change in total body mass does not necessarily correlate to the quantity of lean body mass loss, nor does preservation of total body weight imply conservation of lean body mass.

Muscle and Lean Body Mass

"Lean body mass" refers to nonadipose tissue mass, exclusive of any added mass from acute shifts in water content. because the total mass of viscera and bone matter do not change at rates capable of causing significant change in lean body mass over the course of weeks to months, changes in lean body mass over such periods are interpreted as reflections of change in muscle mass. A patient receiving and assimilating adequate substrate and energy to support all of his or her physiologic needs will maintain or build muscle mass. Accumulation of fat, on the other hand, frequently occurs in the face of significant malnutrition and physiologic deterioration. As such, lean body mass serves as the most appropriate surrogate marker for nutritional well-being available in the context of acute burn care.

Massive thermal injury induces a profound protein wasting state. The loss of muscle seen during the acute response to a massive burn injury represents one of the most impressive and tangible nutritional phenomena one can encounter clinically—a muscular young patient presenting with massive burns can easily waste away to a bony, emaciated appearance over a 2-week period. This negative nitrogen balance is not simply a product of starvation, but also a function of an inexorable upregulation of protein catabolism. Muscle catabolism has been shown to persist in burn patients, even in the setting of aggressive feeding and protein supplementation. The net effect of this metabolic shift is manifest through a rapid and profound loss of lean body mass.[7,12,14,81–83]

Obesity

Multiple studies have identified high rates of critical malnutrition in obese patients who, despite generous fat stores, show markedly low lean body masses—a phenomenon termed *sarcopenic obesity*.[84,85] Furthermore patients will often continue to lose lean body mass despite their excessive caloric stores. In patients with sarcopenic obesity, surgical morbidity and mortality rates correlate far more closely with lean body mass than with gross mass or any calculated "ideal" weight. As such, obesity should not be interpreted as a state of overnourishment, but quite the opposite.

In the broader critical care literature, there has been a compelling discussion of the potential benefits of hypocaloric, high-protein feeding regimens in the critically ill obese.[84] Given the profoundly hypermetabolic state associated with thermal injury, use of an "underfeeding" strategy in an obese burn patient raises considerable concerns for safety and is probably best reserved for a research setting.

Even in those patients not obese at time of injury, body composition in burn patients frequently moves toward a state of sarcopenic obesity. As emphasized earlier, the metabolic shift toward proteolysis persists even in the face of aggressive nutrition. In the context of this muscle-wasting milieu, any access or "free" calories available are more likely to be stored as fat while muscle is broken down during periods of acute caloric debt. Thus Hart et al. demonstrated that "increased feeding leads to fat rather than lean mass accretion."[13]

Ideal Body Weight

The term "ideal" is not particularly apt, as there is not a particular limit to how much lean body mass a patient can healthfully maintain—with lean body masses for well-nourished nonobese patients determined by a combination of environmental and genetic factors. Nonetheless equations for "ideal body weight" (IBW) are useful in patients whose total weight is distorted by pathologic processes. While limited in their accuracy, they do provide rough estimates of baseline weight for patients whose total weight is distorted by pathologic processes such as chronic morbid obesity or, particularly in burn patients, massive fluid shifts.

Derived ideal body weights can be helpful when using weight-based formulas to determine starting points for quantitative treatment decisions such as drug doses, tidal volume settings, endpoint physiologic indices, and the like. Values for IBW can be found in standardized tables that relate height to expected weight, or IBW can be estimated by the following equations:

- Men: 48 kg for the first 152 cm and 2.7 kg for each additional 2.54 cm
- Women: 45 kg for the first 152 cm and 2.3 kg for each additional 2.54 cm

Clinical Imaging

Dual-Energy X-Ray Absorptiometry. Dual-energy x-ray absorptiometry (DEXA) is a useful technique for monitoring long-term nutritional progress by measuring changes in body tissue composition, including lean body mass, fat mass, and bone density. DEXA's precision, accuracy, and versatility make it extremely useful in a research setting. Practically speaking, though, few burn centers have the infrastructure in place to regularly perform such assessments on critically ill patients.

Computed Tomography and Ultrasound. More readily available, high-resolution computed tomography (CT) scanners have been shown to reliably predict DEXA results. However significant cost, radiation exposure, and need for patient transport all serve as barriers to widespread clinical use. More recently, multiple groups have shown that measurements from a limited bedside ultrasound (US) exam can be used as an accurate and convenient means of serial assessment. The thickness of a patient's quadriceps measured at bedside has been shown to be powerfully predictive of CT and DEXA assessments of total lean body mass.[86,87] Given its ubiquitous availability, low cost, ease of use, and minimally invasive nature, bedside ultrasound has significant potential for widespread clinical application in nutritional assessment and monitoring. For burn patients, who are at a uniquely high risk from nutritional morbidity and frequently present a myriad of unique transportation challenges, this bedside measure may prove quite valuable.

Albumin and Serum Markers for Nutrition

Serum protein markers, most notably albumin, have demonstrated significant value in assessing nutritional status and predicting outcomes in the setting of patients considered for elective surgery. Unfortunately the value of serum protein levels as indicators of nutritional status is extremely limited during the acute-phase response to injury, inflammation, infection, and surgical stress. The physiologic stress response upregulates expression of acute-phase reactive proteins, with unpredictable effects on "marker" protein levels. In the setting of acute burn care, presenting albumin levels or short-term changes therein should not be interpreted as being indicative of nutritional progress.[34,88,89]

Conclusion

Burns involving more than 20% of the total body surface area represent a massive metabolic injury. The metabolic response to massive burns creates an immediate, intense, and persistent strain on the patient's nutritional status. The systemic response to burn injury alters essentially all aspects of energy substrate metabolism. The net total energy expenditure and requirements are markedly augmented by massive burn. Alterations in glucose metabolism favor gluconeogenesis and limited oxidation capacity. Alterations in lipid metabolism favor lipogenesis and the accretion and sequestration of fat in a manner that diverts energy from critical functions. Finally a surge in proteolysis creates an immediate and prolonged protein-wasting state that results in profound lean body mass loss and, at worst, compromises in immune, respiratory, and healing processes.

Given the immense metabolic challenges created by burn injury, optimizing nutritional support is essential to improving outcomes in this patient population. Total calories provided should be based on ongoing assessment of energy expenditure, ideally using indirect calorimetry. Providing calories in excess of the patient's needs (i.e., overfeeding) is counterproductive. While carbohydrates delivered will frequently provide the majority of calories given, care should be taken not to give loads that exceed established limits of glucose oxidation. Provision of adequate protein is critical to effective nutritional support, and protein supplementation is likely the ideal means to augment caloric load when carbohydrate provision is "maxed out." The amount of exogenous fat required to avoid essential fatty-acid deficiencies is relatively modest and can be met with relatively minimal amounts of fat alimentation. Administration of excessive amounts of fat-based calories can be detrimental to care—although significant research is required to determine how the risk–benefit profile of fat alimentation may differ with use of alternate fat sources.

EN is the first line of nutritional support in the burn patient, and enteral feeding should be administered as soon as possible. While oral feeding is theoretically possible, few patients with massive thermal injuries will be capable of meeting their full nutritional needs through oral intake alone. Typically EN will be provided in part or in whole via enteric access tubes. The enteral system can be accessed via the stomach for feeding if necessary, although this may be compromised by gastroparesis. Postpyloric feeding access offers the benefit of circumventing the potentially paretic stomach, thus allowing for more dependable sustained feeding early in the course of treatment. Care should be taken to minimize the risk of aspiration by undertaking frequent assessment for nausea or distention. Routine serial evaluations of gastric residuals have not been shown to be beneficial. Care should be taken to minimize interruptions in feeding to ensure that the gap between calories prescribed and delivered is minimized as much as possible.

Accurate serial assessment of nutritional status and body composition is central to identifying patient needs, trajectory, and efficacy of care. Unfortunately serum protein markers and changes in total body weight are inaccurate reflections of nutritional status, with poor specificity and sensitivity. Changes in lean body mass and body composition represent the ultimate reflection of cumulative nutritional status, and evolving applications of imaging technology have made routine serial evaluation of lean body mass feasible.

The physiologic response to massive thermal injury represents an enormous nutritional insult. The consequences of this intense acute malnutrition include compromises in immune function, wound healing, and mobility—all major drivers of morbidity and mortality in thermal trauma. As such, thoughtful and comprehensive nutritional support based on continuous assessment of nutritional needs is essential to optimizing outcomes in acute burn care.

Complete references available online at www.expertconsult.inkling.com

Further Reading

Boelens P. Reduction of postoperative ileus by early enteral nutrition in patients undergoing major rectal surgery: prospective, randomized, controlled trial. *Ann Surg*. 2014;259(4):649-655.

Casaer MP, et al. Impact of early parenteral nutrition on muscle and adipose tissue compartments during critical illness. *Crit Care Med*. 2013;41(10):2298-2309.

Garrel DI. Length of care in patients with severe burns with or without early enteral nutritional support. A retrospective study. *J Burn Care Rehabil*. 1991;12(1):85-90.

Gore D. Acute response of human muscle protein to catabolic hormones. *Ann Surg*. 1993;218(5):679-684.

Harvey S. A multicentre, randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of early nutritional support via the parenteral versus the enteral route in critically ill patients (CALORIES). *Health Technol Assess*. 2016;20(28):1-144.

Heyland D. Enhanced protein-energy provision via the enteral route feeding protocol in critically ill patients: results of a cluster randomized trial. *Crit Care Med*. 2013;41(12):2743-2753.

Khalid IP. Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation. *Am J Crit Care*. 2010;19(3):261-268.

Reiss EE. The metabolic response to burns. *J Clin Invest*. 1956;35(1):62-77.

Wolfe R. Caloric Requirements of the burned patient. *J Trauma*. 1981;21:712-714.

Yan H. Effects of early enteral arginine supplementation on resuscitation of severe burn patients. *Burns*. 2007;33(2):179-184.

Zhou Y. The effect of supplemental enteral glutamine on plasma levels, gut function, and outcome in severe burns: a randomized, double-blind, controlled clinical trial. *JPEN J Parenter Enteral Nutr*. 2003;37(4):241-245.

References

1. Abdullahi A. Nutrition and anabolic pharmacotherapies in the care of burn patients. *Nutr Clin Pract*. 2014;29(5):621-630.
2. Jeschke M. Pathophysiologic response to severe burn injury. *Ann Surg*. 2008;248(3):387-401.
3. Wolfe R. Regulation of lipolysis in severely burned children. *Ann Surg*. 1987;206(2):214-221.
4. Goodall M, Stone C, Haynes BW Jr. Urinary output of adrenaline and noradrenaline in severe thermal burns. *Ann Surg*. 1957;145(4):479-487.
5. Coombes E. Urine cortisol levels after burn injury. *Burns Incl Therm Inj*. 1982;8(5):333-337.
6. Jahoor F. Dynamics of the protein metabolic response to burn injury. *Metabolism*. 1988;37(4):330-337.
7. Chao T. Skeletal muscle protein breakdown remains elevated in pediatric burn survivors up to one-year post-injury. *Shock*. 2015;44(5):397-401.
8. Wilmore D. Catecholamines: mediatros of hypermetabolic response to thermal injury. *Ann Surg*. 1974;180:653-668.
9. Herndon D. Mediators of metabolism. *J Trauma*. 1981;21:701-704.
10. Curreri P. Dietary requirements of patients with major burns. *J Am Diet Assoc*. 1974;65(4):415-417.
11. Wolfe R. Effect of severe burn injury on substrate cycling by glucose and fatty acids. *N Engl J Med*. 1987;317(7):403-408.
12. Yu Y. The metabolic basis of the increase of the increase in energy expenditure in severely burned patients. *J Parenter Enteral Nutr*. 1999;23(3):160-168.
13. Hart D. Energy expenditure and caloric balance after burn: increased feeding leads to fat rather than lean mass accretion. *Ann Surg*. 2002;235(1):152-161.
14. Hart D. Determinants of skeletal muscle catabolism after severe burn. *Ann Surg*. 2000;232(4):455-465.
15. Burke J. Glucose requirements following burn injury. Parameters of optimal glucose infusion and possible hepatic and respiratory abnormalities following excessive glucose intake. *Ann Surg*. 1979;190(3):274-285.
16. Sheridan R. Maximal parenteral glucose oxidation in hypermetabolic young children: a stable isotope study. *JPEN J Parenter Enteral Nutr*. 1998;22(4):212-216.
17. McClave S. Summary points and consensus recommendations from the North American Surgical Nutrition Summit. *JPEN J Parenter Enteral Nutr*. 2013;37(5s):99s-105s.
18. Prelack KM. Practical guidelines for nutritional management of burn injury and recovery. *Burns*. 2007;33(1):14-24.
19. Hall KS. Enteral nutrition support in burn care: a review of current recommendations as instituted in the Ross Tilley Burn Centre. *Nutrients*. 2012;4(11):1554-1565.
20. Rousseau A. ESPEN endorsed recommendations: nutritional therapy in major burns. *Clin Nutr*. 2013;32(4):497-502.
21. Garrel D. Improved clinical status and length of care with low-fat nutrition support in burn patients. *JPEN J Parenter Enteral Nutr*. 1995;19(6):482-491.
22. Gottschlich M. Differential effects of three enteral dietary regimens on selected outcome variables in burn patients. *JPEN J Parenter Enteral Nutr*. 1990;14(3):225-236.
23. Hart D. Efficacy of a high-carbohydrate diet in catabolic illness. *Crit Care Med*. 2001;29(7):1318-1324.
24. Moore FA. (missing).
25. Rodriguez N. Nutrition in burns: Galveston contributions. *JPEN J Parenter Enteral Nutr*. 2011;35(6):704-714.
26. Williams F. What, how, and how much should patients with burns be fed? *Surg Clin North Am*. 2011;91(3):609-629.
27. Patterson B. Urea and protein metabolism in burned children: effect of dietary protein intake. *Metabolism*. 1997;46(5):573-578.
28. Kozar RA, Verner-Cole E, Schultz SG, et al. The immune-enhancing enteral agents arginine and glutamine differentially modulate gut barrier function following mesenteric ischemia/reperfusion. *J Trauma*. 2004;57(6):1150-1156.
29. Heyland D. A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med*. 2013;368(16):1489-1497.
30. Alexander J. Beneficial effects of aggressive protein feeding in severely burned children. *Ann Surg*. 1980;192(4):505-517.
31. Wolfe RR. Isotopic approaches to the estimation of protein requirements in burn patients. *Adv Shock Res*. 1983;9:81-98.
32. Berger MM, Soguel L, Charrière M, et al. Impact of the reduction of the recommended energy target in the ICU on protein delivery and clinical outcomes. *Clin Nutr*. 2017;36(1):281-287.
33. Czapran A. International observational study of nutritional support in mechanically ventilated patients following burn injury. *Burns*. 2015;41(3):510-518.
34. Perez-Guisado J. Serum albumin levels in burn people are associated to the total body surface burned and the length of hospital stay but not to the initiation of the oral/enteral nutrition. *Int J Burns Trauma*. 2013;3(3):159-163.
35. Alverdy JE. Total parenteral nutrition promotes bacterial translocation from the gut. *Surgery*. 1988;104(2):185-190.
36. Groos SG. Parenteral versus enteral nutrition: morphological changes in human adult intestinal mucosa. *J Submicrosc Cytol Pathol*. 1996;28(1):61-74.
37. Barlow R. Prospective multicentre randomised controlled trial of early enteral nutrition for patients undergoing major upper gastrointestinal surgical resection. *Clin Nutr*. 2011;30(5):560-566.
38. Osland E. Early versus traditional postoperative feeding in patients undergoing resectional gastrointestinal surgery: a meta-analysis. *JPEN J Parenter Enteral Nutr*. 2011;35(4):473-487.
39. Deitch E. Intestinal permeability is increased in burn patients shortly after injury. *Surgery*. 1990;107(4):411-416.
40. Mochizuki H. Mechanism of prevention of postburn hypermetabolism and catabolism by early enteral feeding. *Ann Surg*. 1984;200(3):297-310.
41. Dominioni L. Enteral feeding in burn hypermetabolism: nutritional and metabolic effects of different levels of calorie and protein intake. *JPEN J Parenter Enteral Nutr*. 1985;9(3):269-279.
42. Guo YH. Early enteral nutrition versus late enteral nutrition for burns patients: A systematic review and meta-analysis. *Burns*. 2015.
43. Chiarelli A. Very early nutrition supplementation in burned patients. *Am J Clin Nutr*. 1990;51(6):1035-1039.
44. Khorasani E. Effect of early enteral nutrition on morbidity and mortality in children with burns. *Burns*. 2010;36(7):1067-1071.
45. Lam NN. Early enteral feeding for burned patients – an effective method which should be encouraged in developing countries. *Burns*. 2008;34(2):192-196.
46. Venter M. Enteral resuscitation and early enteral feeding in children with major burns – effect on McFarlane response to stress. *Burns*. 2007;33(4):464-471.
47. Peng YZ. Effects of early enteral feeding on the prevention of enterogenic infection in severely burned patients. *Burns*. 2001;27(2):145-149.
48. Shields B. A pilot review of gradual versus goal re-initiation of enteral nutrition after burn surgery in the hemodynamically stable patient. *Burns*. 2014;40(8):1587-1592.
49. Kesey J. A protocol of early aggressive acceleration of tube feeding increases ileus without perceptible benefit in severely burned patients. *J Burn Care Res*. 2013;34(5):515-520.
50. Davies A. A multicenter, randomized controlled trial comparing early nasojejunal with nasogastric nutrition in critical illness. *Crit Care Med*. 2012;40(8):2342-2348.
51. Montejo J. Gastric residual volume during enteral nutrition in ICU patients: the REGANE study. *Intensive Care Med*. 2010;36(8):1386-1393.
52. Reignier J. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial. *JAMA*. 2013;309(3):249-256.
53. Deane A. Comparisons between intragastric and small intestinal delivery of enteral nutrition in the critically ill: a systematic review and meta-analysis. *Crit Care*. 2013;17(3):R125.
54. Pontes-Arruda A. Enteral nutrition with eicosapentaenoic acid, gamma-linolenic acid and antioxidants in the early treatment of sepsis: results from a multicenter, prospective, randomized, double-blinded, controlled study: the INTERSEPT study. *Crit Care*. 2011;15(3):R144.
55. Lin J. A meta-analysis of trials using the intention to treat principle for glutamine supplementation in critically ill patients with burn. *Burns*. 2013;39(4):565-570.
56. Coudray-Lucas C. Ornithine alpha-ketoglutarate improves wound healing in severe burn patients: a prospective randomized double-blind trial versus isonitrogenous controls. *Crit Care Med*. 2000;28(6):1772-1776.
57. De Bandt J. Therapeutic use of branched-chain amino acids in burn, trauma, and sepsis. *J Nutr*. 2006;136(1S):308S-313S.

58. De Bandt J. A randomized controlled trial of the influence of the mode of enteral ornithine alpha-ketoglutarate administration in burn patients. *J Nutr*. 1998;128(3):563-569.
59. Garrel D. Decreased mortality and infectious morbidity in adult burn patients given enteral glutamine supplements: a prospective, controlled, randomized clinical trial. *Crit Care Med*. 2003;31(10):2444-2449.
60. Garrel D. The effect of supplemental enteral glutamine on plasma levels, gut function, and outcome in severe burns. *JPEN J Parenter Enteral Nutr*. 2004;28(2):123.
61. Le Bricon T. Ornithine alpha-ketoglutarate metabolism after enteral administration in burn patients: bolus compared with continuous infusion. *Am J Clin Nutr*. 1997;65(2):512-518.
62. Peng X. Clinical and protein metabolic efficacy of glutamine granules-supplemented enteral nutrition in severely burned patients. *Burns*. 2005;31(3):342-346.
63. Peng X. Effects of enteral supplementation with glutamine granules on intestinal mucosal barrier function in severe burned patients. *Burns*. 2004;30(2):135-139.
64. Peng X. Glutamine granule-supplemented enteral nutrition maintains immunological function in severely burned patients. *Burns*. 2006;32(5):589-593.
65. Wischmeyer P. Glutamine administration reduces Gram-negative bacteremia in severely burned patients: a prospective, randomized, double-blind trial versus isonitrogenous control. *Care Med*. 2001;29(11):2075-2080.
66. Doig G. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a full economic analysis of a multicenter randomized controlled trial based on US costs. *Clinicoecon Outcomes Res*. 2013;5:369-379.
67. Heidegger C. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. *Lancet*. 2013;381(9864):385-393.
68. Kutsogiannis J. Early use of supplemental parenteral nutrition in critically ill patients: results of an international multicenter observational study. *Crit Care Med*. 2011;39(12):2691-2699.
69. Singer P. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Med*. 2011;37(4):601-609.
70. Harvey S. Trial of the route of early nutritional support in critically ill adults. *N Engl J Med*. 2014;371(18):1673-1684.
71. Herndon D. Failure of TPN supplementation to improve liver function, immunity, and mortality in thermally injured patients. *J Trauma*. 1987;27(2):195-204.
72. Herndon D. Increased mortality with intravenous supplemental feeding in severely burned patients. *J Burn Care Rehabil*. 1989;10(4):309-313.
73. Mochizuki 1984 (missing).
74. Briet 2001 (missing).
75. Casaer, 2011 (missing).
76. De Jonghe B, Appere-de-vechi C, Fournier M. A prospective survey of nutritional support practices in intensive care unit patients: what is prescribed? What is delivered? *Crit Care Med*. 2001;29(1):8-12.
77. Sudenis T, Hall K. Enteral nutrition: what the dietitian prescribes is not what the burn patient gets! *J Burn Care Res*. 2015;36(2):297-305.
78. Lavrentieva AT. Enteral nutrition intolerance in critically ill septic burn patients. *J Burn Care Res*. 2014;35(4):313-318.
79. Boullata J. Accurate determination of energy needs in hospitalized patients. *J Am Diet Assoc*. 2007;107(3):393-401.
80. Shields B. Determination of resting energy expenditure after severe burn. *J Burn Care Res*. 2013;34(1):e22-e28.
81. Newsome TA. Weight loss following thermal injury. *Ann Surg*. 1973;178(2):215-217.
82. Hart D. Persistence of muscle catabolism after severe burn. *Surgery*. 2000;128(2):312-319.
83. Porter C. Long-term skeletal muscle mitochondrial dysfunction is associated with hypermetabolism in severely burned children. *J Burn Care Res*. 2016;37(1):53-63.
84. Choban P. A.S.P.E.N. Clinical guidelines: nutrition support of hospitalized adult patients with obesity. *JPEN J Parenter Enteral Nutr*. 2013;37(6):714-744.
85. Jensen G. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. *JPEN J Parenter Enteral Nutr*. 2010;34(2):156-159.
86. Tillquist M. Bedside ultrasound is a practical and reliable measurement tool for assessing quadriceps muscle layer thickness. *JPEN J Parenter Enteral Nutr*. 2014;38(7):886-890.
87. Gruther W. Muscle wasting in intensive care patients: ultrasound observation of the M. quadriceps femoris muscle layer. *J Rehabil Med*. 2008;40(3):185-189.
88. Ishida S. Serum albumin levels correlate with inflammation rather than nutrition supply in burns patients: a retrospective study. *J Med Invest*. 2014;61(3-4):361-368.
89. Yang H. Serum transthyretin level is associaated with clinical severity rather than nutrition status in massively burned patients. *JPEN J Parenter Enteral Nutr*. 2014;38(8):966-972.

29 Modulation of the Hypermetabolic Response after Burn Injury

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Introduction

A severe burn elicits a stress response that initially assists the body in compensating for and adapting to a traumatic injury. There is an elevation in circulating concentrations of catecholamines such as epinephrine and norepinephrine alongside a concurrent increase in inflammatory cytokine production. This stress response is also associated with a significant increase in metabolic rate.[1–3] Altered protein and glucose metabolism are key factors contributing to burn-induced hypermetabolism.[4] This hypermetabolic, hyperinflammatory state promotes muscle protein catabolism and organ failure, among other detrimental effects.[5] If this response continues unchecked, as occurs in severely burned patients, the resultant hypermetabolic state hinders patient recovery and reintegration into society. Thus the mechanisms underlying the development and persistence of the post-burn stress response, as well as interventions to ameliorate these responses, remain areas of intense research.

Cardiovascular Dysfunction

One of the most profound and well-documented components of the burn-induced hypermetabolic response is cardiac dysfunction. Immediately following injury, patients experience shock accompanied by reduced heart rate, cardiac output, and contractility. By 2–3 days after injury, the cardiovascular system rebounds, and heart rate and cardiac work increase significantly above normal levels.[6,7] Post-burn heart rates approach 160% of those in nonburned, healthy patients.[5] Systolic dysfunction and increased myocardial energy demand also occur.[8,9] These alterations in cardiac function are associated with longer stays in the ICU in addition to increased morbidity, as quantified by number of surgical interventions.[10] Furthermore tachycardia and energy expenditure remained elevated for up to 3 years after the external wounds were healed, underscoring the longevity of the cardiovascular response to severe burns.[11,12]

Skeletal Muscle Catabolism and Regeneration

Post-burn pathophysiological skeletal muscle catabolism and loss of lean body mass (LBM) significantly prolong rehabilitation. Muscle wasting occurs due to an imbalance in the ratio of protein synthesis to protein breakdown.[13] Catabolism of LBM correlates with increased morbidity and mortality in burn victims. After an LBM loss of 10%, marked delays in wound healing and higher infection rates proportionally increase as the percentage of LBM loss increases.[14] Acutely the net LBM losses from muscle wasting lead to prolonged mechanical ventilation, inhibition of cough reflexes, and a delay in mobilization, contributing to increased mortality in these patients.[15] Chronically these losses reduce strength and the possibility for full rehabilitation. Similar to other characteristics of hypermetabolism, burn-related cachexia can continue for several years following injury.[3] Furthermore, persistent protein catabolism has been hypothesized to account for the growth delay that frequently occurs in our pediatric burn patients.[16]

LBM wasting is hypothesized to be due to a redistribution of protein as well as use of the skeletal muscle as a fuel source.[8] Nitrogen balance studies (whole-body and cross-leg) show persistent muscle breakdown for nearly a year post-burn.[17] Our patients experience an average nitrogen loss of 20–25 grams per square meter of total body surface area (TBSA) per day, a rate at which lethal muscle cachexia becomes imminent in less than 1 month if left untreated.[8] Since a significant portion of insulin-stimulated glucose uptake occurs in the skeletal muscle, significant LBM loss may contribute to post-burn insulin resistance.[18] Flakoll and coworkers showed that increased plasma glucose levels stimulated whole-body proteolysis in the absence of changes in leucine oxidation or nonoxidative disposal.[19] While LBM catabolism is elevated, a decrease in regenerative capacity occurs, further reducing LBM. Satellite cells, the muscle stem cells that regenerate skeletal muscle, are impacted by burn injury. Within the skeletal muscle tissue, although there is an increase in satellite cell proliferation, there is a concurrent increase in apoptosis, leading to a net reduction in satellite cells. The end result of the increase in net protein breakdown alongside a decrease in satellite cells appears to be a reduction in total LBM.[20]

In addition to the alterations in skeletal muscle protein synthesis, breakdown, and regeneration, oxygen consumption is also greatly increased after burn injury.[21] However the molecular mechanism underlying these alterations is not clearly defined. Recently Porter and colleagues reported burn-induced derangements of skeletal muscle mitochondrial function and posited that these changes are a key contributor to the mechanism of burn-induced

hypermetabolism.[22] Mitochondrial respiration in severely burned patients is uncoupled for more than 1 year post-burn, resulting in increased heat production. This heat production accounts for nearly a third of the total energy expenditure of the patient and provides a novel therapeutic target to alleviate hypermetabolism.[23,24]

Insulin Resistance and Hyperglycemia

Hyperglycemia is another common metabolic derangement in response to burn injury that occurs in both pediatric and adult burn patients and persists well after the initial discharge from the ICU.[7,25,26] Insulin resistance and hyperglycemia contribute to poor wound healing as well as muscle catabolism.[27–29] Elevated cortisol and catecholamine levels increase the delivery of glucose to vital organs, thus inhibiting insulin's anabolic functions.[30] Catecholamines impair glucose disposal and contribute to peripheral insulin resistance by inhibiting both insulin release and glucose uptake (Fig. 29.1).[31,32] The availability of gluconeogenic substrates such as glycerol lactate and alanine is increased by lipolysis of adipose tissue, glycogenolysis, and proteolysis of skeletal muscle post-burn, which augments hepatic glucose production (Fig. 29.1).[31,33–37] Moreover, elevated blood glucose levels fail to suppress hepatic glucose release, exacerbating hyperglycemia in burn patients.[38] This is further complicated by catecholamine-mediated glycogen breakdown.[35] Impaired mitochondrial function in the liver and the skeletal muscle has been associated with altered lipolysis and insulin signaling post-burn by dampening insulin's inhibition of glucose production in the liver and altering glucose uptake into skeletal muscle.[33,38–40] Glucagon and pro-inflammatory cytokines such as interleukin-6 (IL-6) also play a role in modulating glycogenolysis, gluconeogenesis, and insulin signal transduction, resulting in further augmentation of hyperglycemia and insulin resistance.[41–49]

Alterations in Lipid Metabolism and Fat Composition

Catecholamine-induced lipolysis increases plasma free fatty acid concentrations, which contributes to organ steatosis and insulin resistance in patients with severe burns. Kraft et al. showed that increased plasma triglyceride levels in severely burned children correlated with poorer outcomes, including impaired organ function, thus confirming an earlier report linking elevated triglycerides with morbidity.[50,51] Loss of peripheral subcutaneous fat may also play a role in the development and persistence of insulin resistance after a severe burn.[52] Recently browning of white adipose tissue (the adoption of a thermogenic brown phenotype by

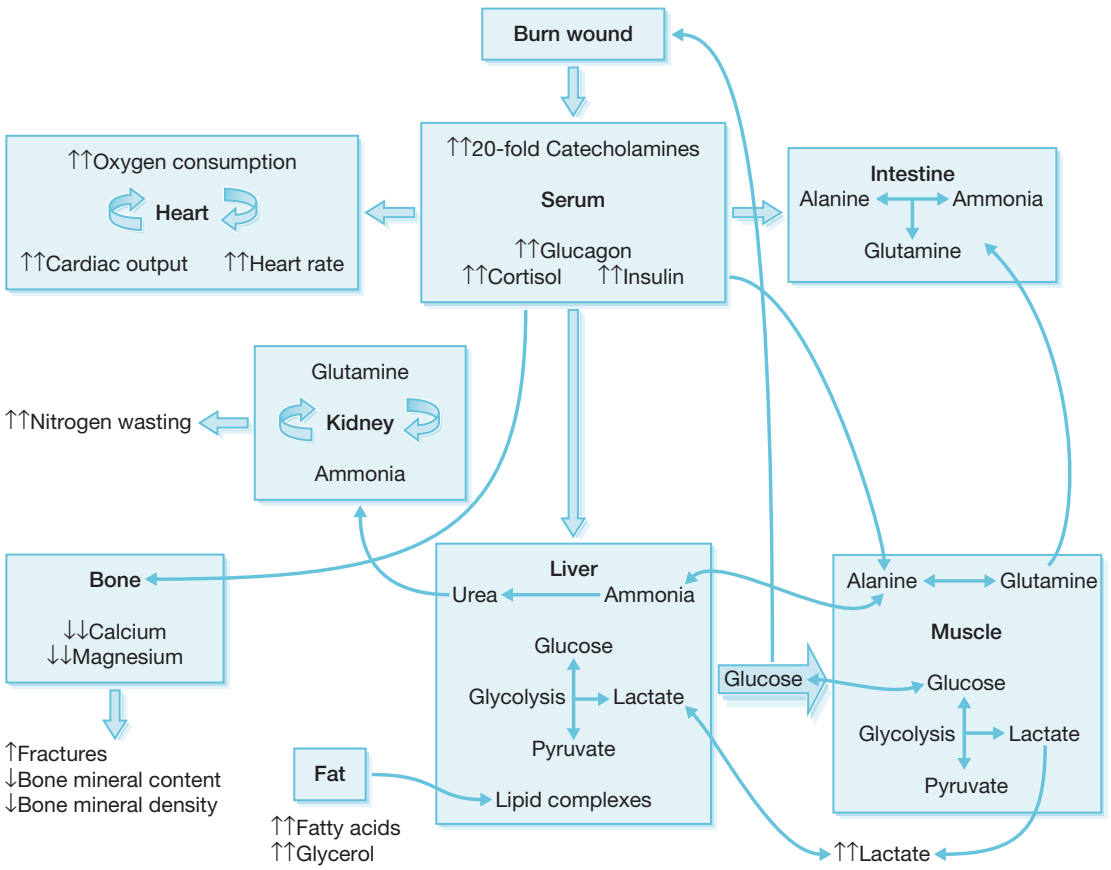

Fig. 29.1 The effects of metabolic dysfunction after severe burn injury. (From Williams FN, Jeschke MG, Chinkes DL, Suman OE, Branski LK, Herndon DN. Modulation of the hypermetabolic response to trauma: temperature, nutrition, and drugs. *J Am Coll Surg.* 2009;208(4):489–502.)

white adipocytes) and the implications this potentially has for patients with diabetes and/or metabolic syndrome has become the topic of intense research. White adipose tissue isolated from severely burned patients underwent browning, where the development of smaller adipocytes with more mitochondria in addition to elevated expression of uncoupling protein 1 were observed.[53] This response has since been confirmed by others, affirming that increased adrenergic and inflammatory stress in white adipose tissue post-burn is associated with browning.[54] Browning of white adipose tissue has been proposed to play a role in burn-induced hypermetabolism, where adipose tissue becomes a more thermogenic tissue in response to severe burn trauma. Emphasis of future research should be placed on developing both nonpharmacologic and pharmacologic therapeutic approaches to attenuate or reverse this hypermetabolic response in adipose tissue.

Nonpharmacological Modulation of the Hypermetabolic Response

ENVIRONMENTAL SUPPORT

In addition to acting as a protective barrier, the skin plays a critical role in insulation and thermoregulation. Burn patients with extensive burn wounds and skin loss also lose a significant portion of body water, which is also accompanied by heat loss.[55] Despite increased water evaporation and heat loss, core and skin temperatures are elevated in these patients.[56] Resting energy expenditure is increased more than twofold post-burn (prior to current treatments such as early wound excision) but can be reduced by approximately 30% by increasing the temperature of the room and using occlusive wound dressings.[56] Thus environmental modulation is a key primary treatment goal that is too often underutilized.

EARLY WOUND EXCISION AND CLOSURE

The practice of early excision of necrotic tissue and burn wound closure has improved mortality and morbidity rates.[57–59] Early burn wound closure is also associated with diminished incidence of excessive scars and joint contractures, which results in faster patient rehabilitation.[57] The use of various skin substitutes to cover wounds can reduce hypermetabolism by restoring the protective barrier required for thermoregulation and prevention of heat loss and water evaporation. Of note, blood loss is a critical issue during these operations, as approximately 5% of the total blood volume is lost with the excision of every 1% of the body surface.[60,61] Blood loss is a major determinant of morbidity and mortality, and a variety of techniques need to be used to control bleeding, including the local application of fibrin or thrombin sprays, epinephrine-soaked pads (1 : 40 000), topically administered epinephrine (1 : 10 000–1 : 20 000), or electrocautery of blood vessels.[62] Additional use of tourniquets for pre-excisional tumescence with epinephrine and saline may also help limit blood loss.[63] Thus novel skin substitutes and therapies to improve wound healing and prevent blood loss are the focus of ongoing research.

NUTRITIONAL SUPPORT

Adequate nutrition is a critical issue for severely burned patients because patients treated solely with oral supplementation may still lose one-quarter of their preadmission weight within the first several weeks.[64] The marked post-burn changes in lipid, carbohydrate, and protein metabolism determine the caloric needs of each respective patient. Insufficient nutrition may exacerbate muscle wasting and prolong wound healing. However high-fat nutritional intake is associated with obesity and hepatic steatosis after burn injury, negatively impacting morbidity and mortality.[65,66] Caloric enteral intake guided by energy expenditure is currently recommended to provide sufficient energy while avoiding overfeeding, which may exacerbate hypermetabolism.[8,57] Over the past 40 years, several formulas have been derived to calculate patient-specific caloric requirements including the Curreri formula (25 kcal/kg per day plus 40 kcal/% TBSA burned per day).[67–70] Recently, the European Society for Clinical Nutrition and Metabolism and the American Society for Parenteral and Enteral Nutrition released guidelines recommending that enteral feeding begin as soon as possible after admission with 1.5–2 g/kg and 3 g/kg of protein for severely burned adults and children, respectively.[71,72] Many ICUs deliver a substantial percentage of calories as fat (>25%) because essential fatty acid deficiency frequently accompanies long-term nutritional supplementation.[73] This approach reduces carbohydrate requirements and burn-induced glucose intolerance, and, therefore, dietary compositions of 30–50% fat are now the standard of care when treating critically ill patients. Unfortunately enhanced fat administration in burn patients is associated with hepatic steatosis, hypoxemia, hyperlipidemia, higher infection rates, and higher postoperative mortality rates.[51,74] Hepatic triglyceride levels are higher, thereby limiting the utility of exogenous lipids as a post-burn energy source.[33,73,76,77] The incidence of fatty liver is reduced in patients receiving Vivonex T.E.N. compared to those fed milk.[78] Additional benefits attributed to Vivonex T.E.N. included improved survival, significantly lower incidences of sepsis, and reduced length of ICU stay per %TBSA.[78] A high-carbohydrate enteral diet was associated with a reduction in muscle wasting compared to a high-fat, low-carbohydrate formula.[79] We thus advocate nutritional regimens for burn patients that reduce fat intake to no more than 3% of the total energy provided.

EXERCISE

Despite nutritional interventions, cachexia and wound contractures are common comorbidities of major burns.[17] While undergoing the hormone and inflammatory stress responses, patients with large burns are immobile for extended periods, further prolonging rehabilitation and recovery. The utilization of exercise therapy attenuates loss of muscle mass and function and improves cardiopulmonary function. A regimented exercise program improved pulmonary and skeletal muscle function in both pediatric and adult burn patients.[80–83] A 12-week exercise program beginning immediately following discharge from the ICU also significantly increased percent predicted peak heart rate and maximal oxygen consumption.[84] Progressive resistance

exercises maintain or even increase LBM, facilitate the formation of muscle proteins by incorporating amino acids, enhance muscle strength, and increase walking distances by 50%.[82,85] Celis et al. reported fewer corrective surgeries in burned children after resistance exercise training.[86] Similarly, Paratz et al. reported that severely burned adults who participated in an exercise program required fewer contracture releases.[87]

Recent studies have shown that exercise training in adults improves psychosocial outcomes, such as quality of life, in addition to the expected improvements in physical function.[87] This finding was corroborated by Rosenberg and colleagues in pediatric patients.[88] The combination of exercise training and pharmacological therapies to attenuate hypermetabolism, such as propranolol or oxandrolone, is also being investigated. Peak oxygen consumption was significantly higher in patients receiving both propranolol and exercise training.[89] The combination of oxandrolone and exercise resulted in a significant increase in lean body mass.[90] Finally Wurzer et al. reported that the benefits of a 12-week post-ICU discharge exercise program were no longer apparent at 2 years post-burn, indicating that patients should continue to exercise to maintain the aforementioned benefits.[84]

Pharmacological Modulation of the Hypermetabolic Response

RECOMBINANT HUMAN GROWTH HORMONE (rhGH)

As demonstrated by our group, during the acute hospitalization period, daily intramuscular injection of rhGH (0.2 mg/kg) reduces the hepatic acute-phase response, improves muscle protein kinetics, maintains muscular growth, blunts hypermetabolism, reduces cardiac output, and decreases donor site healing times by approximately 1.5 days.[91–96] Pediatric patients receiving rhGH for 1 year had significantly higher body weight and LBM at the end of the treatment period compared to their placebo-treated counterparts. Additionally rhGH-treated patients had improved growth as measured by bone mineral content and height percentiles at both 1 and 2 years after injury.[95] Similar improvements with rhGH treatment, such as increased LBM and muscle strength, have been reported in burned adults.[97]

RhGH mediates its effects through its secondary mediator insulin-like growth factor 1 (IGF-1).[98] In patients receiving rhGH, serum IGF-1 and IGF-binding protein (IGFBP)-3 increased 100% over the levels measured in healthy controls.[99] Nevertheless, as demonstrated in a study by Takala and colleagues, in 532 nonburned critically ill patients, increased rhGH (0.10 ± 0.02 mg/kg) correlated with increased morbidity and mortality rates and was associated with hyperglycemia and insulin resistance.[100–102] This may be reflective of an age-specific effect, however, because in severely burned children, mortality rates were not affected by either short- or long-term rhGH administration.[95,103] However rhGH-treated burn patients did display an increased incidence of hyperglycemic episodes and increased plasma levels of free fatty acids and triglycerides.[91]

INSULIN-LIKE GROWTH FACTOR-1

Since the positive effects of rhGH on the post-burn hypermetabolic response are predominantly mediated by the secondary mediator IGF-1, it is not surprising that administration of recombinant human IGF-1 would have similar results. Indeed, administration of equimolar amounts of recombinant human IGF-1 along with its binding protein, IGFBP-3, attenuated muscle catabolism, restored gut mucosal integrity, enhanced immune function, and returned serum concentrations of constitutive proteins to nonburned levels.[104–108] However the administration of IGFBP-3 was associated with increased neuropathies in this patient population and is not currently recommended for clinical use.

OXANDROLONE

The use of oxandrolone, an analog of testosterone possessing only 5% of testosterone's virilizing androgenic effects, enhances anabolism of muscle protein by improving the efficiency of protein synthesis in severely burned children.[109] Oxandrolone administration decreases loss of body weight and improves healing of the donor site wound.[110] In a large clinical trial by our group, 0.1 mg/kg oxandrolone administered twice daily reduced length of the acute hospitalization, sustained LBM, and improved liver protein synthesis.[111] Severely burned pediatric patients receiving oxandrolone for 1 year experienced improved growth, decreased cardiac work, and improved muscle strength.[112] Oxandrolone treatment also improved lung function at rest and during exercise in this patient population.[113] These improvements were maintained for up to 4 years after treatment had ended.[112] The benefits of oxandrolone administration after burn injury were further enhanced when the treatment period was increased from 1 to 2 years.[114]

PROPRANOLOL

The catecholamines norepinephrine and epinephrine activate cardiac β-adrenergic receptors to increase heart rate and cardiac work in response to severe burn trauma. Propranolol is a nonspecific β-adrenergic antagonist that prevents catecholamine activation of β-adrenergic receptor-mediated signal transduction. The administration of propranolol (titrated to decrease heart rate by 15–20%) diminishes cardiac work and reduces hepatic steatosis, as shown in several studies.[9,77,115–118] Also, administration of propranolol leads to reduced skeletal muscle catabolism and increased LBM post-burn, as demonstrated using stable isotope studies and body composition analysis.[5] In the post-burn environment of heightened protein breakdown and peripheral lipolysis, propranolol enhances protein synthesis and improves post-burn morbidity.[119,120] Similar to oxandrolone, long-term propranolol administration was associated with decreased cardiac work, resting energy expenditure, and other key markers of the hypermetabolic, hypercatabolic response to burn injury.[118] Furthermore patients treated with propranolol for 12 months showed improved LBM accretion and reduced bone mass.[118] While the majority of investigation into the use of propranolol post-burn has been in pediatric patients, we have shown that, in adult

patients, propranolol administration can reduce blood loss as well as improve wound healing.[121] Thus, β-adrenergic blockade with propranolol may represent the most efficacious anti-catabolic therapy for severe burns.

There are also several published studies that investigated the use of rhGH in severely burned patients who were also receiving propranolol. The premise of these studies was that the co-administration of rhGH and propranolol would have an additive effect to reduce post-burn hypermetabolism and catabolism. In a cross-over study of six burned children, heart rate and the rate of release of free fatty acids were significantly reduced with co-administration of propranolol and rhGH.[119] In a later study, there was no evidence of an additive effect of combining rhGH and propranolol, although propranolol did reduce heart rate and energy expenditure and improve anabolism. This study also did not find evidence of an anabolic effect of rhGH alone.[122] A prospective randomized control led trial of rhGH and propranolol co-administration showed that the addition of propranolol reduced rhGH side effects by reducing peripheral lipolysis and inflammation.[123] These data indicate that the beneficial effects of these drugs have different mechanisms and do not display characteristics of a synergistic or additive relationship.

Recently we investigated whether co-administration of oxandrolone and propranolol would further improve post-burn outcomes. Indeed, co-administration of these drugs decreased duration of growth arrest and increased growth rate following the resumption of growth in pediatric burned patients.[124] Thus oxandrolone, either alone or with propranolol co-administration, is a viable and promising therapeutic for attenuating post-burn hypermetabolism and catabolism.

INSULIN

Like other components of the stress response to burns, hyperglycemia and insulin resistance persist for up to 3 years post-injury and may have further long-term health implications for burn survivors.[7,17,27] The most common in-hospital treatment for post-burn hyperglycemia is insulin administration. In addition to its well-known effects on gluconeogenesis, proteolysis, and fatty acid synthesis, insulin also promotes antiinflammatory signaling pathways. Pediatric burn patients treated with insulin had significantly better outcomes as evidenced by faster wound healing and reduced muscle wasting.[125–127] Despite these improvements, insulin administration in this patient population must be performed cautiously. Studies in critically ill patients using either an intensive insulin dosing regimen or a continuous hyperinsulinemic, euglycemic clamp showed that high insulin doses increased episodes of severe hypoglycemia.[128–132] In addition to the risks associated with high doses of insulin, it is difficult to maintain a continuous hyperinsulinemic, euglycemic clamp in severely burned patients because of their dependence on enteral feeding in the early stages of recovery. Burned patients also undergo frequent procedures that require the cessation of enteral nutrition, such as operations and dressing changes. These periods of feeding cessation result in an increased risk of hypoglycemia.[8] In a study of 243 severely burned children, those who did not receive insulin had shorter length of stay and no mortality compared to children who received insulin. Therefore, burned patients receiving insulin had significantly higher resting energy expenditure and mortality rates than patients who did not receive insulin.[133] These results indicate that, although attenuating some aspects of the post-burn hypermetabolic response, insulin treatment may still contribute to post-burn morbidities and should be used with caution.

METFORMIN

Metformin is a biguanide drug that corrects hyperglycemia by stimulating peripheral glucose disposal and blunting hepatic glucose production. Moreover, unlike insulin, metformin is not associated with hypoglycemic events.[134–136] In severely burned patients, metformin not only improved glucose levels but also improved muscle protein synthesis.[136,137] A recent study in burned adult patients confirmed the benefits of metformin treatment on glucose levels and insulin resistance.[138] Similar to insulin, metformin reduced the post-burn inflammatory response.[138] Insulin sensitivity was also enhanced with metformin administration.[139] One contraindication of metformin administration in burned patients is the development of lactic acidosis.[140] There has been one case report of lactic acidosis in a burn patient who was receiving metformin clinically for type 2 diabetes mellitus prior to injury.[141] However, in a cohort of 18 metformin-treated severely burned adult patients, lactic acidosis was not observed.[138] Studies are ongoing to evaluate the incidence of lactic acidosis in burn patients and whether metformin will continue to be a valid hyperglycemia treatment in this patient population. Preliminary data indicate that metformin is safe and effective in severely burned patients.[138]

Alternative Therapeutic Options

There have been a variety of drugs investigated to attenuate the post-burn hypermetabolic hypercatabolic response. Many of these drugs work to resolve hyperglycemia, such as glucagon-like-peptide-1 (GLP-1) and peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists. An analog of GLP-1, exenatide, decreased burn-induced hyperglycemia but required adjunctive insulin therapy to be effective.[142] Fenofibrate, a PPAR-γ agonist, not only improved plasma glucose levels but also improved insulin signaling in the muscle and liver, with the end result of increased insulin sensitivity.[38] Fenofibrate also improved skeletal muscle mitochondrial enzyme activity and respiratory function as well as whole-body and muscle fat oxidation.[38,143] Ketoconazole is an antifungal agent that has been shown to reduce cortisol production, and it was hypothesized that cortisol reduction would diminish post-burn hypermetabolism and inflammation. However, despite effectively reducing urine cortisol levels, ketoconazole did not significantly reduce any other aspect of the hypermetabolic response.[144]

Conclusion

The physiologically exhaustive metabolic derangements accompanying severe burns contribute to morbidity and mortality in this patient population. Outcomes for these

Table 29.1 Summary of the Effects of Various Pharmacologic Interventions on Key Components of the Hypermetabolic Response to Burn Injury

Drug	Cardiovascular	Skeletal Muscle	Insulin Resistance	Lipid Metabolism and Fat Composition
rhGH	↓Cardiac output	↑Protein kinetics ↑Body weight ↑Bone mineral content ↑Height percentiles	↑Hyperglycemia	Unknown
IGF-I	Unknown	↓Muscle catabolism	↑Insulin sensitivity hypoglycemia	Unknown
Oxandrolone	↓Cardiac work ↓Lung function	↑Protein synthesis ↓Loss of lean body mass ↑Growth ↑Muscle strength	No difference	↓Free fatty acids
Insulin	↑Resting energy expenditure	↓Loss of lean body mass	↓Hyperglycemia	↑Liver fat ↑Free fatty acids ↓Fat oxidation
Metformin	↑Resting energy expenditure	↑Protein synthesis	↓Hyperglycemia ↑Insulin sensitivity	Antilipolytic
Fenofibrate	Unknown	↑Mitochondrial enzyme activity	↓Hyperglycemia ↑Insulin sensitivity	↑Fat oxidation
GLP-1	No difference	Unknown	↓Hyperglycemia	Unknown
Propranolol	↓Cardiac work ↓Tachycardia ↓Resting energy expenditure	↓Skeletal muscle catabolism ↑Lean body mass	↑Insulin sensitivity	↓Hepatic steatosis ↓Free fatty acids
Ketoconazole	No difference	No difference	No difference	No difference
rhGH + propranolol	↓Resting energy expenditure ↓Cardiac work	↓Skeletal muscle catabolism ↑Lean body mass	↑Insulin sensitivity	↓Free fatty acids
Oxandrolone + propranolol	Unknown	↓Duration of growth arrest ↑Growth rate	Unknown	Unknown

patients have been significantly improved by advances in nonpharmacologic and pharmacologic therapies (Table 29.1). However therapeutic strategies to abate the persistent hypermetabolism and hyperglycemia remain challenging. Early burn wound excision and grafting represents one of the greatest improvements in the past two decades, improving both morbidity and mortality. Currently the most effective therapy to reduce the burn-induced hypermetabolic and hypercatabolic responses is β-adrenergic blockade via propranolol administration. rhGH, IGF-1, and oxandrolone (Table 29.1) have also been successfully used in the attenuation of the hypermetabolic and hypercatabolic responses. While intensive insulin therapy can improve mortality and morbidity, there is a need for additional strategies, such as metformin, that lack the increased risk of hypoglycemic events associated with insulin treatment. Nonetheless further work is needed to elucidate the ideal glucose ranges and safety of the aforementioned therapies in this unique patient population.

Complete references available online at www.expertconsult.inkling.com

References

1. Hart DW, Wolf SE, Mlcak R, et al. Persistence of muscle catabolism after severe burn. *Surgery*. 2000;128(2):312-319.
2. Gore DC, Rutan RL, Hildreth M, Desai MH, Herndon DN. Comparison of resting energy expenditures and caloric intake in children with severe burns. *J Burn Care Rehabil*. 1990;11(5):400-404.
3. Jeschke MG, Gauglitz GG, Kulp GA, et al. Long-term persistance of the pathophysiologic response to severe burn injury. *PLoS ONE*. 2011;6(7):e21245.
4. Yu YM, Tompkins RG, Ryan CM, Young VR. The metabolic basis of the increase of the increase in energy expenditure in severely burned patients. *JPEN J Parenter Enteral Nutr*. 1999;23(3):160-168.
5. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR. Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med*. 2001;345(17):1223-1229.
6. Wolfe RR. Review: acute versus chronic response to burn injury. *Circ Shock*. 1981;8(1):105-115.
7. Jeschke MG, Chinkes DL, Finnerty CC, et al. Pathophysiologic response to severe burn injury. *Ann Surg*. 2008;248(3):387-401.
8. Herndon DN, Tompkins RG. Support of the metabolic response to burn injury. *Lancet*. 2004;363(9424):1895-1902.
9. Baron PW, Barrow RE, Pierre EJ, Herndon DN. Prolonged use of propranolol safely decreases cardiac work in burned children. *J Burn Care Rehabil*. 1997;18(3):223-227.
10. Howard TS, Hermann DG, McQuitty AL, et al. Burn-induced cardiac dysfunction increases length of stay in pediatric burn patients. *J Burn Care Res*. 2013;34(4):413-419.
11. Horton JW, Garcia NM, White DJ, Keffer J. Postburn cardiac contractile function and biochemical markers of postburn cardiac injury. *J Am Coll Surg*. 1995;181(4):289-298.
12. Mlcak RP, Suman OE, Murphy K, Herndon DN. Effects of growth hormone on anthropometric measurements and cardiac function in children with thermal injury. *Burns*. 2005;31(1):60-66.
13. Chao T, Herndon DN, Porter C, et al. Skeletal muscle protein breakdown remains elevated in pediatric burn survivors up to one-year post-injury. *Shock*. 2015;44(5):397-401.
14. McClave SA, Snider HL. Use of indirect calorimetry in clinical nutrition. *Nutr Clin Pract*. 1992;7(5):207-221.
15. Arora NS, Rochester DF. Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. *Am Rev Respir Dis*. 1982;126(1):5-8.
16. Rutan RL, Herndon DN. Growth delay in postburn pediatric patients. *Arch Surg*. 1990;125(3):392-395.
17. Hart DW, Wolf SE, Chinkes DL, et al. Determinants of skeletal muscle catabolism after severe burn. *Ann Surg*. 2000;232(4):455-465.
18. DeFronzo RA, Jacot E, Jequier E, et al. The effect of insulin on the disposal of intravenous glucose. Results from indirect calorimetry and hepatic and femoral venous catheterization. *Diabetes*. 1981;30(12):1000-1007.
19. Flakoll PJ, Hill JO, Abumrad NN. Acute hyperglycemia enhances proteolysis in normal man. *Am J Physiol*. 1993;265(5 Pt 1):E715-E721.
20. Fry CS, Porter C, Sidossis LS, et al. Satellite cell activation and apoptosis in skeletal muscle from severely burned children. *J Physiol*. 2016;594(18):5223-5236.
21. Wilmore DW, Aulick LH. Systemic responses to injury and the healing wound. *JPEN J Parenter Enteral Nutr*. 1980;4(2):147-151.
22. Porter C, Herndon DN, Borsheim E, et al. Long-term skeletal muscle mitochondrial dysfunction is associated with hypermetabolism in severely burned children. *J Burn Care Res*. 2016;37(1):53-63.
23. Porter C, Hurren NM, Herndon DN, Borsheim E. Whole body and skeletal muscle protein turnover in recovery from burns. *Int J Burns Trauma*. 2013;3(1):9-17.
24. Porter C, Herndon DN, Borsheim E, et al. Uncoupled skeletal muscle mitochondria contribute to hypermetabolism in severely burned adults. *Am J Physiol Endocrinol Metab*. 2014;307(5):E462-E467.
25. Fram RY, Cree MG, Wolfe RR, Barr D, Herndon DN. Impaired glucose tolerance in pediatric burn patients at discharge from the acute hospital stay. *J Burn Care Res*. 2010;31(5):728-733.
26. Rehou S, Mason S, Burnett M, Jeschke MG. Burned adults develop profound glucose intolerance. *Crit Care Med*. 2016;44(6):1059-1066.
27. Gauglitz GG, Herndon DN, Kulp GA, Meyer WJ 3rd, Jeschke MG. Abnormal insulin sensitivity persists up to three years in pediatric patients post-burn. *J Clin Endocrinol Metab*. 2009;94(5):1656-1664.
28. Mowlavi A, Andrews K, Milner S, Herndon DN, Heggers JP. The effects of hyperglycemia on skin graft survival in the burn patient. *Ann Plast Surg*. 2000;45(6):629-632.
29. Gore DC, Chinkes DL, Hart DW, et al. Hyperglycemia exacerbates muscle protein catabolism in burn-injured patients. *Crit Care Med*. 2002;30(11):2438-2442.
30. Khani S, Tayek JA. Cortisol increases gluconeogenesis in humans: its role in the metabolic syndrome. *Clin Sci*. 2001;101(6):739-747.
31. Gearhart MM, Parbhoo SK. Hyperglycemia in the critically ill patient. *AACN Clin Issues*. 2006;17(1):50-55.
32. Hunt DG, Ivy JL. Epinephrine inhibits insulin-stimulated muscle glucose transport. *J Appl Physiol*. 2002;93(5):1638-1643.
33. Wolfe RR, Herndon DN, Jahoor F, Miyoshi H, Wolfe M. Effect of severe burn injury on substrate cycling by glucose and fatty acids. *N Engl J Med*. 1987;317(7):403-408.
34. Gore DC, Jahoor F, Wolfe RR, Herndon DN. Acute response of human muscle protein to catabolic hormones. *Ann Surg*. 1993;218(5):679-684.
35. Robinson LE, van Soeren MH. Insulin resistance and hyperglycemia in critical illness: role of insulin in glycemic control. *AACN Clin Issues*. 2004;15(1):45-62.
36. Williams FN, Jeschke MG, Chinkes DL, et al. Modulation of the hypermetabolic response to trauma: temperature, nutrition, and drugs. *J Am Coll Surg*. 2009;208(4):489-502.
37. Carlson GL. Insulin resistance and glucose-induced thermogenesis in critical illness. *Proc Nutr Soc*. 2001;60(3):381-388.
38. Cree MG, Zwetsloot JJ, Herndon DN, et al. Insulin sensitivity and mitochondrial function are improved in children with burn injury during a randomized controlled trial of fenofibrate. *Ann Surg*. 2007;245(2):214-221.
39. Cree MG, Aarsland A, Herndon DN, Wolfe RR. Role of fat metabolism in burn trauma-induced skeletal muscle insulin resistance. *Crit Care Med*. 2007;35(9 suppl):S476-S483.
40. Wolfe RR, Durkot MJ, Allsop JR, Burke JF. Glucose metabolism in severely burned patients. *Metabolism*. 1979;28(10):1031-1039.
41. Gustavson SM, Chu CA, Nishizawa M, et al. Interaction of glucagon and epinephrine in the control of hepatic glucose production in the conscious dog. *Am J Physiol Endocrinol Metab*. 2003;284(4):E695-E707.
42. Mastorakos G, Chrousos GP, Weber JS. Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. *J Clin Endocrinol Metab*. 1993;77(6):1690-1694.
43. Lang CH, Dobrescu C, Bagby GJ. Tumor necrosis factor impairs insulin action on peripheral glucose disposal and hepatic glucose output. *Endocrinology*. 1992;130(1):43-52.
44. Akita S, Akino K, Ren SG, et al. Elevated circulating leukemia inhibitory factor in patients with extensive burns. *J Burn Care Res*. 2006;27(2):221-225.
45. Fan J, Li YH, Wojnar MM, Lang CH. Endotoxin-induced alterations in insulin-stimulated phosphorylation of insulin receptor, IRS-1, and MAP kinase in skeletal muscle. *Shock*. 1996;6(3):164-170.
46. del Aguila LF, Claffey KP, Kirwan JP. TNF-alpha impairs insulin signaling and insulin stimulation of glucose uptake in C2C12 muscle cells. *Am J Physiol*. 1999;276(5 Pt 1):E849-E855.
47. Sell H, Dietze-Schroeder D, Kaiser U, Eckel J. Monocyte chemotactic protein-1 is a potential player in the negative cross-talk between adipose tissue and skeletal muscle. *Endocrinology*. 2006;147(5):2458-2467.
48. Baracos V, Rodemann HP, Dinarello CA, Goldberg AL. Stimulation of muscle protein degradation and prostaglandin E2 release by leukocytic pyrogen (interleukin-1). A mechanism for the increased degradation of muscle proteins during fever. *N Engl J Med*. 1983;308(10):553-558.
49. Jahoor F, Desai M, Herndon DN, Wolfe RR. Dynamics of the protein metabolic response to burn injury. *Metabolism*. 1988;37(4):330-337.
50. Kraft R, Herndon DN, Finnerty CC, Hiyama Y, Jeschke MG. Association of postburn fatty acids and triglycerides with clinical outcome in severely burned children. *J Clin Endocrinol Metab*. 2013;98(1):314-321.
51. Barret JP, Jeschke MG, Herndon DN. Fatty infiltration of the liver in severely burned pediatric patients: autopsy findings and clinical implications. *J Trauma*. 2001;51(4):736-739.
52. Patel P, Sallam HS, Ali A, et al. Changes in fat distribution in children following severe burn injury. *Metab Syndr Relat Disord*. 2014;12(10):523-526.
53. Sidossis LS, Porter C, Saraf MK, et al. Browning of subcutaneous white adipose tissue in humans after severe adrenergic stress. *Cell Metab*. 2015;22(2):219-227.
54. Saraf MK, Herndon DN, Porter C, et al. Morphological changes in subcutaneous white adipose tissue after severe burn injury. *J Burn Care Res*. 2016;37(2):e96-e103.

55. Zawacki BE, Spitzer KW, Mason AD Jr, Johns LA. Does increased evaporative water loss cause hypermetabolism in burned patients? *Ann Surg*. 1970;171(2):236-240.
56. Wilmore DW, Mason AD Jr, Johnson DW, Pruitt BA Jr. Effect of ambient temperature on heat production and heat loss in burn patients. *J Appl Physiol*. 1975;38(4):593-597.
57. Ramzy PI, Barret JP, Herndon DN. Thermal injury. *Crit Care Clin*. 1999;15(2):333-352, ix.
58. Chan BP, Kochevar IE, Redmond RW. Enhancement of porcine skin graft adherence using a light-activated process. *J Surg Res*. 2002;108(1):77-84.
59. Munster AM, Smith-Meek M, Sharkey P. The effect of early surgical intervention on mortality and cost-effectiveness in burn care, 1978–91. *Burns*. 1994;20(1):61-64.
60. Budny PG, Regan PJ, Roberts AH. The estimation of blood loss during burns surgery. *Burns*. 1993;19(2):134-137.
61. Housinger TA, Lang D, Warden GD. A prospective study of blood loss with excisional therapy in pediatric burn patients. *J Trauma*. 1993;34(2):262-263.
62. Jeschke MG, Chinkes DL, Finnerty CC, et al. Blood transfusions are associated with increased risk for development of sepsis in severely burned pediatric patients. *Crit Care Med*. 2007;35(2):579-583.
63. Sheridan RL, Szyfelbein SK. Staged high-dose epinephrine clysis is safe and effective in extensive tangential burn excisions in children. *Burns*. 1999;25(8):745-748.
64. Newsome TW, Mason AD Jr, Pruitt BA Jr. Weight loss following thermal injury. *Ann Surg*. 1973;178(2):215-217.
65. Hart DW, Wolf SE, Chinkes DL, et al. Effects of early excision and aggressive enteral feeding on hypermetabolism, catabolism, and sepsis after severe burn. *J Trauma*. 2003;54(4):755-761, discussion 761-764.
66. Herndon DN, Barrow RE, Stein M, et al. Increased mortality with intravenous supplemental feeding in severely burned patients. *J Burn Care Rehabil*. 1989;10(4):309-313.
67. Curreri PW, Richmond D, Marvin J, Baxter CR. Dietary requirements of patients with major burns. *J Am Diet Assoc*. 1974;65(4):415-417.
68. Allard JP, Pichard C, Hoshino E, et al. Validation of a new formula for calculating the energy requirements of burn patients. *JPEN J Parenter Enteral Nutr*. 1990;14(2):115-118.
69. Hildreth MA, Herndon DN, Desai MH, Broemeling LD. Current treatment reduces calories required to maintain weight in pediatric patients with burns. *J Burn Care Rehabil*. 1990;11(5):405-409.
70. Herndon DN, Curreri PW. Metabolic response to thermal injury and its nutritional support. *Cutis*. 1978;22(4):501-506, 14.
71. Rousseau AF, Losser MR, Ichai C, Berger MM. ESPEN endorsed recommendations: nutritional therapy in major burns. *Clin Nutr*. 2013;32(4):497-502.
72. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2016;40(2):159-211.
73. Demling RH, Seigne P. Metabolic management of patients with severe burns. *World J Surg*. 2000;24(6):673-680.
74. Garrel DR, Razi M, Lariviere F, et al. Improved clinical status and length of care with low-fat nutrition support in burn patients. *JPEN J Parenter Enteral Nutr*. 1995;19(6):482-491.
75. Reference removed at revises
76. Aarsland A, Chinkes D, Wolfe RR. Contributions of de novo synthesis of fatty acids to total VLDL-triglyceride secretion during prolonged hyperglycemia/hyperinsulinemia in normal man. *J Clin Invest*. 1996;98(9):2008-2017.
77. Herndon DN, Nguyen TT, Wolfe RR, et al. Lipolysis in burned patients is stimulated by the beta 2-receptor for catecholamines. *Arch Surg*. 1994;129(12):1301-1304, discussion 1304-1305.
78. Lee JO, Gauglitz GG, Herndon DN, et al. Association between dietary fat content and outcomes in pediatric burn patients. *J Surg Res*. 2011;166(1):e83-e90.
79. Hart DW, Wolf SE, Zhang XJ, et al. Efficacy of a high-carbohydrate diet in catabolic illness. *Crit Care Med*. 2001;29(7):1318-1324.
80. Grisbrook TL, Wallman KE, Elliott CM, et al. The effect of exercise training on pulmonary function and aerobic capacity in adults with burn. *Burns*. 2012;38(4):607-613.
81. de Lateur BJ, Magyar-Russell G, Bresnick MG, et al. Augmented exercise in the treatment of deconditioning from major burn injury. *Arch Phys Med Rehabil*. 2007;88(12 suppl 2):S18-S23.
82. Al-Mousawi AM, Williams FN, Mlcak RP, et al. Effects of exercise training on resting energy expenditure and lean mass during pediatric burn rehabilitation. *J Burn Care Res*. 2010;31(3):400-408.
83. Suman OE, Mlcak RP, Herndon DN. Effect of exercise training on pulmonary function in children with thermal injury. *J Burn Care Rehabil*. 2002;23(4):288-293, discussion 7.
84. Wurzer P, Voigt CD, Clayton RP, et al. Long-term effects of physical exercise during rehabilitation in patients with severe burns. *Surgery*. 2016;160(3):781-788.
85. Cucuzzo NA, Ferrando A, Herndon DN. The effects of exercise programming vs traditional outpatient therapy in the rehabilitation of severely burned children. *J Burn Care Rehabil*. 2001;22(3):214-220.
86. Celis MM, Suman OE, Huang TT, Yen P, Herndon DN. Effect of a supervised exercise and physiotherapy program on surgical interventions in children with thermal injury. *J Burn Care Rehabil*. 2003;24 (1):57-61, discussion 56.
87. Paratz JD, Stockton K, Plaza A, Muller M, Boots RJ. Intensive exercise after thermal injury improves physical, functional, and psychological outcomes. *J Trauma Acute Care Surg*. 2012;73(1):186-194.
88. Rosenberg M, Celis MM, Meyer W 3rd, et al. Effects of a hospital based Wellness and Exercise program on quality of life of children with severe burns. *Burns*. 2013;39(4):599-609.
89. Porro LJ, Al-Mousawi AM, Williams F, et al. Effects of propranolol and exercise training in children with severe burns. *J Pediatr*. 2013;162(4):799-803.
90. Przkora R, Herndon DN, Suman OE. The effects of oxandrolone and exercise on muscle mass and function in children with severe burns. *Pediatrics*. 2007;119(1):e109-e116.
91. Jeschke MG, Barrow RE, Herndon DN. Recombinant human growth hormone treatment in pediatric burn patients and its role during the hepatic acute phase response. *Crit Care Med*. 2000;28(5):1578-1584.
92. Wu X, Herndon DN, Wolf SE. Growth hormone down-regulation of Interleukin-1beta and Interleukin-6 induced acute phase protein gene expression is associated with increased gene expression of suppressor of cytokine signal-3. *Shock*. 2003;19(4):314-320.
93. Aili Low JF, Barrow RE, Mittendorfer B, et al. The effect of short-term growth hormone treatment on growth and energy expenditure in burned children. *Burns*. 2001;27(5):447-452.
94. Hart DW, Herndon DN, Klein G, et al. Attenuation of posttraumatic muscle catabolism and osteopenia by long-term growth hormone therapy. *Ann Surg*. 2001;233(6):827-834.
95. Branski LK, Herndon DN, Barrow RE, et al. Randomized controlled trial to determine the efficacy of long-term growth hormone treatment in severely burned children. *Ann Surg*. 2009;250(4):514-523.
96. Herndon DN, Barrow RE, Kunkel KR, Broemeling L, Rutan RL. Effects of recombinant human growth hormone on donor-site healing in severely burned children. *Ann Surg*. 1990;212(4):424-429, discussion 430-431.
97. Kim JB, Cho YS, Jang KU, et al. Effects of sustained release growth hormone treatment during the rehabilitation of adult severe burn survivors. *Growth Horm IGF Res*. 2016;27:1-6.
98. Jeschke MG, Chrysopoulo MT, Herndon DN, Wolf SE. Increased expression of insulin-like growth factor-I in serum and liver after recombinant human growth hormone administration in thermally injured rats. *J Surg Res*. 1999;85(1):171-177.
99. Klein GL, Wolf SE, Langman CB, et al. Effects of therapy with recombinant human growth hormone on insulin-like growth factor system components and serum levels of biochemical markers of bone formation in children after severe burn injury. *J Clin Endocrinol Metab*. 1998;83(1):21-24.
100. Takala J, Ruokonen E, Webster NR, et al. Increased mortality associated with growth hormone treatment in critically ill adults. *N Engl J Med*. 1999;341(11):785-792.
101. Demling RH. Comparison of the anabolic effects and complications of human growth hormone and the testosterone analog, oxandrolone, after severe burn injury. *Burns*. 1999;25(3):215-221.
102. Gore DC, Honeycutt D, Jahoor F, et al. Effect of exogenous growth hormone on glucose utilization in burn patients. *J Surg Res*. 1991;51 (6):518-523.
103. Ramirez RJ, Wolf SE, Barrow RE, Herndon DN. Growth hormone treatment in pediatric burns: a safe therapeutic approach. *Ann Surg*. 1998;228(4):439-448.
104. Moller S, Jensen M, Svensson P, Skakkebaek NE. Insulin-like growth factor 1 (IGF-1) in burn patients. *Burns*. 1991;17(4):279-281.

105. Herndon DN, Ramzy PI, DebRoy MA, et al. Muscle protein catabolism after severe burn: effects of IGF-1/IGFBP-3 treatment. *Ann Surg*. 1999;229(5):713-720, discussion 720-722.
106. Spies M, Wolf SE, Barrow RE, Jeschke MG, Herndon DN. Modulation of types I and II acute phase reactants with insulin-like growth factor-1/binding protein-3 complex in severely burned children. *Crit Care Med*. 2002;30(1):83-88.
107. Jeschke MG, Herndon DN, Barrow RE. Insulin-like growth factor I in combination with insulin-like growth factor binding protein 3 affects the hepatic acute phase response and hepatic morphology in thermally injured rats. *Ann Surg*. 2000;231(3):408-416.
108. Cioffi WG, Gore DC, Rue LW 3rd, et al. Insulin-like growth factor-1 lowers protein oxidation in patients with thermal injury. *Ann Surg*. 1994;220(3):310-316, discussion 316-319.
109. Hart DW, Wolf SE, Ramzy PI, et al. Anabolic effects of oxandrolone after severe burn. *Ann Surg*. 2001;233(4):556-564.
110. Demling RH, Orgill DP. The anticatabolic and wound healing effects of the testosterone analog oxandrolone after severe burn injury. *J Crit Care*. 2000;15(1):12-17.
111. Jeschke MG, Finnerty CC, Suman OE, et al. The effect of oxandrolone on the endocrinologic, inflammatory, and hypermetabolic responses during the acute phase postburn. *Ann Surg*. 2007;246(3):351-360, discussion 360-362.
112. Porro LJ, Herndon DN, Rodriguez NA, et al. Five-year outcomes after oxandrolone administration in severely burned children: a randomized clinical trial of safety and efficacy. *J Am Coll Surg*. 2012;214(4):489-502, discussion 4.
113. Sousse LE, Herndon DN, Mlcak RP, et al. Long-term administration of oxandrolone improves lung function in pediatric burned patients. *J Burn Care Res*. 2016;37(5):273-277.
114. Reeves PT, Herndon DN, Tanksley JD, et al. Five-year outcomes after long-term oxandrolone administration in severely burned children: a randomized clinical trial. *Shock*. 2016;45(4):367-374.
115. Herndon DN, Barrow RE, Rutan TC, et al. Effect of propranolol administration on hemodynamic and metabolic responses of burned pediatric patients. *Ann Surg*. 1988;208(4):484-492.
116. Barrow RE, Wolfe RR, Dasu MR, Barrow LN, Herndon DN. The use of beta-adrenergic blockade in preventing trauma-induced hepatomegaly. *Ann Surg*. 2006;243(1):115-120.
117. Williams FN, Herndon DN, Kulp GA, Jeschke MG. Propranolol decreases cardiac work in a dose-dependent manner in severely burned children. *Surgery*. 2011;149(2):231-239.
118. Herndon DN, Rodriguez NA, Diaz EC, et al. Long-term propranolol use in severely burned pediatric patients: a randomized controlled study. *Ann Surg*. 2012;256(3):402-411.
119. Aarsland A, Chinkes D, Wolfe RR, et al. Beta-blockade lowers peripheral lipolysis in burn patients receiving growth hormone. Rate of hepatic very low density lipoprotein triglyceride secretion remains unchanged. *Ann Surg*. 1996;223(6):777-787, discussion 787-789.
120. Pereira CT, Jeschke MG, Herndon DN. Beta-blockade in burns. *Novartis Found Symp*. 2007;280:238-248, discussion 248-251.
121. Ali A, Herndon DN, Mamachen A, et al. Propranolol attenuates hemorrhage and accelerates wound healing in severely burned adults. *Crit Care*. 2015;19:217.
122. Hart DW, Wolf SE, Chinkes DL, et al. Beta-blockade and growth hormone after burn. *Ann Surg*. 2002;236(4):450-456, discussion 456-457.
123. Jeschke MG, Finnerty CC, Kulp GA, et al. Combination of recombinant human growth hormone and propranolol decreases hypermetabolism and inflammation in severely burned children. *Pediatr Crit Care Med*. 2008;9(2):209-216.
124. Herndon DN, Voigt CD, Capek KD, et al. Reversal of growth arrest with the combined administration of oxandrolone and propranolol in severely burned children. *Ann Surg*. 2016;264(3):421-428.
125. Jeschke MG, Klein D, Herndon DN. Insulin treatment improves the systemic inflammatory reaction to severe trauma. *Ann Surg*. 2004;239(4):553-560.
126. Dandona P, Chaudhuri A, Mohanty P, Ghanim H. Anti-inflammatory effects of insulin. *Curr Opin Clin Nutr Metab Care*. 2007;10(4):511-517.
127. Pidcoke HF, Wade CE, Wolf SE. Insulin and the burned patient. *Crit Care Med*. 2007;35(9 suppl):S524-S530.
128. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345(19):1359-1367.
129. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008;358(2):125-139.
130. Langouche L, Vanhorebeek I, Van den Berghe G. Therapy insight: the effect of tight glycemic control in acute illness. *Nat Clin Pract Endocrinol Metab*. 2007;3(3):270-278.
131. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36(1):296-327.
132. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. *JAMA*. 2003;290(15):2041-2047.
133. Finnerty CC, Ali A, McLean J, et al. Impact of stress-induced diabetes on outcomes in severely burned children. *J Am Coll Surg*. 2014;218(4):783-795.
134. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med*. 1995;333(9):541-549.
135. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1995;333(9):550-554.
136. Gore DC, Herndon DN, Wolfe RR. Comparison of peripheral metabolic effects of insulin and metformin following severe burn injury. *J Trauma*. 2005;59(2):316-322, discussion 322-323.
137. Gore DC, Wolf SE, Herndon DN, Wolfe RR. Metformin blunts stress-induced hyperglycemia after thermal injury. *J Trauma*. 2003;54(3):555-561.
138. Jeschke MG, Abdullahi A, Burnett M, Rehou S, Stanojcic M. Glucose control in severely burned patients using metformin: an interim safety and efficacy analysis of a phase II randomized controlled trial. *Ann Surg*. 2016;264(3):518-527.
139. Gore DC, Wolf SE, Sanford A, Herndon DN, Wolfe RR. Influence of metformin on glucose intolerance and muscle catabolism following severe burn injury. *Ann Surg*. 2005;241(2):334-342.
140. Luft D, Schmulling RM, Eggstein M. Lactic acidosis in biguanide-treated diabetics: a review of 330 cases. *Diabetologia*. 1978;14(2):75-87.
141. Riesenman PJ, Braithwaite SS, Cairns BA. Metformin-associated lactic acidosis in a burn patient. *J Burn Care Res*. 2007;28(2):342.
142. Mecott GA, Herndon DN, Kulp GA, et al. The use of exenatide in severely burned pediatric patients. *Crit Care*. 2010;14(4):R153.
143. Cree MG, Newcomer BR, Herndon DN, et al. PPAR-alpha agonism improves whole body and muscle mitochondrial fat oxidation, but does not alter intracellular fat concentrations in burn trauma children in a randomized controlled trial. *Nutr Metab (Lond)*. 2007;4:9.
144. Jeschke MG, Williams FN, Finnerty CC, et al. The effect of ketoconazole on post-burn inflammation, hypermetabolism and clinical outcomes. *PLoS ONE*. 2012;7(5):e35465.

30 Etiology and Prevention of Multisystem Organ Failure

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Introduction

Burn trauma begins via a cutaneous thermal injury with or without an inhalation injury. These local primary injuries initiate a series of pathophysiologic cascades previously discussed. Fluid shifts into thermally damaged tissue as well as global endothelial activation; glycocalyx damage and systemic inflammation cause burn edema. The resultant distributive shock combines with humorally mediated myocardial suppression to induce burn shock requiring fluid resuscitation. Immune hyperactivation, hypermetabolism, and adrenal hyperreactivity exacerbate this primary injury. Concomitantly, host defenses such as intact skin[1] and gastrointestinal mucosa[2,3] are compromised, resulting in significant microbial insult from commensal and pathologic organisms.[1] Ultimately, the common lethal end point of burn trauma and shock is multisystem organ failure (MOF). In one cohort of 821 severe pediatric burns there was a 19% incidence of MOF with a 100% mortality when involving three or more organ systems.[4]

Many scoring systems are currently used to quantify MOF. The DENVER2 system is widely used in research and clinical care by scoring pulmonary, renal, hepatic, and cardiac function from 0 to 3 with a total of 12 points available (Table 30.1). There is an inflection point after a score of 3 with significantly increased mortality. The Sequential Organ Failure Assessment score is based on scores of six systems from 0 to 4 for pulmonary, coagulation, liver, cardiovascular, central nervous, and renal (Table 30.2).[5] This definition system, popularized in sepsis and shock arenas, is at the core of the SEPSIS3 criteria to define septic shock recently published in the *Journal of the American Medical Association*.[6]

Regardless of the definition used, the more organ systems fail, the greater the mortality. Currently the best predictive model for burn mortality is proteomics combined with clinical covariates.[4] The time course of these failures and patterns of multiple failures are demonstrated in Fig. 30.1 and Table 30.3.[4] There are two well-described pathways to MOF in burn patients: early and late.[8] The early clinical sequence is characterized by resuscitation failure leading to adult respiratory distress syndrome (ARDS), hemodynamic failure, renal failure, liver failure, gut failure, and sepsis. In the late cascade seen in patients surviving resuscitation, pulmonary failure, hemodynamic instability, renal failure, gut failure, and liver failure also occur. Vasomotor and cardiac failures are terminal events in both. Survival can be seen in patients with greater than three organ system failures, but mortality increases with more failed systems.[7] Understanding the progression of the syndrome aids in prognostication and simplifies decisions regarding termination of futile efforts.[8,9] This chapter discusses the etiology and prevention of MOF; management will be covered in the critical care chapter.

Jeschke and Herndon reviewed 573 patients and determined that burn sizes associated with mortality, sepsis, infection, and MOF are 60% total body surface area (TBSA) in children and 40% in adults.[10] Kraft and Jeschke monitored MOF in 821 patients to define its course. Respiratory failure had the highest incidence in the first 5 days. Cardiac failure occurred throughout the hospital stay. Hepatic failure increased with hospitalization length and is associated with high mortality in the late cascade. Renal failure had an unexpectedly low incidence but was associated with high mortality in the first 3 weeks. Three or more organ failures was universally fatal in their cohorts. Overall mortality for patients with MOF was 41% compared to 2% without.[4] The Helsinki Burn Center reported their adult burn mortalities between 1999 and 2005 as 71 burn deaths of 1370 patients with 40% caused by MOF and 40% due to untreatable burn injury. On average, four organ failures were noted in the deaths, with acute renal failure being the most common. Sepsis was associated with MOF in all of their deaths.[11]

Etiology and Cellular Response

Attempts to define the etiology of MOF range from genomic and cellular to systemic and epidemiologic. Inadequate oxidative metabolism secondary to hypoperfusion leads to further organ failure as well as the release of humoral inflammatory mediators causing further cellular dysfunction. In ischemia–reperfusion models, oxygen radicals are generated resulting in peroxidation of cell membrane lipids and accumulation of activated neutrophils,[12] with progressive cellular and whole-organ dysfunction. Critically ill patients suffer from supply-dependent oxygen consumption because of defects in cellular oxygen extraction and utilization.[13,14] This results in inadequate aerobic metabolism unless supranormal levels of oxygen are supplied.[15] Grossly inadequate delivery of oxygen to cells dependent on aerobic metabolism can lead to cellular dysfunction, and this may be followed by organ failures.[16]

Mitochondrial-specific damage is one of the earliest responses to burn injury. There is tissue-specific damage to

Table 30.1 DENVER2 Criteria for Multisystem Organ Failure

Component	Measurement	Score			
		0	1	2	3
Pulmonary	PaO_2/FiO_2	≥250	175–249	100–174	<100
Renal	Creatinine	≤1.8	>1.8–2.5	>2.5–5.0	>5.0
Hepatic	Bilirubin	≤2.0	>2.0–4.0	>4.0–8.0	>8.0
Cardiac	Inotropes	See definitions below			

Cardiac Score: Scoring for cardiac component is a combination of number and dosage of inotropes administered.
S = small dose, M = moderate dose, L = large dose
Patient receives 0 agents: cardiac score = 0

Patient receives 1 agent:				**Patient receives 2 agents:**				
Dose size	S	M	L	Dose size	(S, S)	(S, M)	M, M)	(L, anything)
Cardiac score	1	2	3	Cardiac score	2	2	3	3

Patient receives 3 or more agents: cardiac score = 3

Table 30.2 Sequential Organ Failure Assessment Criteria

SOFA Score	0	1	2	3	4
					WITH RESPIRATORY SUPPORT
Respiration, Pao_2/Flo_2, mm Hg	>400	≤400	≤399	≤200	≤100
Coagulation, platelets × 10^3/mm^3	>150	≤150	≤100	≤50	≤20
Liver, bilirubin, mg/dL (µmol/L)	<1.2 (<20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0
Cardiovascular, hypotension	No hypotension	MAP <79 mm Hg	Dopamine ≤5 or dobutamine (any dose)[a]	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1[a]	Dopamine > 15 or epinephrine >0.1 or no epinephrine >0.1[a]
Central nervous system, Glasgow Coma Scale score	15	13–14	10–12	6–9	<6
Renal, creatinine, mg/dL (µmol/L)	<1.2 (<110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (>440)
Or urine output				Or <500 mL/day	Or <200 mL/day

MAP, Mean arterial pressure.
[a]Adrenergic agents administered for ≥1 h (doses given are in µg/kg/min).
From Dubois MJ, Orellana-Jimenez C, Melot C, et al. Albumin administration improves organ function in critically ill hypoalbuminemic patients: a prospective, randomized, controlled, pilot study. *Crit Care Med*. 2006;34(10):2536–2540.

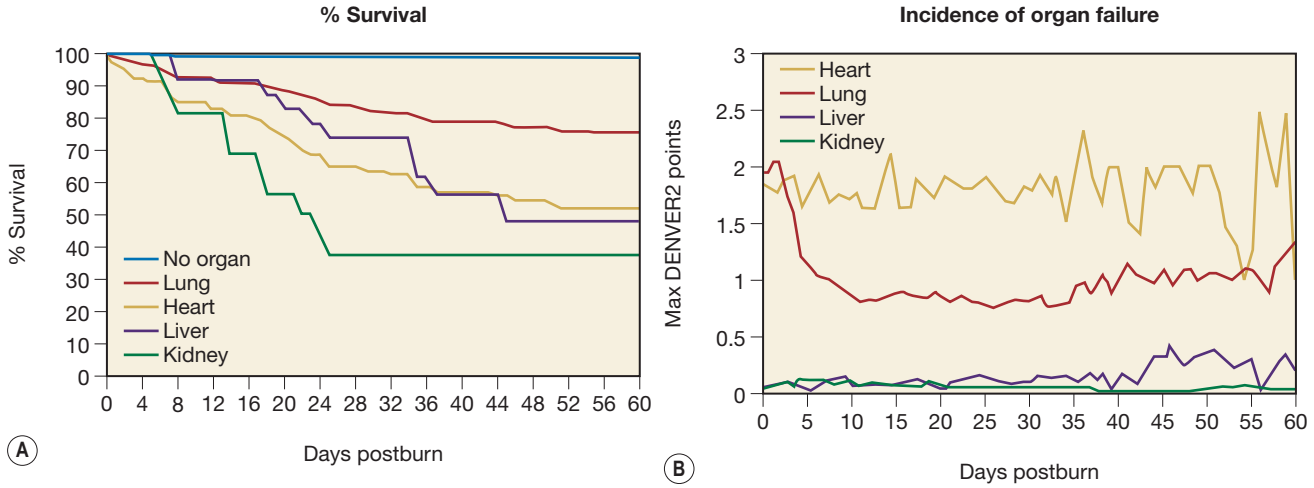

Fig. 30.1 The time course of organ failure over 60 days post burn. (**A**) The mortality associated with each individual organ failure. (**B**) DENVER2 scores associated with each organ failure. (From Kraft R, Herndon DN, Finnerty CC, Shahrokhi S, Jeschke MG. Occurrence of multiorgan dysfunction in pediatric burn patients: incidence and clinical outcome *Ann Surg*. 2014;259(2) 381–387)

Table 30.3 Coincidence and Correlation Between Organ Failures

Part A	Heart	Lung	Kidney	Liver
Heart (77)	NA	73	10	16*
Lung (230)	73	NA	16	22
Kidney (16)	10	16	NA	6
Liver (23)	16*	22	6*	NA
Part B	**1 Organ**	**2 Organs**	**3 Organs**	**4 Organs**
Heart (77)	4	51	18	4
Lung (230)	147	59	20	4
Kidney (16)	0	4	8	4
Liver (23)	1	4	14	4
Failures				

Part A displays the coincidence of the single-organ failures. Logistic regression revealed a statistically significant relationship between liver failure accompanied by heart and renal failure. Part B depicts the incidence of single and combined organ failures in the patient population.

*P <0.05.

NA, Not applicable.

From Kraft R, Herndon DN, Finnerty CC, Shahrokhi S, Jeschke MG. Occurrence of multiorgan dysfunction in pediatric burn patients: incidence and clinical outcome. *Ann Surg.* 2014;259(2):381–387.

mitochondrial DNA, most profoundly in the lungs and hearts of burned mice associated with a time-dependent increase in oxidative stress and neutrophil infiltration.[17] Porter and Herndon investigated postburn mitochondrial dysfunction by measuring mitochondrial respiration in saponin-permeabilized myofiber bundles and noted diminished mitochondrial coupling control persisting at 2 years postburn.[18] Uncoupling protein-1 thermogenesis increases after burn trauma and is a mechanism of hypermetabolism in burn victims.[19] This response is both adrenergic-mediated and responsive to ambient temperature, linking thermal regulation to skeletal muscle metabolism.[20] Jeschke and Herndon described the pathophysiologic response to severe burn injury in 242 children with a mean burn size of 56%. All patients were hypermetabolic with significant muscle protein loss, loss of bone mineral content, and profound alterations of serum proteome. Cardiac function was compromised, insulin resistance appeared in the first week, and patients were hyperinflammatory with marked changes in interleukin (IL)-8, monocyte chemotactic protein-1 (MCP-1), and IL-6.[21] Among 821 severely burned children, 586 never developed organ failure by the DENVER2 criteria. Respiratory failure was the most common organ failure occurring in 230, then cardiac in 77, with renal only occurring in 16[4] (Fig. 30.1).

The Inflammation and Host Response to Injury Large-Scale Collaborative Research Program defined the leukocyte transcriptome after severe trauma and burn injury and found a similar "genomic storm" among different injuries, revealing a fundamental human response to severe inflammatory stress.[22] The transcriptome of leukocytes following burn was linked to their immunologic response and related to outcomes. In their study of 167 subjects over 28 days they defined greater than twofold transcriptome changes in 80% of leukocyte genes (5136) compared to healthy controls. Within the first 12 hours the gene expression favors innate immunity and inflammatory response, including NB1, MMP8 (neutrophil collagenase), lactotransferrin (LTF), and haptoglobin (HP) with a marked downregulation of T-cell function and antigen presentation (Fig. 30.2). They found the genomic response was similar between isolated endotoxin challenge, minor trauma, and severe burn, differing primarily in the magnitude and duration of the response, thus postulating that the persistence of cellular debris in the plasma as a danger-associated molecular pattern (DAMP) continues the nonresolving inflammation[23] (Fig. 30.3). These descriptions of genomic response to burn injury reflect a global response and do not account for complex interplays or subpopulations of different cell types within the total leukocyte populations, the microenvironmental effects within different compartments where the immune cells exert their effects, proteomic or metabolomic effects, nor that certain transcripts in low abundance or with a small change may have profound effects. These data do highlight the complexity and universality of the immunologic response to severe injury or minor endotoxemia.

Tompkin's data demonstrate systemic inflammatory response syndrome (SIRS) underlies cellular events leading to MOF. Although many MOF patients will have different engines,[24] such as sterile burn wounds, sepsis is the most common late initiator of SIRS.[1] One overwhelming infection is not required; small repetitive infections may trigger the cascade,[25] perhaps by priming immune cells and making them react more profoundly to each consecutive stimulus.[25] Endotoxin from Gram-negative bacteria is a major intermediary via Toll-like receptor (TLR) pathways,[26] but Gram-positive bacteria cause similar insults.[27] With the advent of early burn wound excision,[28] infected wounds and wound sepsis are decreasing in incidence; pneumonia rather than wound sepsis causes most infectious deaths in burn patients today.[29] Complete wound closure, without donor sites (e.g., with skin substitutes), decreases oxygen consumption[30] thereby ameliorating the inflammatory response to the open wound. Incomplete wound closure does not have this effect.[31] Increased levels of circulating mediators such as IL-6, IL-8, and tumor necrosis factor (TNF) have been shown to originate from the burn wound[32] and contribute to hypermetabolic and inflammatory states seen in burn patients. IL-8 has been demonstrated to be upregulated in the lung after burn injury.[32] The stimulus for this upregulation, which is associated with pulmonary dysfunction, may come from the wound.[32]

A significant source of endotoxemia and septic load leading to MOF is gut barrier failure.[33] Bacterial densities range from near 0 in the stomach, to 10^4–10^5 in the distal small bowel, to 10^{11}–10^{12}/g of stool in the normal colon.[34] Although not seen immediately after trauma,[35] serial insults result in increased translocation of bacteria and their products into the portal and lymphatic circulations. Hemorrhagic shock,[36] endotoxin administration,[37] burns,[38] and burn wound sepsis[39] have each been shown to result in increased translocation of bacteria from the gut. Using polyethylene glycol 3350 as a tracer, increasing burn wound size was demonstrated to increase gut permeability to macromolecules such as endotoxin.[40] Smaller molecules,

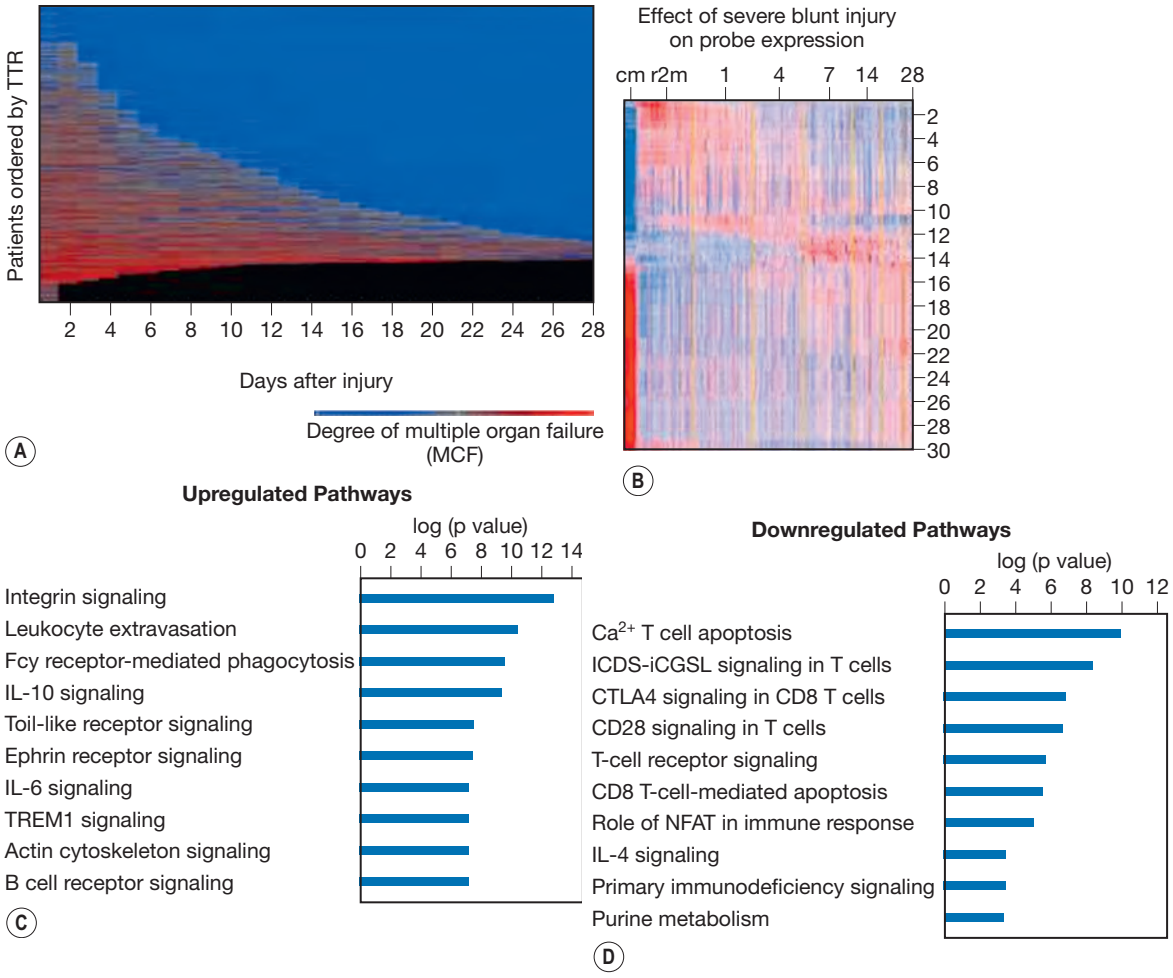

Fig. 30.2 The genomic response of leukocytes to burn injury. (From Xiao W, Mindrinos MN, Seok J, et al. A genomic storm in critically injured humans. *J Exp Med*. 2011;208(13):2581–2590.)

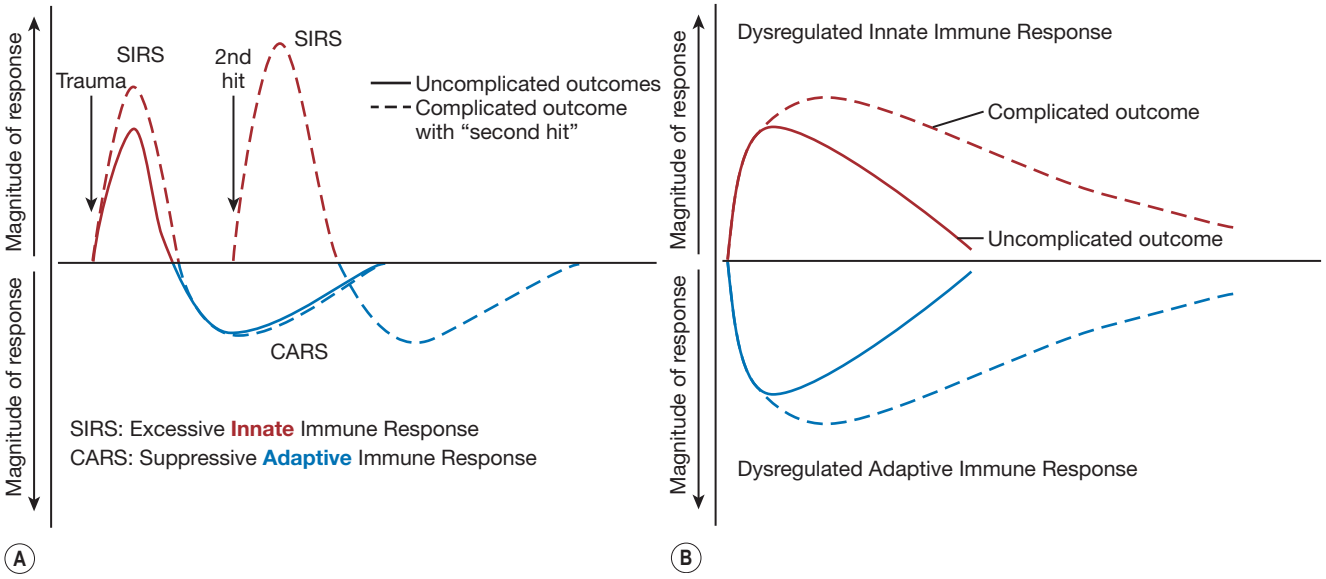

Fig. 30.3 Comparison of the genomic response of leukocytes to burn in complicated and uncomplicated outcomes. (From Xiao W, Mindrinos MN, Seok J, et al. A genomic storm in critically injured humans. *J Exp Med*. 2011;208(13):2581–2590.)

with lactulose as the tracer, passed more readily through the gastrointestinal membrane after injury.[41] Both intra- and transcellular processes allow transloaction.[42,43] Consequences of loss of the gastrointestinal barrier are profound. Translocating whole bacteria can be a direct source of sepsis or can activate Kupffer cells[2,3] and promulgate an inflammatory response in conjunction with bacterial products such as endotoxin.

COMMON GROUND: HUMORAL MEDIATORS

In patients receiving critical care (fluid resuscitation and wound care) for the acute burn injury and its attendant burn shock, the principal determinants of organ failure are humoral mediators.[44] Investigators are unraveling these humoral factors using blocking antibodies, soluble receptors, and receptor antagonists.[45]

Further studies of leukocyte transcriptome after severe trauma and burn injury demonstrated that humoral inflammatory mediators underlie cascades responsible for mortality in burn patients. Sood and Herndon used early leukocyte mRNA genomics to correlate transcriptome changes with outcomes in 324 severely burned patients. In many ways their mortality findings were as expected. Ages older than 60 carry a relative risk of death (RR) of 4.53, burns greater than 40% carry an RR of 4.24, and inhalation carries an RR of 2.08, all independently associated with mortality. They found 39 gene signatures within the leukocyte transcriptome inherent in the "genomic storm" associated with platelet activation and degranulation, cellular proliferation, and downregulation of proinflammatory cytokines (see Fig. 30.1).[46]

Jeschke and Herndon worked to differentiate burn survivors from nonsurvivors based on profoundly different trajectories in inflammatory and hypermetabolic responses. Nonsurvivors had significantly higher IL-6, IL-8, granulocyte colony-stimulating factor, monocyte chemotactic protein-1, C-reactive protein, glucose, insulin, blood urea nitrogen, creatinine and bilirubin, and hypermetabolic response.[47] IL-8 is a major mediator for inflammatory responses and tracks correspondingly with body surface area burned and incidence of MOF. High levels were associated with sepsis, MOF, and mortality suggesting that IL-8 may provide a valid biomarker for monitoring sepsis, infections, and mortality in burn paitents.[48]

The humoral inflammatory mediators believed to underlie MOF in burn injury are the same factors and cascades governing the fundamental human responses to severe injury and have been discussed for decades: endotoxin, arachidonic acid metabolites, cytokines, platelet activating factor (PAF), activated neutrophils and adherence molecules, nitric oxide, complement, and oxygen free radicals.

Endotoxin, a lipopolysaccharide component of Gram-negative bacteria outer cell walls, induces many of the symptoms associated with sepsis: fever, hypotension, the release of acute-phase proteins, and the production of multiple cytokines including TNF and IL-1 via interaction with TLRs.[49] Endotoxin injection alone causes the same changes in the leukocyte transcriptome as severe burn injury.[23] It also activates complement[50–52] and the coagulation cascade[53] and results in the release of PAF.[54] Potential sources of endotoxin include both Gram-negative bacteria in foci of infection and within the gut when the gut barrier fails.

Arachidonic acid (AA) makes up approximately 20% of cell membranes and is released from these membranes in response to a multitude of stimuli, which activate phospholipases A_2 and C, and is then metabolized by active mediators. The cyclooxygenase pathway yields prostaglandins and thromboxanes, whereas the lipoxygenase pathway results in the production of leukotrienes.[55] Prostaglandins and leukotrienes interact with other mediators in a complex fashion and are later degraded.[56] Cyclooxygenase products like prostacyclin inhibit platelet aggregation, thrombus formation, and gastric secretion,[57] whereas other products like thromboxane A_2 (TXA_2) cause platelet aggregation, have profound vasoconstricting effects on both the splanchnic and pulmonary microvasculature, and induce bronchoconstriction and increased membrane permeability.[58] Aspirin irreversibly inhibits cyclooxygenase, driving AA down the lipoxygenase pathway.[59] The lipoxygenase pathway results in the formation of leukotrienes. There are two types based on their metabolism after the action of 5-lipoxygenase, leukotrienes (LT) C_4, D_4, and E_4 (the sulfidopeptide group), and LTB_4.[51] Multiple stimuli by several cell types, including neutrophils, macrophages, and monocytes, generate leukotrienes.[52] Vessel walls are also capable of generating leukotrienes.[60] LT C_4, D_4, and E_4 have variable actions on vascular tone dependent on the presence or absence of other mediators, including cyclooxygenase products.[61] In addition to their variable effects in redirecting blood flow, LT C_4, D_4, and E_4 increase vascular permeability[62] and are elevated immediately prior to the development of pulmonary failure.[63] The principal effect of LT B_4 is enhancement of neutrophil chemotaxis.[64] Thus, leukotrienes as a group may be involved in the edema formation and pulmonary and systemic vascular changes seen in MOF.

Cytokines are regulatory proteins secreted by immune cells and have multiple paracrine and endocrine effects. There are six major classes:[65] interleukins, TNF, interferons, colony-stimulating factors, chemotactic factors, and growth factors. Those most extensively characterized in sepsis are IL-1, IL-6, and TNF.

IL-1 and IL-6 are elevated in septic states; high levels are associated with fatal outcomes[66] and predict systemic infection.[67] IL-1β causes hypotension and decreased systemic vascular resistance, which may be synergistic with the effects of TNF.[68] TNF causes hypotension, cardiac depression, and pulmonary dysfunction in animals.[69,70] When administered to humans, TNF causes fever, hypotension, decreased systemic vascular resistance, increased protein turnover, elevation of stress hormone levels,[66,71] and activation of the coagulation cascade.[68]

PAF is a nonprotein phospholipid secreted by many cells including platelets and endothelial and inflammatory cells,[72] and it is a major mediator of the pulmonary[73] and hemodynamic[74] effects of endotoxin. The major effects of PAF are vasodilation, cardiac depression, and enhancement of capillary leak. Its complex interactions with other mediators remain poorly understood.

Although tissue injury can occur in the absence of neutrophils,[75] the inflammatory process results in local accumulation of activated inflammatory cells that release various local toxins such as oxygen radicals, proteases,

eicosanoids, PAF, and others. When unregulated, such accumulations of activated cells can cause tissue injury.[76] The initial attachment of neutrophils to the vascular endothelium at an inflammatory site is facilitated by the interaction of adherence molecules on the neutrophil and endothelial cell surfaces.[77]

Induced by numerous stimuli, these neutrophil adherence receptors are, intriguingly, reduced after major thermal and nonthermal injury,[78] perhaps explaining in part the increased incidence of infection. The importance of this adherence mechanism can be seen in patients deficient in one integrin class of neutrophil adherence receptors, CD-18, who suffer from frequent bacterial infections.[79] The biology of the transmembrane polypeptides governing these complex cell-to-cell interactions is an active area of research[80] and holds promise for therapeutic interventions.

Oxygen radicals, such as hydrogen peroxide and superoxide anion, are released by activated neutrophils in response to a variety of stimuli[81] and when xanthine oxidase is activated after reperfusion in ischemia–reperfusion models. These highly reactive products cause cell membrane dysfunction, increased vascular permeability, and release eicosanoids.

Nitric oxide, released when citrulline is formed from arginine, was identified as an endothelial product in the mid-1980s.[82] Its half-life is merely a few seconds because it is quickly oxidized, but it has profound local microvascular effects. Nitric oxide synthesis is stimulated by various cytokines, endotoxin, thrombin, and injury to the vascular endothelium. It is a potent vasodilator,[83] but its actions vary depending on the vascular bed and presence of other mediators.[84] Nitric oxide is one of the major mediators of hypotensive response to sepsis.[85,86]

Antigen–antibody complexes activate the complement cascade, and complement fragments thus generated interact with other cytokines to promulgate the inflammatory response.[87] Diminished levels of the natural inhibitor of C5a have been demonstrated in patients with ARDS.[88] Administration of anti-C5a antibody diminishes hypotension in an animal model of endotoxemia.[89]

Organ-Specific Failure and Prevention

MOF reversal is challenging, making prevention paramount.[90] Genomic data have demonstrated that patients with MOF began on the same path as those who recover without complications.[23] Prevention is based on arresting the "engines" that drive and amplify the process: sepsis, gut barrier breakdown, the wound, and inadequate perfusion (Table 30.4). With current surgical and pharmacologic modalities, it is more practical to halt these engines than deal with an inadequately understood complex web of mediators. The interplay between organ systems and engines of MOF in the burned patient are complex. For expedience, we will discuss major organ systems sequentially.

Table 30.4 Multiple Organ Failure Etiology and Established Preventive Measures

Etiology	Prevention
Sepsis	Early excision and biologic closure of deep wounds Anticipation and early treatment of occult septic foci
Gut barrier failure	Optimize whole-body hemodynamics Early enteral feedings
Reduced organ perfusion	Optimize whole-body hemodynamics Enhanced oxygen delivery

HYPERMETABOLISM

Severe injury is associated with the hypermetabolic response, marked by increased oxygen consumption and carbon dioxide production, hyperdynamic circulation, increased minute ventilation, altered immune responses, and catabolism. Persistently higher metabolic rates are seen in nonsurvivors.[4] An essential component of modern burn management is attenuating the hypermetabolic response. Reducing the patient's metabolic demand via management of the external environment has been an indispensable component of burn care for decades.[20] Presently, β-adrenergic blockade with propranolol is the most efficacious anabolic pharmacologic therapy. While effects of growth hormone[91] were even more profound, it was associated with more adverse outcomes. Insulin-like growth factor, intensive insulin therapy, and oxandrolone have all been studied.[91]

Anabolic steroids such as oxandrolone have been used to reduce post burn catabolism and help shift patients to an anabolic state. Sousse and Suman demonstrated that long-term administration of oxandrolone significantly reduced hypermetabolism and increased height percentile, bone mineralization, lean body mass, and strength. They showed improved pulmonary functions with greater maximum expired ventilation and higher maximum voluntary ventilation.[92] Inhalation injury did not increase burn-induced hypermetabolic stress.[93] Promising investigations continue into the use of anabolic agents to treat severe burn injury, and they are rapidly becoming a standard of care in centers around the world.

CARDIOVASCULAR

Several hours post burn, a profound shock state develops due to loss of preload as burn edema advances. In the immediate post-burn ebb phase, cardiac function is depressed in an IL-1B- and TNFα-dependent manner that can be blocked with a CD14 knockout or halted with nuclear factor (NF-κB) blockers. By 48 h post burn the myocardium becomes tachycardic with increased cardiac output and hyperinflammatory in a β-adrenergic-mediated manner.[94] The decrease in right ventricular ejection fraction seen after endotoxemia can be alleviated by blockade of thromboxane.[95] Initially, systemic vascular resistance is increased; however, as systemic inflammation and sepsis emerge during the flow phase, vasoplegia ensues and exacerbates the cardiogenic and distributive shock states that promote MOF.[96]

Twenty-four to 48 hours after injury the ebb phase ends, the cardiac pathology enters the flow phase, marked by

elevated cardiac outputs. The pathophysiology of this phase of cardiac dysfunction has been thoroughly described.[94] Two primary drivers are prolonged elevated levels of catecholamines and sepsis. Sepsis can continue to produce myocardial dysfunction in a cytokine-mediated process. Persistent β-adrenergic receptor activation causes uncoupling from G-proteins, decreases cyclic adenosine monophosphate (cAMP) production and altered phosphorylation down the mitogen-activated protein kinase (MAPK) and Akt (protein kinase B) pathways away from the target of rapamycin (mTOR), and reduces sarcoplasmic reticulum calcium ATPase 2 (SERCA2) and ryanodine receptor (RyR). Collectively these make the myocardium less responsive to catecholamines and perturb calcium homeostasis. Further nitric oxide secretion from inflamed and burned tissue alters mitochondrial respiration and competes with calcium for binding sites on myosin, thus furthering the calcium dysregulation. The prolonged leakage of calcium from the sarcoplasmic reticulum depletes calcium stores and depresses contractility. These changes conjointly drive the myocardium toward apoptosis, which is detected within 3 hours postburn in the ebb phase but can continue into the flow phase.[94]

Additionally, pulmonary hypertension and right ventricular failure have a high mortality. In burn patients this can result from sepsis-related myocardial effects or acute fluid overload with resuscitation and/or edema mobilization. Left heart failure, acute pulmonary embolism, sepsis, acute lung injury, and perioperative state are other common causes.[97] Jeschke reported nonsurvivors having a 30% higher cardiac index at 29–34 days and 91–180 postburn than survivors, thus demonstrating the increased cardiac demand required in the persistent hyperdynamic state typifying MOF. The data suggest that these patients may need a supraphysiologic cardiac index to meet their hypermetabolic needs, although no definitive studies currently exist. Effective and expeditious management of cardiovascular failure is important to preventing or ameliorating MOF and is a critical component of burn center care.

There is mounting evidence that propranolol improves cardiac outcomes after burn injury by reducing heart rate and cardiac work, thus dampening hypermetabolism and hypercatabolism. Carvedilol may hold additional promise with its added α-blocking and free radical scavenging activities.

LUNGS

Pulmonary failure is caused by direct injury from inhalation of toxins, fluid overload, heart failure, and pulmonary edema resulting from resuscitation, injury from inflammatory and septic mediators draining from the burn wounds to the pulmonary capillary beds, pneumonia, and iatrogenic ventilator injury.[11] Prevention of the pulmonary component of MOF is based on infectious prophylaxis (early ventilator weaning/daily spontaneous breathing trials, suctioning, oral hygiene, chest physiotherapy, elevating head-of-bed) and limiting factors that exacerbate pulmonary injury. Current treatments such as administration of nebulized heparin, albuterol, cortisol, and epinephrine and chest physiotherapy as well as mucolysis improve pulmonary ventilation, function, and outcomes.[4] Cox and Hawkins investigated the integrity of airway epithelium in autopsy specimens of 72 severely burned children, finding airway epithelial loss corresponded to inhalation injury and age.[98] Mortality of inhalation injury was 16.4% and was associated with increased length of mechanical ventilation and length of stay.[99]

Lopez and Enkhbaatar demonstrated that nebulized epinephrine limited pulmonary vascular hyperpermeability to water and protein flux in an ovine burn model with smoke inhalation. This preserved dynamic compliance, mean airway pressure, and P/F ratio.[100] In their ovine burn with inhalation injury model, Traber et al. administered γ-tocopherol, a reactive oxygen species scavenger. They found decreases in arginase and collagen, significantly improved diffusion capacity, decreased lung water, reduced pulmonary shunt fraction, and reduced peak pressures and bronchiolar obstruction, indicating that free radical scavengers may reduce smoke-induced chronic pulmonary dysfunction.[101,102]

In an ovine model of inhalation injury with *Pseudomonas* infection there was severe deterioration in pulmonary gas exchange and increased lung lymph flow and protein content, lung water, nitrite/nitrate concentrations, tracheal blood flow, and vascular endothelial growth factor (VEGF) expression.[103] In a different study with this model evaluating microcirculatory changes in response to activated protein C, significant reductions in heart rate and cardiac output were observed. The changes in microvascular blood flow to the trachea, kidney, and brain were normalized.[104]

For nearly 20 years the ARDSnet doctrine of limited tidal volumes, pressure-limited ventilation, positive end-expiratory pressure (PEEP), and permissive hypercapnea have dominated the field of pulmonary critical care.[105] Application of these principles to burn care has been limited due to increased CO_2 production resulting from the hyperdynamic state requiring higher minute ventilation, pulmonary edema from resuscitation increasing the A-a gradient, and decreasing compliance and airway injury from inhaled toxins causing increased resistance and mucosal sloughing and plugging. For more than 28 years, Sousse and Mlcak analyzed pulmonary outcomes in 932 burned pediatric patients with inhalation injury, stratifying for tidal volume. Their findings are staggeringly divergent from ADRSnet data; they determined high tidal volume (15 ± 3 mL/kg) corresponded to significantly decreased ventilator days and maximum PEEP and significantly increased maximum peak inspiratory pressure. ARDS was significantly decreased, but the pneumothorax rate was increased. They concluded that high tidal volumes might interrupt the events leading to lung injury following inhalation injury.[106] Of note, this study was performed in the setting of early spontaneous breathing trials and aggressive discontinuation of mechanical ventilation. It remains unclear whether these data are an aberration or, as we suspect, there is a fundamental difference in the physiology of burned lungs. In the setting of severe inhalation injury with hypoxia and hypercapnia, we have seen the remarkable ability of pediatric lungs to heal with eventual normalization of gas exchange several months post injury; this phenomenon may be attributable to a still-active stem cell population.[107]

Systemic factors beyond sepsis also affect pulmonary failure. For example, inflammation associated with burns leads to hyperglycemia. A threshold of greater than 150 mg/dL leads to overwhelming growth of bacteria in the bronchopulmonary system. Pneumonia on mechanical ventilation and ARDS were higher in patients with average daily glucose greater than 150; they had significantly longer ventilation and more infection and sepsis.[108]

GASTROINTESTINAL DYSFUNCTION

DENVER2 and SOFA scores only address the gut failure pertaining to the liver. However, other aspects of gastrointestinal dysfunction also cause significant morbidity and contribute to mortality. Intestinal circulatory disturbances, atony, ileus, edema, swelling, and loss of mucosal barrier function gut dysfunction are an engine of MOF that Lautenschlager et al. studied with isolated rat small intestine perfused with PAF. They induced mesenteric vasoconstriction, translocation of fluid and macromolecules from the vasculature to the lumen, edema, and the loss of motility seen in intestinal failure. In this model quinidine, a sodium channel blocker, inhibited this pathology whereas dexamethasone did not.[109] Oliveira and Herndon studied the role of cyclooxygenase-2 inhibitors on gastric and small bowel ileus in prostaglandin-mediated etiology for postburn ileus.[110] Gut mucosal integrity suffers when mesenteric flow is inadequate, and gut blood flow is decreased after burn injury, exacerbated by TXA_2 release.[111] Support of splanchnic blood flow is an important aspect of MOF prevention[112] accomplished as part of whole-body hemodynamic support.

In a chronic porcine model of burn injury, burned pigs were given endotoxin bolus, causing a marked decrease in systemic vascular resistance, blood pressure, cardiac index, and mesenteric blood flow. This state increased gut bacterial translocation into mesenteric lymph nodes, spleen, and burn wounds, possibly due to mesenteric ischemia and reperfusion injury.[113]

Enteral feedings have beneficial effects on outcomes compared with parenteral feedings, possibly via an enhancement of gastrointestinal barrier integrity.[114] Enterocytes are principally supported by intraluminal feedings. Guts deprived of intraluminal feedings develop mucosal atrophy.[115] Early enteral feedings are tolerated in burn patients[116] and attenuate their hypermetabolic response.[117] The value of specific nutrients to support the enterocyte is murkier than that of providing adequate mesenteric blood flow and intraluminal nutrition. Glutamine is the preferred fuel of the small bowel enterocyte.[118] Sepsis has been shown to decrease glutamine uptake by the small bowel enterocyte, which may result in barrier failure,[119] and the addition of glutamine to the nutritional regimen is theorized to improve barrier function. Glutamine is not a component of commercial parenteral nutritional formulas because of its short shelf life, although the dipeptide is well tolerated and has a longer shelf life.[120] While supplemental glutamine may improve protein balance in surgical patients[115] and partially reverse gut atrophy,[121] it has not been shown to improve gut barrier function when given parenterally.[122] The large intestinal mucosa are trophic to butyrate, a fatty acid liberated by fiber fermentation.[123] Enteral pectin may help support the colonic mucosa, but the value of such support in the hypermetabolic burn patient remains unclear.

Limited research suggests possible benefits of probiotics for gut barrier support.[124] Probiotics may improve gastrointestinal barrier function, avoiding colonization with pathogenic microorganisms and immunomodulation. They reduce bacterial translocation in the gut of burned rats.[125] Interestingly, they seem to increase diarrhea rates. Accumulating data suggest probiotics may reduce ventilator-associated pneumonia rates. There are some concerns in the current datasets that the control groups have too high an incidence of ventilator-acquired pneumonia (VAP), and there have been case reports of sepsis from probiotic organisms in high-risk patients.[126] In a series of 20 severely burned children, probiotics were found to be safe and tended toward fewer surgeries and less time to achieve complete wound closure.[127]

Decontamination of the gut lumen might diminish the impact of gastrointestinal barrier failure. Attempts have been made to assess the impact of selective decontamination of the gut[128] by coating enteric bacteria to inhibit their ability to attach to the intestinal mucosa and translocate.[129] While the rate of pneumonia may decrease by such mechanisms, there is no apparent impact on mortality.

Acute pancreatitis is also notable after severe burn injury as defined as a threefold increase in amylase or lipase with abdominal pain or feeding intolerance. In a pediatric cohort, Rivero and Jeschke reported an incidence of 13/2699 or 0.05% and found pathological evidence in 11/78 autopsies. This is in contrast to 40% of patients developing a hyperamylasemia or hyperlipidemia without symptoms. They postulated that the etiology of these pancreatitis cases was from ischemic injuries due to shock. They also noted increased mortality in the pancreatitis cohort.[130]

In a severe burn the liver plays a pivotal role in modulating inflammatory processes, immune functions, metabolic pathways, and the acute-phase response. Thermal injury causes hepatic damage by inducing hepatic edema, fatty infiltration, apoptosis, and the metabolic derangements associated with insulin resistance. Insulin administration decreases the rate of infections and the synthesis of proinflammatory cytokines and improves hepatic structure and function in severely burned and critically ill patients.[131]

Burn injury promotes catabolism and lipolysis in burned children.[132] The resulting free fatty acids are re-esterified in the liver to triglycerides where they are not secreted as very-low-density lipoprotein (VLDL) due to downregulation of transport proteins, thus leading to progressive fatty liver metamorphosis. Carbohydrates are utilized as a major energy source for critically burned patients. Lee and Herndon demonstrated that low-fat, high-carbohydrate feeds promote shorter ICU stay per %TBSA, a lower incidence of sepsis, and decreased hepatic steotosis.[133]

Acute liver failure (ALF) is uncommon after burn but carries a high mortality. It presents with hepatic encephalopathy, jaundice, and coagulopathy in the absence of chronic liver disease and carries a mortality rate of 40–50%. The cause of death is cerebral herniation in 34%, refractory hypotension, and MOF. Herndon et al. studied 142 consecutive cases of ALF in the ICU and found that 70% were due to heart failure, 13% from respiratory failure, and 13%

from toxins or sepsis.[134] Most commonly, low flow states cause ALF. The liver receives most of its blood flow via the portal system, and the dependence on portal supply is increased in critical illness because the arterial supply is reduced while the central lobular oxygen requirements increase due to metabolic and synthetic demands. In the setting of heart failure, high central venous pressures, associated with fluid overload or the need for high preload, decrease the pressure gradient across the liver and compromise portal flow (and oxygenation), leading to centrilobular necrosis. Thus, most post-burn acute liver failure is hypoxemic liver failure, with high hepatic (central) venous pressures a major (unrecognized) cause of reduced hepatic oxygen delivery.[134] Less common causes are toxins and viruses. Many drugs used in the burn ICU can cause acute liver failure: acetaminophen, amoxicillin, moxifloxacin, trimethoprim-sulfamethoxazole, fluconazole, voriconazole, amiodarone, metformin, isoflurane, opiates, phenytoin, ibuprofen, iron, and anabolic steroids make up a short list. Immunosuppression associated with burn injury predisposes activation of latent hepatitis and herpes viruses (especially cytomegalovirus), which can cause ALF. Loss of clotting factors causes coagulopathy, whereas loss of anticoagulants can causes thrombosis, collectively promoting disseminated intravascular coagulation (DIC). Burn patients with liver dysfunction become prone to hypoglycemia due to loss of glucose homeostasis.[135] ALF feeds back into MOF causing vasoplegia with diminished hepatic clearance of circulating vasoactive compounds, increased nitric oxide (NO) production, acute renal failure due to ischemia, and acute tubular necrosis (ATN), and it may progress to hepatorenal and/or compartment syndromes.

RENAL

To survive a burn injury adequate renal clearance is essential. Twenty-four h following resuscitation it is necessary to clear the excess volume administered. Renal function is critical to clear extensive metabolic wastes associated with injury and the hyperdynamic state.[136] Concurrently the kidney is subjected to prerenal insults, such as hypovolemia and shock, and to direct renal toxins, such as myoglobin and medications.[137] Aggressive treatment of compartment syndromes to prevent myoglobinemia, monitoring of abdominal compartment pressures to prevent compromise of renal blood flow, and avoidance of nephrotoxic medications are critical to maintaining renal function. Mason and Jeschke et al. prospectively analyzed 330 resuscitations dividing the patients relative to the Parkland formula resuscitation. The groups receiving greater than Parkland resuscitation had a higher APACHE score. Patients resuscitated with less than Parkland resuscitation demonstrated greater probability of acute kidney injury (AKI) (odds ratio [OR] 3.25; 95% confidence interval [CI] 1.18–8.94) without difference in infectious complications.[138] Maintenance of sufficient renal blood flow with appropriate volume resuscitation is vital to maintaining renal function. In a retrospective review of 41,179 burned Finnish patients, 86 had AKI related to the burn and 43 developed end-stage renal disease (ESRD) and required renal replacement therapy (RRT).[139] In the absence of diuretics, urine output of 0.5–1 mL/kg per hour generally indicates sufficient renal perfusion. In patients with increasing creatinine or decreased urine output, the finding of granular casts on centrifuged microscopic urinalysis is helpful in promptly differentiating organ damage (tubular necrosis) from appropriate renal response to decreased blood flow (prerenal state) and can promptly guide therapy.

Prevention of Sepsis

Sepsis is a major engine of MOF, and MOF predisposes patient to sepsis; a lethal feed-forward loop. The post-burn surge of proinflammatory mediators and resultant hypermetabolic response and protein wasting contribute to infection and sepsis.[4] In multiple series all mortalities with MOF were septic. MOF patients may have more major infections (non-MOF 2.1 versus MOF 3.3), and they do experience more sepsis (non-MOF 5%, MOF 31%).[4] Early burn excision, wound closure, regular wound surveillance and culture, and strict infection control remain the principal adjuncts to control invasive infections in burn patients.[140] Sepsis accounts for at least half of MOF cases. Overt wound sepsis and smaller septic insults are prevented by early removal of devitalized tissue because manipulation of heavily colonized burn wounds is a frequent source of transient bacteremia.[141,142] Multiple episodes of occult bacteremia occurring during frequent manipulation of heavily colonized wounds contribute to the development of MOF by priming immune cells, making them react more intensively to each subsequent insult.[25]

The role of perioperative and prophylactic antibiotics in minimizing bacteremia in the perioperative period remains controversial. There is a clear benefit to patients with injuries greater than 60% TBSA and for any patient in whom the probability of bacteremia with wound manipulation is considered to be high.[143] Culture-directed antibiotics are an important consideration because burn patients are prone to a large number of unusual and often occult infections.[144] Rapid diagnosis and treatment are assisted by a high index of suspicion.

Intravascular infections such as suppurative thrombophlebitis and endocarditis typically present in burn patients with fever and bacteremia without localizing signs. Burn patients with endocarditis rarely develop a murmur (just 9% of cases)[145] with only 10% reported antemortem.[146] Septic thrombophlebitis often presents without localizing signs, with 68% of cases having only fever and positive blood cultures.[147] Diagnosis is made by thorough examination of all sites of prior cannulation, surgical exposure of suspicious sites, and complete excision of involved veins.[148] Vigilant care, scheduled replacement, and early removal of intravascular devices will minimize the occurrence of catheter-related sepsis. Occult intracompartmental sepsis can also present with fever and bacteremia without localizing signs and is diagnosed only by careful examination and exploration of suspicious compartments.[149]

Pneumonia, seen in approximately 35% of patients with inhalation injury, adds 20–60% to the expected mortality.[150] Pneumonia should be vigilantly anticipated and aggressively treated with pulmonary care and specific antibiotics. The incidence of nosocomial pneumonia increases with longer durations of intubation,[151] emphasizing the importance of judicious use of mechanical ventilation and

early extubation protocols such as daily spontaneous breathing trials.

Suppurative sinusitis is a rare cause of sepsis in the ICU traditionally described as resulting from transnasal tube placement in a case series published in 1986.[152] Many burn centers routinely use prolonged nasotracheal tubes due to their dramatically lower rates of dislodgement and lower sedation requirements and do not report high rates of sinusitis. Subsequent studies have brought this etiology into question, and, in our experience, we have had zero episodes in the past 20 years.[153] Furthermore this is not a typical cause of septic shock even when it occurs. If suppurative sinusitis does occur, it is treated with tube removal, topical decongestants, and appropriate antibiotics, rarely requiring surgical drainage.

Acalculous cholecystitis presents with generalized sepsis without localizing signs, making diagnosis difficult.[154] Percutaneous cholecystectomy tube drainage has become the management of choice in suspected cholecystitis in critically ill patients.[155] This allows diagnosis and decompression in patients too unstable for immediate operation.

Ensuring Adequate Oxygen Delivery

Oxygen is one of the most sensitive substrates in cells. The normal intracellular partial pressure of oxygen is 0.5 mm Hg for all mitochondrial function. Failure to deliver adequate oxygen resulting in organ dysfunction is a definition of shock and a common cause of MOF. Inadequate oxygen delivery shifts cells to anaerobic metabolism and increases in the liberation of intracellular oxygen free radicals with the activation of xanthine oxidase.[156]

Sufficient oxygen delivery requires adequate resuscitation and re-establishment of cardiovascular and pulmonary homeostasis. The practical details of resuscitation, particularly resuscitation endpoints, remain controversial. The Rivers et al.[157] study highlighted the utility of aggressive pursuit of predetermined resuscitation endpoints in septic shock. Large trials failed to replicate their results, which may be the result of the early goal-directed therapy protocols becoming the standard of care with resultant improvements in control group mortality. Regardless, optimizing preload, assuring appropriate afterload, optimizing inotropy, and tracking end organ perfusion remain the hallmarks of critical care support in algorithms from the Advanced Burn Life Support to the Surviving Sepsis Campaign.[158] Additional resuscitation endpoints beyond urine output, such as lactic acid and base deficit,[159] and advanced hemodynamic monitoring tools are improving resuscitation accuracy and minimizing the morbidity of under- and overresuscitation. Computerized resuscitation algorithms help achieve sufficient fluid resuscitation while minimizing overresuscitation. Resuscitation strategies and their effects are discussed at length in other chapters of this text. Complications of anasarca caused by massive crystalloid resuscitation can be reduced with the addition of colloid to resuscitation.[160]

Inadequate oxygen delivery leads to organ dysfunction. Clinicians should ensure that injured patients are resuscitated to conventional clinical endpoints of appropriate urine output, skin perfusion, blood pressure, and sensorium. In selected critically ill patients, invasive and noninvasive monitoring is justified to optimize preload, afterload, inotropy, and oxygen delivery and consumption particularly in patients where urine output becomes an unreliable endpoint.

The Potential Role of Nutritional and Specific Immunomodulators

Prevention of MOF by modulating the common pathway that leads to organ dysfunction is the holy grail of critical care. The three general approaches to this goal are nutritional, nonspecific, and specific immunomodulation.

NUTRITIONAL IMMUNOMODULATION

Three categories of substances show promise as potential nutritional immunomodulators: long-chain fatty acids; arginine, glutamine, and branched-chain amino acids; and nucleotides. Long-chain fatty acids are important constituents of cell membranes and can profoundly influence cell function.[161] Omega-3 long-chain fatty acids play a particularly important role in the membranes of immunocompetent cells.[162] Animal data suggest that supplementation of a diet with omega-3 fatty acids may improve immune function after burn injury;[163] however, there are no clear clinical data.

The potential immunostimulating effects of specific amino acids, particularly arginine, glutamine, and the branched-chain amino acids leucine, isoleucine, and valine, remain an area of research. Arginine has important functions in the urea cycle and in generating nitric oxide and may have important effects on immunity.[164–166] Animal data suggest improved immunocompetence and outcome after burn with arginine supplementation,[167–169] but human data are not adequate to support its routine administration. Glutamine may be essential in hypermetabolic patients,[118,119] and its administration may support the gut barrier, thereby abrogating the consequences of barrier failure.

NONSPECIFIC AND SPECIFIC IMMUNOMODULATION

It seems unlikely that a magic immunomodulating bullet will prevent the development of MOF in critically ill patients, particularly with uncontrolled sepsis, compromised gut barrier, unaddressed burn wounds, or inadequate hemodynamic support. Efforts at nonspecific immunomodulation include the use of steroids,[170] immunoglobulin G,[171] and naloxone[172] with no significant impact on patient outcomes. With the exception of steroids for adrenal insufficiency[173] and naloxone for those with opiate intoxication, there is currently no role for these substances in critically ill burn patients.

Addressing toxicity of lipopolysaccharide has been attempted by absorption,[174] prevention with polymyxin B,[175] and antiendotoxin antibodies. Although multiple trials have been attempted with multiple antibodies no compelling data have yet brought one into broad clinical practice.[176–179]

Immunomodulation has also targeted arachidonic acid metabolites or eicosanoids, both cyclooxygenase and lipoxygenase products. Animal models of sepsis demonstrate that cyclooxygenase pathway blockade has demonstrated improved survival,[180] improved pulmonary hemodynamics,[181] and improved mesenteric blood flow.[182] Human data are currently lacking, but it has been suggested that nonsteroidal antiinflammatory agents improve symptoms associated with endotoxin infusion in normal volunteers[183] and septic patients[184] and may improve immune function after surgical trauma.[181] In an animal model, infusion of the vasodilating AA metabolite prostacyclin ameliorates the pulmonary dysfunction associated with endotoxin infusion.[38] Lipoxygenase pathway blockade reduces pulmonary dysfunction in mice,[185] sheep,[186] and pigs.[187] The ultimate role of lipoxygenase blockade in human remains to be investigated.

Cytokines have also been targeted. IL-1 receptor antagonist enhances survival in an animal model.[188] Infusion of IL-1 may improve immune function in humans.[189] Current understanding of the complex functions of this cytokine is inadequate to allow intelligent intervention. TNF blockade attenuated the physiological effects of both endotoxin infusion and Gram-negative sepsis in animal models.[190,191] Anti-TNF administration prior to experimental sepsis[192] and endotoxemia[193] has variable effects on survival.

Interference with the effects of PAF has been shown to decrease neutrophil priming by human burn serum,[194] improve endotoxin-induced pulmonary dysfunction,[195] decrease eicosanoid release,[196] attenuate thromboxane release, and improve survival[197] in various animal models of endotoxemia. These exciting initial results, and the availability of several blockers and receptor antagonists portend a future use for PAF modification.

Efforts to modulate both the adherence and function of inflammatory cells are an exciting area of research because activated neutrophils play an important role in the development of MOF. Blockade of neutrophil adhesion receptors with monoclonal antibodies enhances survival in animal models of endotoxic and hemorrhagic shock.[198]

Oxygen free radicals generated by activated neutrophils or xanthine oxidase may oxidize membrane lipids, forming lipid peroxides and resulting in membrane dysfunction.[199] Native antioxidant systems do exist but can be overwhelmed. Circulating levels of vitamin E, a natural antioxidant, are low in patients with ARDS.[200] Efforts to modify oxidant activity include blockade of free radical generation, addition of free radical scavengers, augmentation of host antioxidant defenses, and prevention of amplification of tissue damage by neutrophils.[199] Particularly intriguing are free radical scavengers such as superoxide dismutase[201] and spin-trapping nitrones,[202] which improve survival in animal models of endotoxic and hemorrhagic shock. Despite encouraging initial animal studies, such therapy is not yet appropriate in human patients.

The continuous synthesis of NO plays an important role in the regulation of pulmonary and systemic vascular tone in sepsis,[203] and this presents potential opportunities for intervention.[204] Aerosolized NO has been shown to be useful in reversing the pulmonary hypertension associated with ARDS as well as in improving V:Q mismatch,[205] and NO synthesis blockade may improve the hypotension and renal dysfunction associated with sepsis. Its complex interactions with other cytokines and variable effects on different vascular beds currently render any NO-based interventions investigational or for selected critical care indications.

Most patients who die in the burn unit after surviving the initial injury and resuscitation succumb to MOF.[206] Modifying the cascade leading to MOF at the cellular and subcellular levels is enticing, but our fragmented understanding of these processes mitigates against such therapy in human patients at present.

Complete references available online at www.expertconsult.inkling.com.

References

1. Fry DE, Pearlstein L, Fulton RL, Polk HC Jr. Multiple system organ failure. The role of uncontrolled infection. *Arch Surg*. 1980; 115(2):136-140.
2. Yost CC, Weyrich AS, Zimmerman GA. The platelet activating factor (PAF) signaling cascade in systemic inflammatory responses. *Biochimie*. 2010;92(6):692-697.
3. Saadia R, Schein M, MacFarlane C, Boffard KD. Gut barrier function and the surgeon. *Br J Surg*. 1990;77(5):487-492.
4. Kraft R, Herndon DN, Finnerty CC, Shahrokhi S, Jeschke MG. Occurrence of multiorgan dysfunction in pediatric burn patients: incidence and clinical outcome. *Ann Surg*. 2014;259(2):381-387.
5. Dubois MJ, Orellana-Jimenez C, Melot C, et al. Albumin administration improves organ function in critically ill hypoalbuminemic patients: a prospective, randomized, controlled, pilot study. *Crit Care Med*. 2006;34(10):2536-2540.
6. Canto JG, Rogers WJ, Goldberg RJ, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA*. 2012;307(8):813-822.
7. Huang YS, Yang ZC, Liu XS, et al. Serial experimental and clinical studies on the pathogenesis of multiple organ dysfunction syndrome (MODS) in severe burns. *Burns*. 1998;24(8):706-716.
8. Choong K, Cupido C, Nelson E, et al. A framework for resolving disagreement during end of life care in the critical care unit. *Clin Invest Med*. 2010;33(4):E240-E253.
9. Poulton B, Ridley S, Mackenzie-Ross R, Rizvi S. Variation in end-of-life decision making between critical care consultants. *Anaesthesia*. 2005;60(11):1101-1105.
10. Porro LJ, Al-Mousawi AM, Williams F, et al. Effects of propranolol and exercise training in children with severe burns. *J Pediatr*. 2013;162(4):799-803 e791.
11. Kallinen O, Maisniemi K, Bohling T, Tukiainen E, Koljonen V. Multiple organ failure as a cause of death in patients with severe burns. *J Burn Care Res*. 2012;33(2):206-211.
12. Schoenberg MH, Beger HG. Reperfusion injury after intestinal ischemia. *Crit Care Med*. 1993;21(9):1376-1386.
13. Bihari D, Smithies M, Gimson A, Tinker J. The effects of vasodilation with prostacyclin on oxygen delivery and uptake in critically ill patients. *N Engl J Med*. 1987;317(7):397-403.
14. Poeze M, Solberg BC, Greve JW, Ramsay G. Monitoring global volume-related hemodynamic or regional variables after initial resuscitation: what is a better predictor of outcome in critically ill septic patients? *Crit Care Med*. 2005;33(11):2494-2500.
15. Mira JP, Fabre JE, Baigorri F, et al. Lack of oxygen supply dependency in patients with severe sepsis. A study of oxygen delivery increased by military antishock trouser and dobutamine. *Chest*. 1994;106(5):1524-1531.
16. Schumacker PT, Samsel RW. Oxygen delivery and uptake by peripheral tissues: physiology and pathophysiology. *Crit Care Clin*. 1989;5(2):255-269.
17. Szczesny B, Brunyanszki A, Ahmad A, et al. Time-dependent and organ-specific changes in mitochondrial function, mitochondrial DNA integrity, oxidative stress and mononuclear cell infiltration in a mouse model of burn injury. *PLoS ONE*. 2015;10(12): e0143730.
18. Porter C, Herndon DN, Borsheim E, et al. Long-term skeletal muscle mitochondrial dysfunction is associated with hypermetabolism in severely burned children. *J Burn Care Res*. 2016;37(1):53-63.
19. Porter C, Herndon DN, Bhattarai N, et al. Severe burn injury induces thermogenically functional mitochondria in murine white adipose tissue. *Shock*. 2015;44(3):258-264.
20. Porter C, Herndon DN, Borsheim E, et al. Uncoupled skeletal muscle mitochondria contribute to hypermetabolism in severely burned adults. *Am J Physiol Endocrinol Metab*. 2014;307(5):E462-E467.
21. Jeschke MG, Chinkes DL, Finnerty CC, et al. Pathophysiologic response to severe burn injury. *Ann Surg*. 2008;248(3):387-401.
22. Xiao W, Mindrinos MN, Seok J, et al. A genomic storm in critically injured humans. *J Exp Med*. 2011;208(13):2581-2590.
23. Zimmerman JJ, Sullivan E, Yager TD, et al. Diagnostic Accuracy of a Host Gene Expression Signature That Discriminates Clinical Severe Sepsis Syndrome and Infection-Negative Systemic Inflammation Among Critically Ill Children. *Crit Care Med*. 2017;45(4):e418-e425.
24. Bone RC, Fisher CJ Jr, Clemmer TP, et al. Sepsis syndrome: a valid clinical entity. Methylprednisolone Severe Sepsis Study Group. *Crit Care Med*. 1989;17(5):389-393.
25. Meakins JL. Etiology of multiple organ failure. *J Trauma*. 1990;30(12 suppl):S165-S168.
26. Kox M, de Kleijn S, Pompe JC, et al. Differential ex vivo and in vivo endotoxin tolerance kinetics following human endotoxemia. *Crit Care Med*. 2011;39(8):1866-1870.
27. Ahmed AJ, Kruse JA, Haupt MT, Chandrasekar PH, Carlson RW. Hemodynamic responses to gram-positive versus gram-negative sepsis in critically ill patients with and without circulatory shock. *Crit Care Med*. 1991;19(12):1520-1525.
28. Merrell SW, Saffle JR, Larson CM, Sullivan JJ. The declining incidence of fatal sepsis following thermal injury. *J Trauma*. 1989;29(10):1362-1366.
29. Peck MD, Heimbach DM. Does early excision of burn wounds change the pattern of mortality? *J Burn Care Rehabil*. 1989;10(1):7-10.
30. Herndon DN, Barrow RE, Rutan RL, et al. A comparison of conservative versus early excision. Therapies in severely burned patients. *Ann Surg*. 1989;209(5):547-552, discussion 552-553.
31. Demling RH, Lalonde C. Effect of partial burn excision and closure on postburn oxygen consumption. *Surgery*. 1988;104(5): 846-852.
32. Rodriguez JL, Miller CG, Garner WL, et al. Correlation of the local and systemic cytokine response with clinical outcome following thermal injury. *J Trauma*. 1993;34(5):684-694, discussion 694-695.
33. Deitch EA. The role of intestinal barrier failure and bacterial translocation in the development of systemic infection and multiple organ failure. *Arch Surg*. 1990;125(3):403-404.
34. Schaedler RW, Goldstein F. Bacterial populations of the gut in health and disease; basic microbiologic aspects. In: Brochus HL, Beck JE, Haubrich WS, et al, eds. *Gastroenterology*. Philadelphia: WB Saunders; 1976:147-149.
35. Magnotti LJ, Deitch EA. Burns, bacterial translocation, gut barrier function, and failure. *J Burn Care Rehabil*. 2005;26(5):383-391.
36. Baker JW, Deitch EA, Li M, Berg RD, Specian RD. Hemorrhagic shock induces bacterial translocation from the gut. *J Trauma*. 1988;28(7):896-906.
37. Deitch EA, Berg R, Specian R. Endotoxin promotes the translocation of bacteria from the gut. *Arch Surg*. 1987;122(2):185-190.
38. Demling RH. The clinical relevance of defining the mechanism for altered gut permeability in a "two-hit" model of injury and infection. *Crit Care Med*. 2004;32(11):2356-2357.
39. Jones WG 2nd, Minei JP, Barber AE, et al. Bacterial translocation and intestinal atrophy after thermal injury and burn wound sepsis. *Ann Surg*. 1990;211(4):399-405.
40. Ryan CM, Yarmush ML, Burke JF, Tompkins RG. Increased gut permeability early after burns correlates with the extent of burn injury. *Crit Care Med*. 1992;20(11):1508-1512.
41. Deitch EA. Intestinal permeability is increased in burn patients shortly after injury. *Surgery*. 1990;107(4):411-416.
42. Chang JX, Chen S, Ma LP, et al. Functional and morphological changes of the gut barrier during the restitution process after hemorrhagic shock. *World J Gastroenterol*. 2005;11(35):5485-5491.
43. Gosain A, Gamelli RL. Role of the gastrointestinal tract in burn sepsis. *J Burn Care Rehabil*. 2005;26(1):85-91.
44. Wood JH, Partrick DA, Johnston RB Jr. The inflammatory response to injury in children. *Curr Opin Pediatr*. 2010;22(3):315-320.
45. Dinarello CA. The proinflammatory cytokines interleukin-1 and tumor necrosis factor and treatment of the septic shock syndrome. *J Infect Dis*. 1991;163(6):1177-1184.
46. Sood RF, Gibran NS, Arnoldo BD, et al. Early leukocyte gene expression associated with age, burn size, and inhalation injury in severely burned adults. *J Trauma Acute Care Surg*. 2016;80(2):250-257.
47. Jeschke MG, Gauglitz GG, Finnerty CC, et al. Survivors versus nonsurvivors postburn: differences in inflammatory and hypermetabolic trajectories. *Ann Surg*. 2014;259(4):814-823.
48. Kraft R, Herndon DN, Finnerty CC, et al. Predictive value of IL-8 for sepsis and severe infections after burn injury: a clinical study. *Shock*. 2015;43(3):222-227.
49. Fukushima R, Alexander JW, Gianotti L, Pyles T, Ogle CK. Bacterial translocation-related mortality may be associated with neutrophil-mediated organ damage. *Shock*. 1995;3(5):323-328.
50. Morrison DC, Kline LF. Activation of the classical and properdin pathways of complement by bacterial lipopolysaccharides (LPS). *J Immunol*. 1977;118(1):362-368.
51. Sprague RS, Stephenson AH, Dahms TE, Lonigro AJ. Proposed role for leukotrienes in the pathophysiology of multiple systems organ failure. *Crit Care Clin*. 1989;5(2):315-329.

52. Lewis RA, Austen KF. The biologically active leukotrienes. Biosynthesis, metabolism, receptors, functions, and pharmacology. *J Clin Invest*. 1984;73(4):889-897.
53. Gorbet MB, Sefton MV. Endotoxin: the uninvited guest. *Biomaterials*. 2005;26(34):6811-6817.
54. Chang SW, Feddersen CO, Henson PM, Voelkel NF. Platelet-activating factor mediates hemodynamic changes and lung injury in endotoxin-treated rats. *J Clin Invest*. 1987;79(5):1498-1509.
55. Ramwell PW, Leovey EM, Sintetos AL. Regulation of the arachidonic acid cascade. *Biol Reprod*. 1977;16(1):70-87.
56. Henderson WR Jr. Eicosanoids and lung inflammation. *Am Rev Respir Dis*. 1987;135(5):1176-1185.
57. Whittle BJ, Moncada S. Pharmacological interactions between prostacyclin and thromboxanes. *Br Med Bull*. 1983;39(3):232-238.
58. Westphal M, Noshima S, Isago T, et al. Selective thromboxane A2 synthase inhibition by OKY-046 prevents cardiopulmonary dysfunction after ovine smoke inhalation injury. *Anesthesiology*. 2005;102(5):954-961.
59. FitzGerald GA, Reilly IA, Pedersen AK. The biochemical pharmacology of thromboxane synthase inhibition in man. *Circulation*. 1985;72(6):1194-1201.
60. Leite MS, Pacheco P, Gomes RN, et al. Mechanisms of increased survival after lipopolysaccharide-induced endotoxic shock in mice consuming olive oil-enriched diet. *Shock*. 2005;23(2):173-178.
61. Pfister RR, Haddox JL, Sommers CI. Injection of chemoattractants into normal cornea: a model of inflammation after alkali injury. *Invest Ophthalmol Vis Sci*. 1998;39(9):1744-1750.
62. Wang ML, Huang XJ, Fang SH, et al. Leukotriene D4 induces brain edema and enhances CysLT2 receptor-mediated aquaporin 4 expression. *Biochem Biophys Res Commun*. 2006;350(2):399-404.
63. Davis JM, Meyer JD, Barie PS, et al. Elevated production of neutrophil leukotriene B4 precedes pulmonary failure in critically ill surgical patients. *Surg Gynecol Obstet*. 1990;170(6):495-500.
64. Goetzl EJ, Pickett WC. The human PMN leukocyte chemotactic activity of complex hydroxy-eicosatetraenoic acids (HETEs). *J Immunol*. 1980;125(4):1789-1791.
65. Liu W, Matsumori A. Calcium channel blockers and modulation of innate immunity. *Curr Opin Infect Dis*. 2011;24(3):254-258.
66. Carrol ED, Thomson AP, Jones AP, Jeffers G, Hart CA. A predominantly anti-inflammatory cytokine profile is associated with disease severity in meningococcal sepsis. *Intensive Care Med*. 2005; 31(10):1415-1419.
67. Fassbender K, Pargger H, Muller W, Zimmerli W. Interleukin-6 and acute-phase protein concentrations in surgical intensive care unit patients: diagnostic signs in nosocomial infection. *Crit Care Med*. 1993;21(8):1175-1180.
68. Zhu J, Zhang J, Xiang D, et al. Recombinant human interleukin-1 receptor antagonist protects mice against acute doxorubicin-induced cardiotoxicity. *Eur J Pharmacol*. 2010;643(2-3):247-253.
69. Zhang B, Huang YH, Chen Y, et al. Plasma tumor necrosis factor-alpha, its soluble receptors and interleukin-1beta levels in critically burned patients. *Burns*. 1998;24(7):599-603.
70. Takeyoshi I, Yoshinari D, Kobayashi M, Kurabayashi M, Morishita Y. A dual inhibitor of TNF-alpha and IL-1 mitigates liver and kidney dysfunction and improves survival in rat endotoxemia. *Hepatogastroenterology*. 2005;52(65):1507-1510.
71. Lozano FS, Rodriguez JM, Garcia-Criado FJ, et al. Postoperative evolution of inflammatory response in a model of suprarenal aortic cross-clamping with and without hemorrhagic shock. Systemic and local reactions. *World J Surg*. 2005;29(10):1248-1258.
72. Levine RL, Hergenroeder GW, Francis JL, Miller CC, Hursting MJ. Heparin-platelet factor 4 antibodies in intensive care patients: an observational seroprevalence study. *J Thromb Thrombolysis*. 2010;30(2):142-148.
73. Rabinovici R, Esser KM, Lysko PG, et al. Priming by platelet-activating factor of endotoxin-induced lung injury and cardiovascular shock. *Circ Res*. 1991;69(1):12-25.
74. Qi M, Jones SB. Contribution of platelet activating factor to hemodynamic and sympathetic responses to bacterial endotoxin in conscious rats. *Circ Shock*. 1990;32(2):153-163.
75. Pawlik MT, Schreyer AG, Ittner KP, et al. Early treatment with pentoxifylline reduces lung injury induced by acid aspiration in rats. *Chest*. 2005;127(2):613-621.
76. Weiss SJ. Tissue destruction by neutrophils *N Engl J Med*. 1989;320(6): 365-376.
77. Gross CC, Brzostowski JA, Liu D, Long EO. Tethering of intercellular adhesion molecule on target cells is required for LFA-1-dependent NK cell adhesion and granule polarization. *J Immunol*. 2010;185(5):2918-2926.
78. White-Owen C, Alexander JW, Babcock GF. Reduced expression of neutrophil CD11b and CD16 after severe traumatic injury. *J Surg Res*. 1992;52(1):22-26.
79. Anderson DC, Springer TA. Leukocyte adhesion deficiency: an inherited defect in the Mac-1, LFA-1, and p150,95 glycoproteins. *Annu Rev Med*. 1987;38:175-194.
80. Benton LD, Khan M, Greco RS. Integrins, adhesion molecules and surgical research. *Surg Gynecol Obstet*. 1993;177(3):311-327.
81. Bautista AP, Schuler A, Spolarics Z, Spitzer JJ. Tumor necrosis factor-alpha stimulates superoxide anion generation by perfused rat liver and Kupffer cells. *Am J Physiol*. 1991;261(6 Pt 1):G891-G895.
82. Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature*. 1987;327(6122):524-526.
83. Thatcher GR. An introduction to NO-related therapeutic agents. *Curr Top Med Chem*. 2005;5(7):597-601.
84. Johnson RA, Durante W, Craig T, et al. Vascular arginase contributes to arteriolar endothelial dysfunction in a rat model of hemorrhagic shock. *J Trauma*. 2010;69(2):384-391.
85. Nava E, Palmer RM, Moncada S. Inhibition of nitric oxide synthesis in septic shock: how much is beneficial? *Lancet*. 1991;338(8782-8783):1555-1557.
86. Mathru M, Lang JD. Endothelial dysfunction in trauma patients: a preliminary communication. *Shock*. 2005;24(3):210-213.
87. Harkin DW, Marron CD, Rother RP, et al. C5 complement inhibition attenuates shock and acute lung injury in an experimental model of ruptured abdominal aortic aneurysm. *Br J Surg*. 2005;92(10):1227-1234.
88. Allen JN, Pacht ER, Gadek JE, Davis WB. Acute eosinophilic pneumonia as a reversible cause of noninfectious respiratory failure. *N Engl J Med*. 1989;321(9):569-574.
89. Cohen MJ, Carles M, Brohi K, et al. Early release of soluble receptor for advanced glycation endproducts after severe trauma in humans. *J Trauma*. 2010;68(6):1273-1278.
90. Livingston DH. Management of the surgical patient with multiple system organ failure. *Am J Surg*. 1993;165(2A suppl): 8S-13S.
91. Gauglitz GG, Williams FN, Herndon DN, Jeschke MG. Burns: where are we standing with propranolol, oxandrolone, recombinant human growth hormone, and the new incretin analogs? *Curr Opin Clin Nutr Metab Care*. 2011;14(2):176-181.
92. Sousse LE, Herndon DN, Mlcak RP, et al. Long-term administration of oxandrolone improves lung function in pediatric burned patients. *J Burn Care Res*. 2016;37(5):273-277.
93. Przkora R, Fram RY, Herndon DN, Suman OE, Mlcak RP. Influence of inhalation injury on energy expenditure in severely burned children. *Burns*. 2014;40(8):1487-1491.
94. Guillory AN, Clayton RP, Herndon DN, Finnerty CC. Cardiovascular dysfunction following burn injury: what we have learned from rat and mouse models. *Int J Mol Sci*. 2016;17(1).
95. Redl G, Abdi S, Traber LD, et al. Inhibition of thromboxane synthesis reduces endotoxin-induced right ventricular failure in sheep. *Crit Care Med*. 1991;19(10):1294-1302.
96. Farina Junior JA, Celotto AC, da Silva MF, Evora PR. Guanylate cyclase inhibition by methylene blue as an option in the treatment of vasoplegia after a severe burn. A medical hypothesis. *Med Sci Monit*. 2012;18(5):Hy13-Hy17.
97. Coz Yataco A, Aguinaga Meza M, Buch KP, Disselkamp MA. Hospital and intensive care unit management of decompensated pulmonary hypertension and right ventricular failure. *Heart Fail Rev*. 2016;21(3):323-346.
98. Cox RA, Jacob S, Andersen CR, et al. Integrity of airway epithelium in pediatric burn autopsies: association with age and extent of burn injury. *Burns*. 2015;41(7):1435-1441.
99. Palmieri TL, Warner P, Mlcak RP, et al. Inhalation injury in children: a 10 year experience at Shriners Hospitals for Children. *J Burn Care Res*. 2009;30(1):206-208.
100. Lopez E, Fujiwara O, Lima-Lopez F, et al. Nebulized epinephrine limits pulmonary vascular hyperpermeability to water and protein in ovine with burn and smoke inhalation injury. *Crit Care Med*. 2016;44(2):e89-e96.

101. Yamamoto Y, Sousse LE, Enkhbaatar P, et al. gamma-tocopherol nebulization decreases oxidative stress, arginase activity, and collagen deposition after burn and smoke inhalation in the ovine model. *Shock*. 2012;38(6):671-676.
102. Yamamoto Y, Enkhbaatar P, Sousse LE, et al. Nebulization with gamma-tocopherol ameliorates acute lung injury after burn and smoke inhalation in the ovine model. *Shock*. 2012;37(4):408-414.
103. Lange M, Hamahata A, Traber DL, et al. Pulmonary microvascular hyperpermeability and expression of vascular endothelial growth factor in smoke inhalation- and pneumonia-induced acute lung injury. *Burns*. 2012;38(7):1072-1078.
104. Maybauer MO, Maybauer DM, Fraser JF, et al. Recombinant human activated protein C attenuates cardiovascular and microcirculatory dysfunction in acute lung injury and septic shock. *Crit Care*. 2010;14(6):R217.
105. Slutsky AS, Ranieri VM. Mechanical ventilation: lessons from the ARDSNet trial. *Respir Res*. 2000;1(2):73-77.
106. Sousse LE, Herndon DN, Andersen CR, et al. High tidal volume decreases adult respiratory distress syndrome, atelectasis, and ventilator days compared with low tidal volume in pediatric burned patients with inhalation injury. *J Am Coll Surg*. 2015;220(4):570-578.
107. Rafat N, Tonshoff B, Bierhaus A, Beck GC. Endothelial progenitor cells in regeneration after acute lung injury: do they play a role? *Am J Respir Cell Mol Biol*. 2013;48(4):399-405.
108. Kraft R, Herndon DN, Mlcak RP, et al. Bacterial respiratory tract infections are promoted by systemic hyperglycemia after severe burn injury in pediatric patients. *Burns*. 2014;40(3):428-435.
109. Lautenschlager I, Frerichs I, Dombrowsky H, et al. Quinidine, but not eicosanoid antagonists or dexamethasone, protect the gut from platelet activating factor-induced vasoconstriction, edema and paralysis. *PLoS ONE*. 2015;10(3):e0120802.
110. Oliveira HM, Sallam HS, Espana-Tenorio J, et al. Gastric and small bowel ileus after severe burn in rats: the effect of cyclooxygenase-2 inhibitors. *Burns*. 2009;35(8):1180-1184.
111. Chung DH, Herndon DN. Multiple converging mechanisms for postburn intestinal barrier dysfunction. *Crit Care Med*. 2004;32(8):1803-1804.
112. Herndon DN, Lal S. Is bacterial translocation a clinically relevant phenomenon in burns? *Crit Care Med*. 2000;28(5):1682-1683.
113. Baron P, Traber LD, Traber DL, et al. Gut failure and translocation following burn and sepsis. *J Surg Res*. 1994;57(1):197-204.
114. Gupta R, Patel K, Calder PC, et al. A randomised clinical trial to assess the effect of total enteral and total parenteral nutritional support on metabolic, inflammatory and oxidative markers in patients with predicted severe acute pancreatitis (APACHE II > or =6). *Pancreatology*. 2003;3(5):406-413.
115. Johnson LR, Copeland EM, Dudrick SJ, Lichtenberger LM, Castro GA. Structural and hormonal alterations in the gastrointestinal tract of parenterally fed rats. *Gastroenterology*. 1975;68(5 Pt 1):1177-1183.
116. McDonald WS, Sharp CW Jr, Deitch EA. Immediate enteral feeding in burn patients is safe and effective. *Ann Surg*. 1991;213(2):177-183.
117. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian Critical Care Clinical Practice Guidelines C. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr*. 2003;27(5):355-373.
118. Sheridan RL, Prelack K, Yu YM, et al. Short-term enteral glutamine does not enhance protein accretion in burned children: a stable isotope study. *Surgery*. 2004;135(6):671-678.
119. Weitzel LR, Wischmeyer PE. Glutamine in critical illness: the time has come, the time is now. *Crit Care Clin*. 2010;26(3):515-525, ix-x.
120. Wischmeyer PE. Glutamine: mode of action in critical illness. *Crit Care Med*. 2007;35(9 suppl):S541-S544.
121. Wischmeyer PE. Can glutamine turn off the motor that drives systemic inflammation? *Crit Care Med*. 2005;33(5):1175-1178.
122. Spaeth G, Gottwald T, Haas W, Holmer M. Glutamine peptide does not improve gut barrier function and mucosal immunity in total parenteral nutrition. *JPEN*. 1993;17(4):317-323.
123. Roediger WE. Utilization of nutrients by isolated epithelial cells of the rat colon. *Gastroenterology*. 1982;83(2):424-429.
124. Fedorak RN, Madsen KL. Probiotics and prebiotics in gastrointestinal disorders. *Curr Opin Gastroenterol*. 2004;20(2):146-155.
125. Gun F, Salman T, Gurler N, Olgac V. Effect of probiotic supplementation on bacterial translocation in thermal injury. *Surg Today*. 2005;35(9):760-764.
126. Blot S, Torres A, Francois B. Evidence in the eye of the beholder: about probiotics and VAP prevention. *Intensive Care Med*. 2016;42(7):1182-1184.
127. Mayes T, Gottschlich MM, James LE, et al. Clinical safety and efficacy of probiotic administration following burn injury. *J Burn Care Res*. 2015;36(1):92-99.
128. Gastinne H, Wolff M, Delatour F, Faurisson F, Chevret S. A controlled trial in intensive care units of selective decontamination of the digestive tract with nonabsorbable antibiotics. The French Study Group on Selective Decontamination of the Digestive Tract. *N Engl J Med*. 1992;326(9):594-599.
129. Giamarellos-Bourboulis EJ, Bengmark S, Kanellakopoulou K, Kotzampassi K. Pro- and synbiotics to control inflammation and infection in patients with multiple injuries. *J Trauma*. 2009;67(4):815-821.
130. Rivero HG, Lee JO, Herndon DN, et al. The role of acute pancreatitis in pediatric burn patients. *Burns*. 2011;37(1):82-85.
131. Jeschke MG, Boehning DF, Finnerty CC, Herndon DN. Effect of insulin on the inflammatory and acute phase response after burn injury. *Crit Care Med*. 2007;35(9 suppl):S519-S523.
132. Wolfe RR, Herndon DN, Peters EJ, et al. Regulation of lipolysis in severely burned children. *Ann Surg*. 1987;206(2):214-221.
133. Lee JO, Gauglitz GG, Herndon DN, et al. Association between dietary fat content and outcomes in pediatric burn patients. *J Surg Res*. 2011;166(1):e83-e90.
134. Henrion J, Schapira M, Luwaert R, et al. Hypoxic hepatitis: clinical and hemodynamic study in 142 consecutive cases. *Medicine (Baltimore)*. 2003;82(6):392-406.
135. Wang DW, Yin YM, Yao YM. Advances in the management of acute liver failure. *World J Gastroenterol*. 2013;19(41):7069-7077.
136. Barrow RE, Jeschke MG, Herndon DN. Early fluid resuscitation improves outcomes in severely burned children. *Resuscitation*. 2000;45(2):91-96.
137. Chrysopoulo MT, Jeschke MG, Dziewulski P, Barrow RE, Herndon DN. Acute renal dysfunction in severely burned adults. *J Trauma*. 1999;46(1):141-144.
138. Mason SA, Nathens AB, Finnerty CC, et al. Hold the pendulum: rates of acute kidney injury are increased in patients who receive resuscitation volumes less than predicted by the Parkland Equation. *Ann Surg*. 2016;264(6):1142-1147.
139. Helantera I, Koljonen V, Finne P, Tukiainen E, Gissler M. The risk for end-stage renal disease is increased after burn. *Burns*. 2016;42(2):316-321.
140. Norbury W, Herndon DN, Tanksley J, Jeschke MG, Finnerty CC. Infection in burns. *Surg Infect (Larchmt)*. 2016;17(2):250-255.
141. Sasaki TM, Welch GW, Herndon DN, et al. Burn wound manipulation-induced bacteremia. *J Trauma*. 1979;19(1):46-48.
142. Beard CH, Ribeiro CD, Jones DM. The bacteraemia associated with burns surgery. *Br J Surg*. 1975;62(8):638-641.
143. Piel P, Scarnati S, Goldfarb IW, Slater H. Antibiotic prophylaxis in patients undergoing burn wound excision. *J Burn Care Rehabil*. 1985;6(5):422-424.
144. Sheridan RL. Sepsis in pediatric burn patients. *Pediatr Crit Care Med*. 2005;6(3 suppl):S112-S119.
145. Apple J, Hunt JL, Wait M, Purdue G. Delayed presentations of aortic valve endocarditis in patients with thermal injury. *J Trauma*. 2002;52(2):406-409.
146. Munster AM, DiVincenti FC, Foley FD, Pruitt BA Jr. Cardiac infections in burns. *Am J Surg*. 1971;122(4):524-527.
147. Pruitt BA Jr, Stein JM, Foley FD, Moncrief JA, O'Neill JA Jr. Intravenous therapy in burn patients. Suppurative thrombophlebitis and other life-threatening complications. *Arch Surg*. 1970;100(4):399-404.
148. Pruitt BA Jr, McManus WF, Kim SH, Treat RC. Diagnosis and treatment of cannula-related intravenous sepsis in burn patients. *Ann Surg*. 1980;191(5):546-554.
149. Sheridan RL, Tompkins RG, McManus WF, Pruitt BA Jr. Intracompartmental sepsis in burn patients. *J Trauma*. 1994;36(3):301-305.
150. Shirani KZ, Pruitt BA Jr, Mason AD Jr. The influence of inhalation injury and pneumonia on burn mortality. *Ann Surg*. 1987;205(1):82-87.
151. Silvestri L, van Saene HK, de la Cal MA, Gullo A. Adult hospital and ventilator-associated pneumonia guidelines: eminence- rather than evidence-based. *Am J Respir Crit Care Med*. 2006;173(1):131-133, author reply 133.

152. Deutschman CS, Wilton P, Sinow J, et al. Paranasal sinusitis associated with nasotracheal intubation: a frequently unrecognized and treatable source of sepsis. *Crit Care Med*. 1986;14(2):111-114.
153. Fourrier F, Dubois D, Pronnier P, et al. Effect of gingival and dental plaque antiseptic decontamination on nosocomial infections acquired in the intensive care unit: a double-blind placebo-controlled multicenter study. *Crit Care Med*. 2005;33(8):1728-1735.
154. Huffman JL, Schenker S. Acute acalculous cholecystitis: a review. *Clin Gastroenterol Hepatol*. 2010;8(1):15-22.
155. Morse BC, Smith JB, Lawdahl RB, Roettger RH. Management of acute cholecystitis in critically ill patients: contemporary role for cholecystostomy and subsequent cholecystectomy. *Am Surg*. 2010;76(7):708-712.
156. Crimi E, Sica V, Williams-Ignarro S, et al. The role of oxidative stress in adult critical care. *Free Radic Biol Med*. 2006;40(3):398-406.
157. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-1377.
158. Levy MM, Rhodes A, Phillips GS, et al. Surviving Sepsis Campaign: association between performance metrics and outcomes in a 7.5-year study. *Crit Care Med*. 2015;43(1):3-12.
159. Cancio LC, Galvez E Jr, Turner CE, et al. Base deficit and alveolar-arterial gradient during resuscitation contribute independently but modestly to the prediction of mortality after burn injury. *J Burn Care Res*. 2006;27(3):289-296, discussion 296-297.
160. Alam HB, Rhee P. New developments in fluid resuscitation. *Surg Clin North Am*. 2007;87(1):55-72, vi.
161. Heyland D, Dhaliwal R. Immunonutrition in the critically ill: from old approaches to new paradigms. *Intensive Care Med*. 2005;31(4):501-503.
162. Barton RG, Wells CL, Carlson A, et al. Dietary omega-3 fatty acids decrease mortality and Kupffer cell prostaglandin E2 production in a rat model of chronic sepsis. *J Trauma*. 1991;31(6):768-773, discussion 773-774.
163. Hasselmann M, Reimund JM. Lipids in the nutritional support of the critically ill patients. *Curr Opin Crit Care*. 2004;10(6):449-455.
164. Singer P, Cohen JD. From immune-enhancing diets back to nutritional-enhancing diets. *Nutrition*. 2005;21(2):282-283.
165. Mizock BA. Immunonutrition and critical illness: an update. *Nutrition*. 2010;26(7-8):701-707.
166. Kieft H, Roos AN, van Drunen JD, et al. Clinical outcome of immunonutrition in a heterogeneous intensive care population. *Intensive Care Med*. 2005;31(4):524-532.
167. Hurt RT, Matheson PJ, Mays MP, Garrison RN. Immune-enhancing diet and cytokine expression during chronic sepsis: an immune-enhancing diet containing L-arginine, fish oil, and RNA fragments promotes intestinal cytokine expression during chronic sepsis in rats. *J Gastrointest Surg*. 2006;10(1):46-53.
168. Shang HF, Hsu CS, Yeh CL, Pai MH, Yeh SL. Effects of arginine supplementation on splenocyte cytokine mRNA expression in rats with gut-derived sepsis. *World J Gastroenterol*. 2005;11(45):7091-7096.
169. Hart DW, Wolf SE, Mlcak R, et al. Persistence of muscle catabolism after severe burn. *Surgery*. 2000;128(2):312-319.
170. Wolf SE, Edelman LS, Kemalyan N, et al. Effects of oxandrolone on outcome measures in the severely burned: a multicenter prospective randomized double-blind trial. *J Burn Care Res*. 2006;27(2):131-139, discussion 140-141.
171. Jolles S, Sewell WA, Misbah SA. Clinical uses of intravenous immunoglobulin. *Clin Exp Immunol*. 2005;142(1):1-11.
172. Hackshaw KV, Parker GA, Roberts JW. Naloxone in septic shock. *Crit Care Med*. 1990;18(1):47-51.
173. Siraux V, De Backer D, Yalavatti G, et al. Relative adrenal insufficiency in patients with septic shock: comparison of low-dose and conventional corticotropin tests. *Crit Care Med*. 2005;33(11):2479-2486.
174. McCune S, Short BL, Miller MK, Lotze A, Anderson KD. Extracorporeal membrane oxygenation therapy in neonates with septic shock. *J Pediatr Surg*. 1990;25(5):479-482.
175. Munster AM, Xiao GX, Guo Y, Wong LA, Winchurch RA. Control of endotoxemia in burn patients by use of polymyxin B. *J Burn Care Rehabil*. 1989;10(4):327-330.
176. Ziegler EJ, McCutchan JA, Fierer J, et al. Treatment of gram-negative bacteremia and shock with human antiserum to a mutant Escherichia coli. *N Engl J Med*. 1982;307(20):1225-1230.
177. Greenman RL, Schein RM, Martin MA, et al. A controlled clinical trial of E5 murine monoclonal IgM antibody to endotoxin in the treatment of gram-negative sepsis. The XOMA Sepsis Study Group. *JAMA*. 1991;266(8):1097-1102.
178. Wenzel RP. Anti-endotoxin monoclonal antibodies: a second look. *N Engl J Med*. 1992;326(17):1151-1153.
179. Ziegler EJ, Fisher CJ Jr, Sprung CL, et al. Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin. A randomized, double-blind, placebo-controlled trial. The HA-1A Sepsis Study Group. *N Engl J Med*. 1991;324(7):429-436.
180. Rice TW, Bernard GR. Therapeutic intervention and targets for sepsis. *Annu Rev Med*. 2005;56:225-248.
181. Virdis A, Colucci R, Fornai M, et al. Cyclooxygenase-2 inhibition improves vascular endothelial dysfunction in a rat model of endotoxic shock: role of inducible nitric-oxide synthase and oxidative stress. *J Pharmacol Exp Ther*. 2005;312(3):945-953.
182. Tempel GE, Cook JA, Wise WC, Halushka PV, Corral D. Improvement in organ blood flow by inhibition of thromboxane synthetase during experimental endotoxic shock in the rat. *J Cardiovasc Pharmacol*. 1986;8(3):514-519.
183. Revhaug A, Michie HR, Manson JM, et al. Inhibition of cyclo-oxygenase attenuates the metabolic response to endotoxin in humans. *Arch Surg*. 1988;123(2):162-170.
184. Bernard GR, Reines HD, Halushka PV, et al. Prostacyclin and thromboxane A2 formation is increased in human sepsis syndrome. Effects of cyclooxygenase inhibition. *Am Rev Respir Dis*. 1991;144(5):1095-1101.
185. Schutzer KM, Haglund U, Falk A. Cardiopulmonary dysfunction in a feline septic shock model: possible role of leukotrienes. *Circ Shock*. 1989;29(1):13-25.
186. Coggeshall JW, Christman BW, Lefferts PL, et al. Effect of inhibition of 5-lipoxygenase metabolism of arachidonic acid on response to endotoxemia in sheep. *J Appl Physiol*. 1988;65(3):1351-1359.
187. Patel JP, Beck LD, Briglia FA, Hock CE. Beneficial effects of combined thromboxane and leukotriene receptor antagonism in hemorrhagic shock. *Crit Care Med*. 1995;23(2):231-237.
188. Ohlsson K, Bjork P, Bergenfeldt M, Hageman R, Thompson RC. Interleukin-1 receptor antagonist reduces mortality from endotoxin shock. *Nature*. 1990;348(6301):550-552.
189. Watters JM, Bessey PQ, Dinarello CA, Wolff SM, Wilmore DW. The induction of interleukin-1 in humans and its metabolic effects. *Surgery*. 1985;98(2):298-306.
190. Tracey KJ, Fong Y, Hesse DG, et al. Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. *Nature*. 1987;330(6149):662-664.
191. Hinshaw LB, Tekamp-Olson P, Chang AC, et al. Survival of primates in LD100 septic shock following therapy with antibody to tumor necrosis factor (TNF alpha). *Circ Shock*. 1990;30(3):279-292.
192. Gallagher J, Fisher C, Sherman B, et al. A multicenter, open-label, prospective, randomized, dose-ranging pharmacokinetic study of the anti-TNF-alpha antibody afelimomab in patients with sepsis syndrome. *Intensive Care Med*. 2001;27(7):1169-1178.
193. Eskandari MK, Bolgos G, Miller C, et al. Anti-tumor necrosis factor antibody therapy fails to prevent lethality after cecal ligation and puncture or endotoxemia. *J Immunol*. 1992;148(9):2724-2730.
194. Pitman JM 3rd, Thurman GW, Anderson BO, et al. WEB2170, a specific platelet-activating factor antagonist, attenuates neutrophil priming by human serum after clinical burn injury: the 1991 Moyer Award. *J Burn Care Rehabil*. 1991;12(5):411-419.
195. Chang SW, Fernyak S, Voelkel NF. Beneficial effect of a platelet-activating factor antagonist, WEB 2086, on endotoxin-induced lung injury. *Am J Physiol*. 1990;258(1 Pt 2):H153-H158.
196. Fletcher JR, DiSimone AG, Earnest MA. Platelet activating factor receptor antagonist improves survival and attenuates eicosanoid release in severe endotoxemia. *Ann Surg*. 1990;211(3):312-316.
197. Iwase M, Yokota M, Kitaichi K, et al. Cardiac functional and structural alterations induced by endotoxin in rats: importance of platelet-activating factor. *Crit Care Med*. 2001;29(3):609-617.
198. Eichacker PQ, Farese A, Hoffman WD, et al. Leukocyte CD11b/18 antigen-directed monoclonal antibody improves early survival and decreases hypoxemia in dogs challenged with tumor necrosis factor. *Am Rev Resp Dis*. 1992;145(5):1023-1029.
199. Levy RJ, Stern WB, Minger KI, et al. Evaluation of tissue saturation as a noninvasive measure of mixed venous saturation in children. *Pediatr Crit Care Med*. 2005;6(6):671-675.

200. Richard C, Lemonnier F, Thibault M, Couturier M, Auzepy P. Vitamin E deficiency and lipoperoxidation during adult respiratory distress syndrome. *Crit Care Med*. 1990;18(1):4-9.
201. Bayir H. Reactive oxygen species. *Crit Care Med*. 2005;33(12 suppl):S498-S501.
202. Novelli GP. Oxygen radicals in experimental shock: effects of spin-trapping nitrones in ameliorating shock pathophysiology. *Crit Care Med*. 1992;20(4):499-507.
203. Hauser B, Bracht H, Matejovic M, Radermacher P, Venkatesh B. Nitric oxide synthase inhibition in sepsis? Lessons learned from large-animal studies. *Anesth Analg*. 2005;101(2):488-498.
204. Cobb JP, Cunnion RE, Danner RL. Nitric oxide as a target for therapy in septic shock. *Crit Care Med*. 1993;21(9):1261-1263.
205. Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT, Stone D, Wallwork J. Inhaled nitric oxide as a cause of selective pulmonary vasodilatation in pulmonary hypertension. *Lancet*. 1991; 338(8776):1173-1174.
206. Saffle JR, Sullivan JJ, Tuohig GM, Larson CM. Multiple organ failure in patients with thermal injury. *Crit Care Med*. 1993;21(11): 1673-1683.

31 Acute Renal Failure in Association with Thermal Injury

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Introduction

Acute renal dysfunction represents a critical complication of an acute thermal injury and is associated with a significant increase in morbidity and mortality. Currently, the incidence of acute renal failure (ARF) in burn patients varies between 0.5% and 30%, and the risk of mortality associated with renal failure in burn patients has been reported to be as high as 54–100%.[1–11]

Prior to 1965, there were no reported survivors from ARF following a thermal injury.[12] Clearly the care of patients with renal injuries has improved during the past 50 years. However, while advances have been made in the understanding of burn-associated ARF, very few specific interventions have been clearly shown to change outcomes in these patients. Even renal replacement therapy (RRT), one of the core milestones of modern medical progress, has yet to show a significant improvement in the mortality rate of burn patients suffering from ARF.[13] As such, the optimal treatment for acute renal failure remains prevention.

This chapter will review the definition, etiology, pathophysiology, diagnosis, and treatment of acute renal failure in association with thermal injury (Fig. 31.1).

Definition

Intuitively ARF is easily understood as an abrupt decline in renal function. Precisely how to quantify renal function and where to place the threshold for "failure" has long been open to interpretation. Until 2004, with no consensus regarding a definition for ARF, more than 30 different definitions were used within the literature at the time. The need for a common working definition of renal failure prompted an effort to standardize the definition of renal insufficiency, with the International Acute Dialysis Quality Initiative (ADQI) group developing the RIFLE criteria for kidney injuries in 2004. The RIFLE criteria divided renal compromise into five discrete categories: Risk, Injury, Failure, Loss, and End-stage renal disease (Fig. 31.2). In addition to establishing a common definition, the RIFLE criteria provided a means to quantify degrees of acute kidney insufficiency or injury (AKI).[14] In 2007, the Acute Kidney Injury Network (AKIN) introduced an updated definition of acute kidney injury; see Tables 31.1 and 31.2.[15] The AKIN definition simplified the stratification of renal injury into three stages (I, II, and III), with the RIFLE Failure, Loss, and End-stage renal disease categories folded into grade III. There was also an increased sensitivity (relative to the RIFLE criteria) by virtue of use of an absolute increase in serum creatinine of 0.3 mg/dL or more as sufficient to define a stage I injury. In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group published a consensus definition of renal injury that essentially merged the two previous frameworks, with slight adjustments.[16]

While the proliferation of consensus definitions may seem to undermine the basic goal of establishing a universal metric for research and clinical applications, the three systems have proved fairly interchangeable. Multiple studies applying the different scoring systems to the same patient populations have found that they ultimately yield similar results.[17,18] Specifically in burn populations, Chung et al. found that RIFLE and AKIN identified similar subpopulations when applied to a large cohort of patients.[19]

Etiology

Burn-associated acute kidney injuries can generally be divided into two categories, early and late. AKI presenting within the first 48 hours of the burn injury (i.e., early AKI) typically results from either uncontrolled burn shock, underresuscitation, or protein degradation products. Renal injury manifesting later in the course of acute burn care (i.e., late-onset AKI) typically represents either a medication toxicity or a complication of sepsis.

EARLY

Within the first 24–28 hours of a massive burn injury, AKI results from the pathologic response to thermal injury. Early burn-associated AKI is multifactorial, with hypovolemia, inflammatory mediators, cytokines, extensive tissue destruction and release of denatured proteins, iatrogenic causes (nephrotoxic agents), and cardiac dysfunction all contributing to the renal insult. In the setting of delayed resuscitation, hypovolemia is the most immediate threat to renal function. And yet AKI can still develop in the thermally-injured patient despite aggressive fluid resuscitation and a normal urine output. In such cases, renal injury might reflect a fluid-refractory, inflammatory shock in response to the burned tissue, cardiac dysfunction, or injury from nephrotoxins, which can be either endogenous (denatured proteins) or exogenous (medications) in nature.[20,21]

Hypovolemia

In large surface area burns, decreased renal blood flow results from massive fluid shifts and losses. Local and systemic cytokine release leads to "capillary leak," shifting

fluids from the intravascular to interstitial space. Burn-induced compromise of the water-tight dermal barriers results in rapid evaporative losses from the extravascular compartment, which facilitates further extravasation of the intravascular compartment in a vicious cycle.[22] Given the sheer speed and volume fluid shift seen in burn shock, profound intravascular hypovolemia can result. Renal blood flow is restricted in a compensatory response to hypovolemia resulting in renal ischemia. The ischemic insult is known to produce oxygen free radicals that cause direct tubular damage as well as disruption of tight junctions, resulting in obstructing casts that further reduce effective glomerular filtration rate (GFR).

Hypovolemia can develop within the course of minutes in the absence of appropriate fluid replacement. As such, hypovolemia represents by far the most likely source of AKI

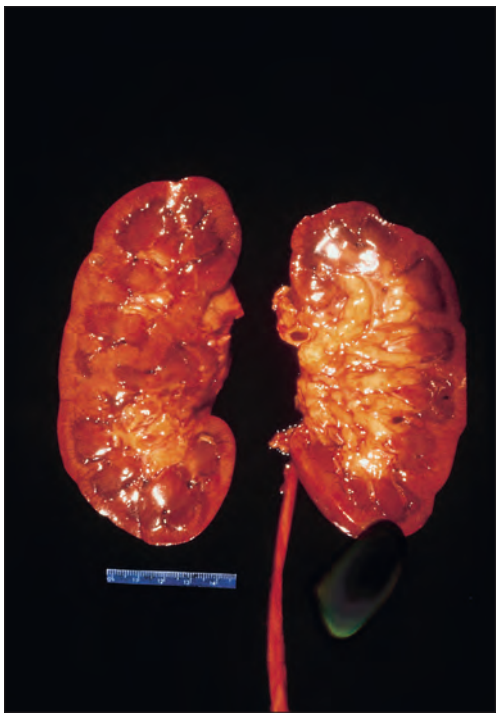

Fig. 31.1 Autopsy specimen from a patient with acute tubular necrosis and renal failure. Note the edema and the alteration of medullar pyramids. Acute renal failure in burn patients carries a high mortality.

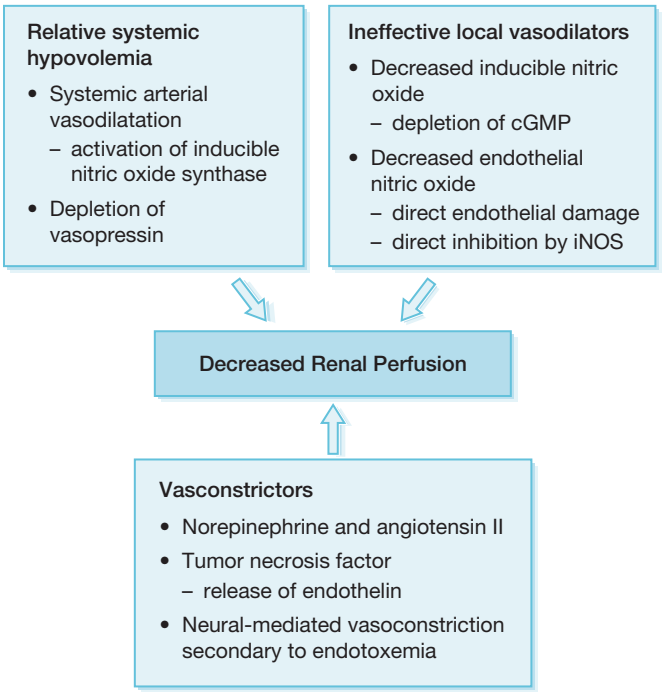

Fig. 31.2 Multifactorial etiology of sepsis-induced acute renal failure (ARF).

Table 31.1 Comparison of Serum Creatinine Criteria in RIFLE, AKIN, and KDIGO Systems

SERUM CREATININE CRITERIA FOR THE DEFINITION AND CLASSIFICATION OF ACUTE KIDNEY INJURY				
RIFLE Criteria—The Acute Dialysis Quality Initiative (ADQI)		**AKIN Criteria—Acute Kidney Injury Network**	**KDIGO Criteria—Kidney Disease Improving Global Outcomes**	
Risk	Increase in serum creatinine ≥1.5 times baseline OR Decrease in GFR ≥25%	Increase to 1.5–1.9 times baseline OR Increase in serum creatinine of ≥3 mg/dL (26.2 µmol/L) from baseline	Increase to 1.5–1.9 times baseline OR Increase in serum creatinine of ≥0.3 mg/dL (26.2 µmol/L) from baseline	Stage I
Injury	Increase in serum creatinine ≥2.0 times baseline or decrease in GFR ≥50%	Increase in serum creatinine to 2–2.9 times baseline	Increase in serum creatinine to 2–2.9 times baseline	Stage II
Failure	Increase in serum creatinine ≥3.0 times baseline OR Decrease in GFR ≥75% OR An absolute serum creatinine ≥354 µmol/L with an acute rise of at least 44 µmol/L	Increase in serum creatinine to ≥3 times baseline OR Serum creatinine ≥4.0 mg/dL (354 µmol/L) with an acute rise of ≥05 mg/dL (44 µmol/L) OR Initiation of renal replacement therapy	Increase in serum creatinine to a level ≥4.0 mg/dL (353.6) OR Initiation of renal replacement therapy	Stage III

Note—Urine output-based criteria are the same in all three systems.

From Brochard L, Abroug F, Brenner M, et al., on behalf of the ATS/ERS/ESICM/SCCM/SRLF Ad Hoc Committee on Acute Renal Failure. An official ATS/ERS/ESICM/SCCM/SRLF statement: prevention and management of ARF in the ICU patient: an international consensus conference in intensive care medicine. *Am J Respir Crit Care Med*. 2010;181(10):1128–1155. Updated with current reference to published KDIGO guidelines.

Table 31.2 Comparison of Serum Creatinine Criteria in RIFLE, AKIN, and KDIGO Systems

KDIGO CRITERIA FOR RENAL INJURY		
Stage	**Serum Creatinine Criteria**	**UO Criteria**
I	Increase to 1.5–1.9 times baseline OR Increase in serum creatinine of ≥0.3 mg/dL (26.2 μmol/L) from baseline	<0.5 mL/kg/h for ≥6 h
II	Increase in serum creatinine to 2–2.9 times baseline	<0.5 mL/kg/h for >12 h
III	Increase in serum creatinine to a level ≥4.0 mg/dL (353.6) OR Initiation of renal replacement therapy	<0.3 mL/kg/h ≥24 h or anuria ≥12 h

From Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120(4):c179–184.

in any burn patient showing signs of renal insult within 24 hours of their burn.

Overresuscitation and Abdominal Compartment Syndrome

Unfortunately, overadministration of fluids can be just as harmful as underresuscitation. Studies have shown that AKI can develop in burn patients despite fluid resuscitation volumes in excess of that recommended by the Parkland formula and despite normal average urine output (0.5–1.0 mL/kg per hour).[5,23] Furthermore the risks of overresuscitation have been well-documented and include pneumonia, acute respiratory distress syndrome (ARDS), compartment syndromes, and an overall increase in mortality.[23,24]

Despite the physician's greatest effort to monitor endpoints of resuscitation, obligatory intercompartmental fluid shifts will occur during resuscitation.[25] These intercompartmental fluid shifts can be particularly hazardous if they occur into fascial bound compartments, such as the peritoneal cavity. Numerous studies from trauma literature have described the adverse physiologic effects of increasing intraabdominal pressure on visceral perfusion.[6,26,27] Intraabdominal hypertension (IAH) is a known pathological process that may occur during initial burn resuscitation as defined by intraabdominal pressures (IAPs) of greater than 12 mm Hg. Abdominal compartment syndrome (ACS) is defined as an IAP of greater than 20 mm Hg with at least one concomitant organ failure. The exact level of abdominal hypertension required to compromise visceral perfusion varies depending on a variety of patient factors and is difficult to predict.[28–30] O'Mara et al. demonstrated that the volume and type of fluid resuscitation affects the development of ACS in the burn patient and suggested that fluid resuscitation with crystalloid of greater than 0.475 L/kg should alert the clinician to possible IAH/ACS and to monitor for decreased cardiac output, decreased lung compliance, or decreased renal perfusion. In a mixed population of critically ill patients, a multicenter prospective trial has demonstrated that the occurrence of IAH during the ICU stay was an independent outcome predictor.[28]

Rhabdomyolysis

Rhabdomyolysis frequently presents within 24 hours of thermal injury and represents a well-documented risk for AKI and subsequent renal failure.[31] Rhabdomyolysis can arise secondary to direct thermal damage or compartment syndrome and is commonly seen following a severe electrical injury. The release of myoglobin into the systemic circulation results in blockage of renal tubules, constriction of afferent arterioles, and the generation of oxygen free radicals. Myoglobinuria occurs when serum myoglobin exceeds 1500–3000 ng/mL. Myoglobinuria does not always result in renal injury, but certain risk factors have been identified. The risk of renal injury is directly related to the amount of iron-containing molecules released, the state of hydration, and the degree of associated acidosis.[32] Elevated creatinine at baseline and creatinine kinase levels greater than 5000 U/L have been associated with the development of AKI and the need for RRT, both in general trauma populations and in studies of burn patients.[32,33]

Cardiac Dysfunction

Patients suffering burns greater than 50% total body surface area (TBSA) are subject to decreased cardiac output, increased myocardial workload, and myocardial ischemia. Several authors have suggested theories to explain the decreased cardiac output associated with thermal injury: (1) increased sympathetic activity with impaired adrenal response, (2) hypovolemia resulting in myocardial ischemia, and (3) direct myocardial suppression.[34–40] Of the potential theories, direct myocardial suppression by tumor necrosis factor (TNF; i.e., myocardial depressant factor) has gained substantial interest. TNF is known to be released by myocytes stimulated by endotoxin or direct thermal injury.[41–47] The effects of TNF on cardiac function include reversible biventricular dilatation, decreased ejection fraction, and decreased stimulation to catecholamines (Fig. 31.2).[41,48,49] This is typically a transient phenomenon, and, with adequate support, it usually resolves within 24–72 hours. Without appropriate support, though, frank heart failure can develop, bringing a myriad of complications with long-lasting or even permanent sequelae. Although most early cardiac dysfunction caused by TNF can be reversed by inotropic support, the key is early diagnosis to prevent ineffective renal perfusion and thus prevent the morbidity and mortality associated with renal insufficiency.

Cardiac dysfunction is known to result in reduced renal blood flow and hence to contribute to AKI. Although diminished cardiac output following thermal injury has been attributed to decreased preload or hypovolemia, there is also evidence of direct myocardial suppression, The impact of this suppression can range from clinically undetectable to frank cardiac shock. Often, this presents as a lack of appropriate cardiac compensation for distributive burn shock. Myocardial dysfunction after thermal injury is commonly overlooked by physicians due to the concentrated effort to correct the overwhelming state of hypovolemic shock and electrolyte abnormalities. In a patient presenting with burn shock (i.e., hypoperfusion) and found to have a cardiac index in "normal" range (rather than the expected supranormal values), serious consideration should be given to

inotropic support, particularly when accompanied by the finding of a low systemic vascular resistance index.

In any case of suspected cardiac dysfunction, a typical workup should be performed to rule out any coronary or mechanical etiology. Absent any such finding, an effective burn surgeon must rapidly reestablish adequate renal blood flow by correcting the diminished preload state while keeping in mind the impact of burn injury on the entire cardiovascular system.

LATE

AKI presenting later in the course of treatment for a massive burn typically occurs as a component of multiorgan failure, most commonly from sepsis. Given the high risk for infection and the difficulty of diagnosing such infections in this patient population, underlying infection and sepsis must be seriously considered in any patient found to have new or worsening renal failure more than 48 hours out from their initial injury.

Iatrogenic renal injury is also an important consideration in late burn-associated AKI, particularly given these patients' frequent exposure to multiple antibiotics and diuretics.

Sepsis

Early aggressive resuscitation and excision have significantly influenced the course of ARF immediately associated with thermal injury. Acute renal dysfunction associated with the septic syndrome nonetheless continues to cause significant mortality.[50,51]

Sepsis and septic shock are the most common cause of death in the ICU and are seen in up to 87% of cases of acute renal dysfunction in the burn ICU.[9,10] Several authors have found the degree of sepsis to be directly related to the incidence of acute renal dysfunction (Table 31.3).[52,53] The pathophysiology of AKI associated with sepsis is multifactorial in nature but begins clinically with a generalized arterial vasodilatation secondary to a decreased systemic vascular resistance (Fig. 31.2). Initially bacteria or their products activate sepsis-associated mediators (cytokines) locally at the site of direct invasion. The homeostatic balance between production and inactivation of these mediators is altered, allowing for systemic release and causing direct damage to the endothelium and vasoparesis, as well as a procoagulant state. It has been theorized that acute renal insufficiency associated with sepsis is the result of each of these pathological processes.

The vasoparesis seen in sepsis results in a profound state of hypotension, which activates the neurohumoral axis. In an effort to maintain systemic arterial circulation, the sympathetic nervous system and the renin–angiotensin–aldosterone axis respond by increasing cardiac output and by direct renal arteriolar vasoconstriction. Furthermore, the systemic inflammatory response results in the release of additional vasoconstricting cytokines (i.e., TNF, endothelin), locally secreted vasodilators (endothelial and inducible nitric oxide) to counterbalance these sepsis-associated vasoconstrictors.[50,54] Ultimately, this compensatory response comes at the cost of renal perfusion by further exaggerating the prerenal state.

Finally, as mentioned previously, sepsis induces a procoagulant state by affecting the expression of complement and the fibrinolytic cascade.[55–57] This alteration in the homeostasis of coagulation may result in a state of disseminated intravascular coagulation (DIC) with direct injury to the kidney by glomeruli microthrombi.[58] The net result is a lack of perfusion to the kidneys during sepsis that will ultimately culminate in ischemic acute tubular necrosis.

Table 31.3 Renal Failure Dysfunction and Sepsis

	Sepsis	Severe Sepsis[a]	Septic Shock[b]
Acute renal dysfunction	19%	23%	51%

[a]Sepsis associated with lactic acidosis or altered mental status.
[b]Sepsis associated with hypotension.

TOXINS

Antibiotics

Given the immunocompromise associated with massive burn injuries, burn patients tend to accrue significant exposure to systemic antibiotics over the course of their care. Unfortunately, many of the systemic antimicrobial agents most commonly used in burn patients carry significant risk of nephrotoxicity.

With meticillin-resistant *Staphylococcus aureus* (MRSA) now endemic in most hospital systems, vancomycin has become a standard first-line agent for empiric coverage of nosocomial infections in ICUs, including burn units. Given the well-documented nephrotoxic potential of vancomycin, alternative options should always be considered in patients already showing signs of early AKI, especially when cultures or Gram stains indicate a source of infection other than MRSA.

When vancomycin is clearly indicated, there are measures one can take to minimize the risk of nephrotoxity. Multiple studies have indicated that longer duration of therapy and higher serum concentration troughs are associated with increased risks of vancomycin-associated renal injury.[59,60] As concomitant aminoglycoside therapy has also been shown to significantly increase the chance of renal insult, these agents are best avoided when using vancomycin as a component of combination antimicrobial therapy. Some have advocated treatment with continuous infusion of vancomycin rather than intermittent boluses to avoid renal injury. In aggregate, though, the literature supporting this approach is fairly underwhelming. Meta-analysis by Hanrahan et al. identified a trend toward decreased rates of AKI in patients treated with vancomycin via continuous infusion versus intermittent bolus administration, but this did not reach statistical significance.

The incidence of multiresistant organisms is and will continue to be an ongoing challenge. This had led to the use of antimicrobial agents that carry a significant risk of nephrotoxicity. The use of these potentially nephrotoxic antimicrobial agents must be weighed on a risk–benefit scale due to the potential morbidity associated with inducing AKI. Antimicrobial therapy should be based on culture data, with the goal of down escalating therapy to the fewest

necessary antimicrobials and safest complication profile (i.e., the least nephrotoxic).

Diagnosis

Technically, using the consensus definitions discussed earlier, diagnosing AKI requires no more than measuring serum creatinine, eGFR, and/or urine output and identifying injury when any of these measures meet criteria set by the chosen definition (i.e., AKIN, RIFLE, or KDIGO). However, additional investigation is often warranted in order to delineate the nature and etiology of each individual case of AKI to allow for more informed treatment. Furthermore, a vigorous research effort is ongoing to identify novel biomarkers which might serve as a means to identify impending AKI earlier in the process.

URINE VOLUME

Urine represents by far the simplest and most intuitive monitor of renal function. Urine volume is a specific but, unfortunately, not very sensitive test for renal failure.[61] Most clinicians regard the presence of "adequate" urine output of little diagnostic value in the evaluation of renal dysfunction since severe renal injury may exist with any volume of urinary output. Urine output is not determined by the GFR alone but by the difference between GFR and tubular reabsorption. As such, AKI-associated tubular dysfunction can offset the decline in GFR, resulting in preserved urine output volume.

However anuria—a urine output of less than 50 mL/day or complete cessation of GFR—is a clinically significant finding.[9] By far, the most common cause is a severe prerenal condition. Although it is true that other conditions (acute cortical necrosis, bilateral arterial occlusion, and rapidly progressive acute glomerulonephritis) may cause anuria, their incidence is exceedingly low in the acute burn care setting, and the diagnosis is usually readily apparent due to additional clinical signs.

While a return of urine output in the oliguric or anuric patient may offer encouragement, it does not necessarily indicate reversal of the inciting renal injury. Of particular concern, one must be careful to watch for a conversion of anuric or oliguric renal failure to polyuric renal failure. Failure to appreciate a polyuric renal failure and replace inappropriate fluid losses could result in a second prerenal insult, increasing the risk of permanent damage.

URINALYSIS

Creatinine Clearance

Creatinine clearance is an inexpensive, consistent, time-tested technique for providing a rough estimate of GFR and renal function. Creatinine clearance measurement does involve the inconvenience of sustained urine collection, traditionally over a 24-hour period. However, this can be markedly simplified by forgoing the 24-hour convention for a more practical short-term (e.g., 6 hours or even 2 hours) collection, which has been shown to be just as accurate as the 24-hour assay and provides a more responsive measure of real-time function.

A significant disadvantage of creatinine clearance is that it becomes less accurate as GFR drops. This is due to the fact that renal tubules secrete a small amount of creatinine into the urine (in addition to that which is filtered). Normally, renal tubular secretion is so minor that it does not significantly impact the creatinine clearance calculations at normal GFRs, but can create significant distortion as the real GFR drops. The impact of these variations in tubular creatinine secretion can be largely overcome by administering cimetidine, which inhibits tubular creatinine secretion, an hour before urine collection.[62,63]

FeNa

The primary goal of evaluating urinary electrolytes in a thermally injured individual is to differentiate between the prerenal and renal forms of AKI. It has been well established that a prerenal state in the presence of a functional nephron is associated with enhanced absorption of sodium or a low fractional excretion of sodium. The fractional excretion of sodium (FeNa) is defined as:

$$\text{FeNa} = [(\text{urine sodium} \times \text{plasma creatinine}) / (\text{plasma sodium} \times \text{urinary creatinine})]$$

with a value less than 1% associated with a prerenal condition and a value greater than 1% associated with organ dysfunction (i.e., "renal" renal failure).[62] There are several conditions which affect renal absorption of sodium and thus have been shown to affect the calculated value (Table 31.4).

Fractional excretion of urea (<0.35) has shown marginally improved sensitivity and specificity over sodium in distinguishing between prerenal and renal forms of ARF.[64] Several additional indexes can be used to differentiate between the two forms of ARF (Table 31.5).

Microscopy

Microscopic examination of urinary sediment is an easy and inexpensive initial evaluation of AKI that often lends insight into the underlying renal pathology.[20,65] The combination of normal urinary sediment, hyaline casts, and oliguric/anuric urinary output would suggest a prerenal condition. The presence of epithelial casts and abundant tubular epithelial cells is pathognomonic for acute tubular necrosis. Similarly the identification of pigmented casts on

Table 31.4 Factors That Affect Fractional Secretion of Sodium

Condition	Effect on Fractional Sodium Excretion
Glycosuria	Increase
Diuretics	Increase
Mannitol	Increase
Dopamine	Increase
Myoglobinuria	Decrease
Radiocontrast media	Decrease

Table 31.5 Differential Diagnosis of Acute Renal Failure

Urinary Index	Pre-Renal	Renal
U_{osm} (mOsmol/L)	>500	<350
U_{Na} (mEq/L)	<20	>40
Specific gravity	1.020	1.010
U_{creat}/P_{creat}	>40	<20
Fractional excretion of sodium	<1	>2
Fractional excretion of urea	<35	>50

Table 31.6 Factors Affecting Serum Creatinine

Factors	Effect on Serum Creatinine
Liver insufficiency	Decreased production
Decreased muscle mass:	
deconditioning	Decreased production
aging	Decreased production
Trauma	Increased production
Fever	Increased production
Immobilization	Increased production

microscopic evaluation signifies the diagnosis of myoglobinuria, likely secondary to rhabdomyolysis.

SERUM BIOMARKERS

Creatinine

For generations, creatinine has served as the most widely used marker of renal function. There is no question that creatinine levels correlate to renal function, and acute elevations of creatinine are clearly associated with an increased risk of renal failure and additional mortality. Indeed, serum creatinine levels (and changes therein) are central components to all of the three consensus AKI definition and staging systems proposed in the past 15 years.

Despite these advantages, serum creatinine levels cannot be counted on for accurate real-time assessment of renal function. Creatinine rises slowly in response to an acute drop in GFR, with a lag time of hours to days seen between the actual drop in GFR and the increase in serum creatinine levels. As serum creatinine levels reflect a balance between the rate of production and excretion of this endogenous protein, it takes time for serum creatinine levels to reach a new equilibrium when one side of this equation (excretion) changes (see Table 31.6). Therefore, even once the serum creatinine has begun to rise, it is typically hours to days before it reaches a new steady state. This makes it difficult to identify real-time changes in renal function and impossible to recognize the real-time stabilization or resolution of renal injuries.

NGAL

Neutrophil gelatinase-associated lipocalin (NGAL) is a polypeptide released by damaged nephron tubular cells in the setting of local inflammation.[64] In multiple settings, NGAL has been shown to be identifiable in the serum and urine within 1–4 hours of ischemic renal insult and highly predictive of AKI. Multiple groups have found NGAL elevations earlier in a patient's course to be predictive of subsequent AKI. Sen et al. and Yang et al. demonstrated that elevations in whole-blood levels of NGAL occurred as early as 4 hours postburn. Furthermore, on multivariate analysis, NGAL levels identified a risk for subsequent AKI well before urine output rates or changes in serum creatinine.[66]

Others

Various investigators have identified additional novel early markers in burn patients. Serum uric acid levels, interleukin-18, and a novel protein named "kidney injury molecule-1" have all been found to predict AKI shortly after injury in isolated single-institution studies.[67,68]

Treatment

The key to the treatment of AKI is prompt diagnosis coupled with a rapid reversal of the underlying pathophysiology while avoiding iatrogenic injury. Early in the course of acute burn care, the emphasis is on treating the underlying burn shock and minimizing the exposure to secondary injury from nephrotoxic injury products. Later in the course of acute care, the focus is on monitoring for the emergence of new signs of renal injury and eliminating or treating the underlying cause—typically infection or chemotherapeutic nephrotoxicity. In either context, the most effective approach is one that detects the presence (or imminence) of renal injury as early as possible such that the underlying insult can be minimized or reversed as soon as possible.

Any injury that progresses to fulminant renal failure despite initial therapeutic maneuvers requires RRT. This section will address treatment and prevention of burn-associated renal injuries.

RENAL PROTECTION IN THE EARLY PHASE OF ACUTE BURN CARE

Resuscitation

As stated previously, the vast majority of cases of AKI presenting within 24 hours of injury results from inadequate renal perfusion.[7,69] Several authors have demonstrated that the timing of initiation of resuscitative fluids is directly related to the incidence of renal dysfunction. Resuscitative efforts should therefore begin immediately to reestablish effective renal perfusion. Several resuscitative formulas have been established based on multivariate logistic regression analysis (Table 31.7). Which formula to use is far less important than the flexibility and care with which they are applied. The clinician must recognize that these formulas are estimates to be used as starting points. The true amount is directly dependent on the patient's own physiologic status

Table 31.7 Burn Formulas for Estimating Initial Resuscitation

	Crystalloid	Colloid
Colloid:		
Evans	NS 1 mL/kg/%burn	1 mL/kg/%burn
Crystalloid:		
Parkland	4 mL/kg/%burn	
Modified Brooke	2 mL/kg/%burn	
Pediatric formulas:		
Cincinnati Shriners Institute for Burn	4 mL/kg/%burn + 1500 mL/m^2	
Children	TBSA	
Galveston Shriners Institute for Burn	5000 mL/m^2 BSA + 2000 mL/m^2	
Children	TBSA	

TBSA, Total body surface area; *BSA*, burn surface area.

and degree of injury, neither of which can be fully captured by a single formula.

Burns of greater than 20% TBSA generally require intravenous resuscitative efforts, and the initial volume of fluids should be proportional to the area of burn injury. Kim et al. showed that burn size is an independent predictor of ARF in the burn population.[70] The timeliness of resuscitation is particularly critical because the duration of ischemic time is critically important to the development of AKI. Nguyen et al. found initial management of the thermally injured individual to be critically important to overall survival.[71] Early aggressive hydration had a protective effect against ARF. Similarly, the Shriners Burn Institute for Children, Galveston, observed that the time to initiation of resuscitative fluids was directly related to the incidence of renal dysfunction and overall mortality. They concluded that early, aggressive fluid resuscitation lessens kidney damage and thus prevents renal dysfunction, which improves overall outcome.[72]

The clinician must continuously monitor parameters of regional and global perfusion in order to guide fluid therapy and prevent overresuscitation. If the ability to assess true volume status (preload) or effective renal perfusion is difficult, one should initiate monitoring of central pressures or global volume-related variables (i.e., global end diastolic volume, extravascular lung water volume, intrathoracic blood volume).[73] The best means to measure the degree of resuscitation is unknown; however, if adequate volume loading does not produce sufficient mean arterial pressure (60–65 mm Hg), the use of vasopressors is indicated. While there has been some recent interest in the strategy of titrating to a higher mean arterial pressure as a possible means of protecting renal function in shock, a multiinstitutional randomized clinical trial comparing resuscitation strategies using high (80–85 mm Hg) versus standard (65–70 mm Hg) goals for mean arterial pressure found no improvement in renal outcomes in those patients in the high-target group.[74] The one exception to this finding was the subgroup of patients with premorbid hypertension who did indeed benefit from the use of higher mean arterial pressure (MAP) endpoints.

As critical as volume repletion is to effective resuscitation, it does not follow that more is always better. Rather, what is required is the continuous application of enough fluid to maintain perfusion and avoid ischemic insult. Administering fluids in excess of those immediately required at any point in time provides no additional benefit and certainly does not help in reversing any prior renal insult.

It must be emphasized that the exact amount of fluid required for any particular burn is not a constant, predetermined value but an ongoing function of the injured patient's dynamic physiology. Several studies of AKI incidence in large burn series found that patients with and without AKI showed no significant difference in the total fluid volumes received in the first 24–48 hours. In contrast, multiple studies have identified longer time to resuscitation as a clear risk factor for early AKI in burn patients. Likewise markers of hypoperfusion (e.g., serum lactate levels, base deficits, and SOFA scores) consistently have been shown as significant associations with renal injury and failure.[7,21,69,75–77] The key to renal protective resuscitation is not so much in providing adequate fluid over the period of resuscitation as it is a matter of minimizing the amount of time the patient spends in a state of hypoperfusion and, thus, minimizing the cumulative ischemic injury.

The primary goal is to reestablish effective renal perfusion through a well thought out resuscitation plan based on demonstrated resuscitation formulas and modified by variables correlated with the degree of resuscitation.

Other Acute Issues

Heart. Although establishing an effective circulating volume is of prime importance, an astute clinician should also carefully assess myocardial contractility to exclude myocardial dysfunction as a contributing factor to ineffective renal perfusion (see preceding discussion).

Remove Nephrotoxins. In addition to the effects of shock and dehydration, a burn injury can result in a renal injury indirectly via secondary rhabdomyolysis. Burn patients can develop rhabdomyolysis via a variety of mechanisms. Most commonly, restrictive eschars from circumferential burns can combine with the burn-associated edema to create a tourniquet effect on the extremities, resulting in ischemic muscle injury. Muscle can also be injured by direct thermal injury in fourth-degree burns or via mechanical trauma in the setting of coincident nonthermal trauma. Unfortunately any significant burden of muscle necrosis results in marked swelling and (if untreated) a spiral of compartment syndrome and additional rhabdomyolysis.

Rhabdomyolysis clearly increases the risk for AKI in burn patients because free myoglobin is quite nephrotoxic in sustained exposures. Fortunately, this is reversible if the pathological source is identified early and appropriate treatment is initiated.[76,78] In the setting of rhabdomyolysis, intensive hydration with isotonic crystalloids is recommended. While alkaline-diuresis with sodium bicarbonate solution and mannitol was long held as the standard therapy for this condition, the theoretic advantages of this therapy failed to translate into any improved outcomes when studied in a clinical setting.[33] Of first priority, though, is arresting the

underlying process by halting progressive ischemia with aggressive escharotomy and fasciotomy and resecting any necrotic muscle to remove the source of myoglobin poisoning.

Late

Workup. An AKI presenting late in the burn patient's course can owe to any combination of a myriad of pathologies. Any indication of new-onset renal injury late in the burn victim's course should prompt a rapid and comprehensive screen for typical sources of renal injury—hypovolemia, cardiac dysfunction, nephrotoxins, obstruction, and the like. Naturally, any such pathology should be addressed immediately if encountered. However, because infection and sepsis are by far the most common etiology of renal failure in a burn patient's course, an intensive search for occult infection should be undertaken immediately upon recognizing a new renal insult regardless of any other identified contributors.

Sepsis Treatment. The most effective therapy is prevention or early recognition of the septic state (Box 31.1). Every thermally injured patient should be continuously monitored for early markers of sepsis (feeding intolerance, increasing insulin resistance, elevation of acute-phase reactants) so that early therapy may be initiated.

Box 31.1 Definition of Sepsis in Burns

At least three of the following:

I. Temperature >39°C or <36.5°C
II. Progressive tachycardia
  A. Adults >110 bpm
  B. Children >2 SD above age-specific norms (85% age-adjusted max heart rate)
III. Progressive tachypnea
  A. Adults >25 bpm not ventilated
    i. Minute ventilation >12 L/min ventilated
  B. Children >2 SD above age-specific norms (85% age-adjusted max resp. rate)
IV. Thrombocytopenia (will not apply until 3 days after initial resuscitation)
  A. Adults <100 000/μL
  B. Children <2 SD below age-specific norms
V. Hyperglycemia (in the absence of pre-existing diabetes mellitus)
  A. Untreated plasma glucose >200 mg/dL or equivalent mM/L
  B. Insulin resistance—examples include
    i. >7 units of insulin per hour intravenous drip (adults)
    ii. Significant resistance to insulin (>25% increase in insulin requirements over 24 h)
VI. Inability to continue enteral feedings >24 h
  A. Abdominal distension
  B. Enteral feeding intolerance (residual >150 mL/h in children or two times feeding rate in adults)
  C. Uncontrollable diarrhea (>2500 mL/d for adults or > mL/d in children)

In addition, it is *required* that a documented infection is identified via:

A. Culture-positive infection, or
B. Pathologic tissue source identified, or
C. Clinical response to antimicrobials

Once a clinically significant infectious organism is identified, early goal-directed therapy should be initiated. Rivers et al. demonstrated a significant reduction in mortality if an early goal-directed algorithm is applied to the septic patient.[79] The principle is simple: establish early source control while providing effective antibiotic therapy and maximizing global, and therefore renal, perfusion. While larger, more recent studies have raised questions about the specific monitoring techniques and intervention thresholds used in the Rivers trial, the basic principle of early diagnosis and treatment remains invaluable.[80]

Rapid identification and correction of underlying sepsis are critical to the preservation of renal function because no renal protective pharmacological agent has been demonstrated to prevent or limit renal dysfunction. The importance of infectious surveillance in the thermally injured patient cannot be overstated. The goal is to effectively treat local infections and prevent systemic dissemination to avoid the morbidity and mortality of septic shock.

Medical Therapy: Fenoldopam. Naturally, there has long been much interest in identifying a pharmacologic agent capable of protecting the kidney from injury in high-risk settings. For many years, intensivists regularly employed low-dose (aka "renal-dose") dopamine infusions with hopes of preserving renal function. In theory, the receptor activation profile of dopamine in these dose ranges should result in selective augmentation of renal perfusion pressure. Unfortunately multiple clinical trials consistently failed to identify any improvement in renal outcomes associated with renal-dose dopamine treatment.

More recently, interest has emerged in the possibility that fenoldopam, another selective adrenergic agonist, might provide more consistent, targeted support of renal perfusion. Fenoldopam is a pure $\alpha 1$ agonist that decreases renal vascular resistance in an NO_2-independent manner. This offers a distinct advantage in the setting of postischemic AKI, where nitric synthase activity is typically saturated early in the course of injury. As of yet, the role of fenoldopam remains unclear. The largest randomized controlled trial of fenoldopam infusion for renal protection (to date) was performed in the context of cardiac surgery and failed to show any reduction in renal outcomes. However the current literature documenting the use of fenoldopam in burn patients is limited to a single retrospective study that did indicate a renal-protective effect in burn patients at high risk for AKI. [81,82]

Renal Replacement Therapy

Fortunately, due to major advances in burn care resuscitation and the treatment of sepsis, renal failure requiring RRT is unusual in the burn setting.[83] The reported incidence is approximately 1–3%. Unfortunately, though, the overall mortality associated with renal failure requiring RRT approaches 80%.[8,10]

Burn patients with preexisting renal insufficiency are at particular risk for RRT due to the large positive fluid balances associated with the initial resuscitation therapy, enhanced catabolism leading to elevated urea levels, and the need for substantial nutritional support to maintain a positive nitrogen balance.[83]

Modalities. Peritoneal dialysis has a long history of successful use in both acute and chronic settings.[84] However, in burn patients, this form of therapy is limited by clearance rates and the need for catheter insertion through the abdominal wall: a common donor site or burned area.

Over the past two decades a number of RRT modes have been studied in general ICU patients: intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), and sustained low-efficiency dialysis (SLED). No consensus exists as to which mode is superior because each has advantages and disadvantages depending on the clinical scenario (Table 31.8).[83,85] It has been suggested that CRRT is best suited for those patients demonstrating severe hemodynamic instability, persistent ongoing metabolic acidosis, and large fluid removal requirements. Preliminary reports using CRRT in the thermally injured population have demonstrated improved survival.[86,87] These studies are limited to single-institutional data.

The optimal time to initiate RRT in the thermally-injured patient with AKI has not been determined. Traditional thresholds (i.e., absolute indications used to initiate dialysis in the setting of chronic renal failure) are less relevant in the thermally injured patient. Burn injury predisposes to organ failure, catabolism causes increased urea generation, large open wounds result in electrolyte shifts, and nephrotoxic agents are often required as treatment. For intensive care populations at large, the standard of care is to initiate CRRT only upon evidence of extreme metabolic derangements or other life-threatening events.[88] However, there continues to be interest in the potential benefit of initiating RRT earlier in the course of AKI, with ongoing clinical studies indicating potential advantages of early RRT.[89,90] A recent randomized multicenter trial by Gaudry et al. challenged this hypothesis by suggesting early RRT has no survival advantages over delayed RRT.[91] In addition, they found potential benefits to delayed RRT if close monitoring of the patient is performed in the ICU setting. Emerging trials continue to offer evidence on both sides of the argument—a controversy which will likely be with us for years to come.[92,93]

Although very early initiation of RRT in ICU patients has not clearly been demonstrated to improve outcome, preliminary evidence exists to suggest a more aggressive approach to RRT initiation in the thermally injured patient.[86,87] As

Table 31.8 Advantages and Disadvantages of Intermittent Hemodialysis (IHD) and Continuous Renal Replacement Therapy (CRRT)

Intermittent Hemodialysis	**Continuous Renal Replacement Therapy**
I. Advantages	**Disadvantages**
Rapid clearance of acidosis, uremia, potassium, and certain toxins	Slow
Patient mobility	Immobility
Can perform without anticoagulation	More frequent need for anticoagulation
Reduced exposure to artificial membrane	Continuous exposure to artificial membrane
Reduced incidence of hypothermia	Hypothermia
Masks fever temporarily	Masks fever continuously
Less blood loss from monitoring and/or filter clotting	Greater potential blood loss from monitoring and/or filter clotting
Lower costs in most centers	Higher costs in most centers
Less risk of dialysate compounding errors	Greater risks of replacement fluid and/or dialysate compounding errors
[a]Less removal of amino acids, endogenous hormones, and cofactors	[b]Increased removal of amino acids, endogenous hormones, and cofactors
II. Disadvantages	**Advantages**
Rapid solute and fluid shifts	Gradual solute and fluid shifts
–hemodynamic instability	–greater hemodynamic stability
–disequilibrium syndrome	–no or little risk of disequilibrium syndrome
–worsens brain edema	–no worsening of brain edema
Frequent need for fluid or nutritional restrictions	Less need tor fluid or nutritional restrictions
Only allows for intermittent adjustment of prescription; less control of uremia, acidosis, phosphate, and fluid balance	Allows for continuous titration and integration of renal support with other ICU care and treatment goals
In many centers, requires a dialysis nurse and other resources that may limit ability to provide extended run-times and/or daily therapy in selected patients	Procedure performed by ICU nursing staff, overall better clearance of uremia, correction of acidosis, and removal of excess fluid

[a]Even with high flux membranes, removes fewer 'middle' molecules.
[b]When configured to use convection as its primary mechanism of solute clearance, removes more "middle molecules."
From Brochard L, Abroug F, Brenner M, et al. on behalf of the ATS/ERS/ESICM/SCCM/SRLF Ad Hoc Committee on Acute Renal Failure. An official ATS/ERS/ESICM/SCCM/SRLF statement: prevention and management of ARF in the ICU patient: an international consensus conference in intensive care medicine. *Am J Respir Crit Care Med*. 2010;181(10):1128–1155.

such, we favor early initiation of RRT in severe burn-associated AKI. However larger studies are clearly needed to clarify the value of this approach in the burn population.

A theoretical benefit of continuous hemofiltration is the removal of proinflammatory mediators, which may be associated with the development of multiple organ failure. The experimental and clinical data suggest that the rate of hemofiltration and the biologic nature of the filters affect the overall results.[20] Currently there are insufficient data to recommend continuous hemofiltration solely on the basis of removal of inflammatory mediators. Future randomized prospective studies may resolve this theoretical benefit.

Conclusion

Acute renal dysfunction is a critical complication of an acute thermal injury and is associated with significant morbidity and mortality. Prior to 1965, there were no reported survivors following a major thermal injury who unfortunately developed ARF. While significant advances have been made in both the treatment of major thermal injures and renal failure over the past 50 years, the combined clinical scenario still represents a significant therapeutic challenge in modern burn therapy. Collectively we have made advances in establishing a common definition of renal failure and its stages, but work must continue to identify early biomarkers of renal injury so that therapeutic interventions can be made in a more timely manner.

An astute burn surgeon or intensivist must understand that the normal renal physiology is under constant threat following a thermal injury. To avoid renal dysfunction, a physician must maintain adequate effective renal perfusion while minimizing nephrotoxic agents.

Complete references available online at
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References

1. Marshall VC. Acute renal failure in surgical patients. *Br J Surg*. 1970;58(1):17-21.
2. Cameron JS, Miller-Jones CM. Renal function and renal failure in badly burned children. *Br J Surg*. 1967;54(2):132-141.
3. Davies DM, Pusey CD, Rainford DJ, et al. Acute renal failure in burns. *Scand J Plast Reconstr Surg*. 1979;13(1):189-192.
4. Schiavon M, Di Landro D, Baldo M, et al. A study of renal damage in seriously burned patients. *Burns Incl Therm Inj*. 1988;14(2): 107-112.
5. Mosier MJ, Pham TN, Klein MB, et al. Early acute kidney injury predicts progressive renal dysfunction and higher mortality in severely burned adults. *J Burn Care Res*. 2010;31(1):83-92.
6. Kashtan J, Green JF, Parsons EQ, et al. Hemodynamic effect of increased abdominal pressure. *J Surg Res*. 1981;30(3):249-255.
7. Palmieri T, Lavrentieva A, Greenhalgh DG. Acute kidney injury in critically ill burn patients. Risk factors, progression and impact on mortality. *Burns*. 2010;36(2):205-211.
8. Brusselaers N, Monstrey S, Colpaert K, et al. Outcome of acute kidney injury in severe burns: a systematic review and meta-analysis. *Intensive Care Med*. 2010;36(6):915-925.
9. Steinvall I, Bak Z, Sjoberg F. Acute kidney injury is common, parallels organ dysfunction or failure, and carries appreciable mortality in patients with major burns: a prospective exploratory cohort study. *Crit Care*. 2008;12(5):R124.
10. Coca SG, Bauling P, Schifftner T, et al. Contribution of acute kidney injury toward morbidity and mortality in burns: a contemporary analysis. *Am J Kidney Dis*. 2007;49(4):517-523.
11. Lopes JA, Jorge S, Neves FC, et al. An assessment of the RIFLE criteria for acute renal failure in severely burned patients. *Nephrol Dial Transplant*. 2007;22(1):285.
12. Davies MP, Evans J, McGonigle RJ. The dialysis debate: acute renal failure in burns patients. *Burns*. 1994;20(1):71-73.
13. Star RA. Treatment of acute renal failure. *Kidney Int*. 1998;54(6): 1817-1831.
14. Bellomo R, Ronco C, Kellum JA, et al. Acute Dialysis Quality Initiative. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8(4):R204-R212.
15. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11(2):R31.
16. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract*. 2012;120(4):c179-c184.
17. Izawa J, Uchino S, Takinami M. A detailed evaluation of the new acute kidney injury criteria by KDIGO in critically ill patients. *J Anesth*. 2016;30(2):215-222.
18. Uchino S, Bellomo R, Goldsmith D, et al. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit Care Med*. 2006;34(7):1913-1917.
19. Chung KK, Stewart IJ, Gisler C, et al. The Acute Kidney Injury Network (AKIN) criteria applied in burns. *J Burn Care Res*. 2012;33(4):483-490.
20. Kellum JA. Acute kidney injury. *Crit Care Med*. 2008;36(4 suppl):S141-S145.
21. Cartotto R, Choi J, Gomez M, et al. A prospective study on the implications of a base deficit during fluid resuscitation. *J Burn Care Rehabil*. 2003;24(2):75-84.
22. Holliday MA. Extracellular fluid and its proteins: dehydration, shock, and recovery. *Pediatr Nephrol*. 1999;13(9):989-995.
23. Klein MB, Hayden D, Elson C, et al. The association between fluid administration and outcome following major burn: a multicenter study. *Ann Surg*. 2007;245(4):622-628.
24. Saffle JIL. The phenomenon of "fluid creep" in acute burn resuscitation. *J Burn Care Res*. 2007;28(3):382-395.
25. Hobson KG, Young KM, Ciraulo A, et al. Release of abdominal compartment syndrome improves survival in patients with burn injury. *J Trauma*. 2002;53(6):1129-1133, discussion 1133.
26. Richardson JD, Trinkle JK. Hemodynamic and respiratory alterations with increased intra-abdominal pressure. *J Surg Res*. 1976;20(5):401-404.
27. Harman PK, Kron IL, McLachlan HD, et al. Elevated intra-abdominal pressure and renal function. *Ann Surg*. 1982;196(5):594-597.
28. O'Mara MS, et al. A prospective, randomized study of intra-abdominal pressure with crystalloid and colloid resuscitation in burn patients. *J Trauma*. 2005;58(5):1011-1018.
29. Greenhalgh DG, Warden GD. The importance of intra-abdominal pressure measurements in burned children. *J Trauma*. 1994;36(5):685-690.
30. Ivy ME, Atweh NA, Palmer J, et al. Intra-abdominal hypertension and abdominal compartment syndrome in burn patients. *J Trauma*. 2000;49(3):387-391.
31. Lazarus D, Hudson DA. Fatal rhabdomyolysis in a flame burn patient. *Burns*. 1997;23(5):446-450.
32. Morris JJ, Mucha PJ, Ross S, et al. Acute posttraumatic renal failure: a multicenter perspective. *J Trauma*. 1991;31(12):1584-1590.
33. Brown CVR, Rhee P, Chan L, et al. Preventing renal failure in patients with rhabdomyolysis: do bicarbonate and mannitol make a difference? *J Trauma*. 2004;56(6):1191-1196.
34. Merriam TW. Myocardial function following thermal injury. *Circ Res*. 1962;11:669-673.
35. Fozzard HA. Myocardial injury in burn shock. *Ann Surg*. 1961;154: 113-119.
36. Mukherjee GD, Basu PG, Roy S, et al. Cardiomegaly following extensive burns. *Ann Plast Surg*. 1987;19(4):378-380.
37. Baxter CR, Cook WA, Shires GT. Serum myocardial depressant factor of burn shock. *Surg Forum*. 1966;17:1-2.
38. Leffler JN, Litvin Y, Barenholz Y. Proteolysis in formation of a myocardial depressant factor during shock. *Am J Physiol*. 1967;213:492-498.
39. Lefer AM, Cowgill R, Marshall FF, et al. Characterization of a myocardial depressant factor present in hemorrhagic shock. *Am J Physiol*. 1967;213(2):492-498.
40. Reilly JM, Cunnion RE, Burch-Whitman C, et al. A circulating myocardial depressant substance is associated with cardiac dysfunction and peripheral hypoperfusion (lactic acidemia) in patients with septic shock. *Chest*. 1989;95(5):1072-1080.
41. Bryant D, Becker L, Richardson J, et al. Cardiac failure in transgenic mice with myocardial expression of tumor necrosis factor-alpha. *Circulation*. 1998;97(14):1375-1381.
42. Giroir BP, Horton JW, White DJ, et al. Inhibition of tumor necrosis factor prevents myocardial dysfunction during burn shock. *Am J Physiol*. 1994;267(1 Pt 2):H118-H124.
43. Herbertson MJ, Werner HA, Goddard CM, et al. Anti-tumor necrosis factor-alpha prevents decreased ventricular contractility in endotoxemic pigs. *Am J Respir Crit Care Med*. 1995;152(2):480-488.
44. Odeh M. Tumor necrosis factor-alpha as a myocardial depressant substance. *Int J Cardiol*. 1993;42(3):231-238.
45. Kapadia S, Lee J, Torre-Amione G, et al. Tumor necrosis factor-alpha gene and protein expression in adult feline myocardium after endotoxin administration. *J Clin Invest*. 1995;96(2):1042-1052.
46. Torre-Amione G, Kapadia S, Lee J, et al. Tumor necrosis factor-alpha and tumor necrosis factor receptors in the failing human heart. *Circulation*. 1996;93(4):704-711.
47. Kumar A, Haery C, Parrillo JE. Myocardial dysfunction in septic shock. *Crit Care Clin*. 2000;16(2):251-287.
48. Hegewisch S, Weh HJ, Hossfeld DK. TNF-induced cardiomyopathy. *Lancet*. 1990;335(8684):294-295.
49. Habib FM, Springall DR, Davies GJ, et al. Tumour necrosis factor and inducible nitric oxide synthase in dilated cardiomyopathy. *Lancet*. 1996;347(9009):1151-1155.
50. Schrier RW, Wang W. Acute renal failure and sepsis. *N Engl J Med*. 2004;351(2):159-169.
51. Chrysopoulo MT, Jeschke MG, Dziewulski P, et al. Acute renal dysfunction in severely burned adults. *J Trauma*. 1999;46(1):141-144.
52. Riedemann NC, Guo R-F, Ward PA. The enigma of sepsis. *J Clin Invest*. 2003;112(4):460-467.
53. Rangel-Frausto MS, Pittet D, Costigan M, et al. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *JAMA*. 1995;273(2):117-123.
54. Hohlfeld T, Klemm P, Thiemermann C, et al. The contribution of tumour necrosis factor-alpha and endothelin-1 to the increase of coronary resistance in hearts from rats treated with endotoxin. *Br J Pharmacol*. 1995;116(8):3309-3315.
55. Riedemann NC, Guo R-F, Neff TA, et al. Increased C5a receptor expression in sepsis. *J Clin Invest*. 2002;110(1):101-108.
56. Huber-Lang MS, Riedeman NC, Sarma JV, et al. Protection of innate immunity by C5aR antagonist in septic mice. *FASEB J*. 2002;16(12):1567-1574.

57. Czermak BJ, Sarma V, Pierson CL, et al. Protective effects of C5a blockade in sepsis. *Nat Med*. 1999;5(7):788-792.
58. Reinhart K, Bayer O, Brunkhorst F, et al. Markers of endothelial damage in organ dysfunction and sepsis. *Crit Care Med*. 2002;30(5 suppl):S302-S312.
59. Hanrahan TP, Kotapati C, Roberts MJ, et al. Factors associated with vancomycin nephrotoxicity in the critically ill. *Anaesth Intensive Care*. 2015;43(5):594-599.
60. Hanrahan T, Whitehouse T, Lipman J, et al. Vancomycin-associated nephrotoxicity: A meta-analysis of administration by continuous versus intermittent infusion. *Int J Antimicrob Agents*. 2015;46(3): 249-253.
61. Lameire N, Hoste E. Reflections on the definition, classification, and diagnostic evaluation of acute renal failure. *Curr Opin Crit Care*. 2004;10(6):468-475.
62. Steiner RW. Interpreting the fractional excretion of sodium. *Am J Med*. 1984;77(4):699-702.
63. Marcen R, Serrano P, Teruel JL, et al. Oral cimetidine improves the accuracy of creatinine clearance in transplant patients on cyclosporine. *Transplant Proc*. 1994;26(5):2624-2625.
64. Mishra J, Ma Q, Prada A, et al. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. *J Am Soc Nephrol*. 2003;14(10):2534-2543.
65. Anderson RJ, Barry DW. Clinical and laboratory diagnosis of acute renal failure. *Best Pract Res Clin Anaesthesiol*. 2004;18(1):1-20.
66. Sen S, Godwin ZR, Palmieri T, et al. Whole blood neutrophil gelatinase-associated lipocalin predicts acute kidney injury in burn patients. *J Surg Res*. 2015;196(2):382-387.
67. Kym D, Cho Y-S, Yoon J, et al. Evaluation of diagnostic biomarkers for acute kidney injury in major burn patients. *Ann Surg Treat Res*. 2015;88(5):281-288.
68. Ren H, Zhou X, Dai D, et al. Assessment of urinary kidney injury molecule-1 and interleukin-18 in the early post-burn period to predict acute kidney injury for various degrees of burn injury. *BMC Nephrol*. 2015;16:142.
69. Schneider DF, Dobrowolsky A, Shakir IA, et al. Predicting acute kidney injury among burn patients in the 21st century: a classification and regression tree analysis. *J Burn Care Res*. 2012;33(2):242-251.
70. Kim G-H, Oh KH, Yoon JW, et al. Impact of burn size and initial serum albumin level on acute renal failure occurring in major burn. *Am J Nephrol*. 2003;23(1):55-60.
71. Nguyen NL, Gun RT, Sparnon AL, et al. The importance of initial management: a case series of childhood burns in Vietnam. *Burns*. 2002;28(2):167-172.
72. Jeschke MG, Barrow RE, Wolf SE, et al. Mortality in burned children with acute renal failure. *Arch Surg*. 1998;133(7):752-756.
73. Poeze M, Solberg BCJ, Greve JWM, et al. Monitoring global volume-related hemodynamic or regional variables after initial resuscitation: what is a better predictor of outcome in critically ill septic patients? *Crit Care Med*. 2005;33(11):2494-2500.
74. Asfar P, Meziani F, Hamel JF, et al. High versus low blood-pressure target in patients with septic shock. *N Engl J Med*. 2014;370(17):1583-1593.
75. Cochran A, Edelman LS, Saffle JR, et al. The relationship of serum lactate and base deficit in burn patients to mortality. *J Burn Care Res*. 2007;28(2):231-240.
76. Heegard KD, Stewart IJ, Cap AP, et al. Early acute kidney injury in military casualties. *J Trauma Acute Care Surg*. 2015;78(5):988-993.
77. Jeng JC, Lee K, Jablonski K, et al. Serum lactate and base deficit suggest inadequate resuscitation of patients with burn injuries: application of a point-of-care laboratory instrument. *J Burn Care Rehabil*. 1997;18(5):402-405.
78. Rosen CL, Adler JN, Rabban JT, et al. Early predictors of myoglobinuria and acute renal failure following electrical injury. *J Emerg Med*. 1999;17(5):783-789.
79. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med*. 2004;32(3):858-873.
80. Yealy D, Kellum J, Huang D, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370(18 SRC-GoogleScholar):1683-1693.
81. Simmons JW, Chung KK, Renz EM, et al. Fenoldopam use in a burn intensive care unit: a retrospective study. *BMC Anesthesiol*. 2010;10:9.
82. Legrand M, Darmon M, Joannidis M. Fenoldopam and acute kidney injury. *JAMA*. 2015;313(9):970-971.
83. Leblanc M, Thibeault Y, Quérin S. Continuous haemofiltration and haemodiafiltration for acute renal failure in severely burned patients. *Burns*. 1997;23(2):160-165.
84. Pomeranz A, Reichenberg Y, Schurr D, et al. Acute renal failure in a burn patient: the advantages of continuous peritoneal dialysis. *Burns*. 1985;11(5):367-370.
85. Bagshaw SM, Berthiaume LR, Delaney A, Bellomo R. Continuous versus intermittent renal replacement therapy for critically ill patients with acute kidney injury: a meta-analysis. *Crit Care Med*. 2008;36(2):610-617.
86. Chung KK, Juncos LA, Wolf SE, et al. Continuous renal replacement therapy improves survival in severely burned military casualties with acute kidney injury. *J Trauma*. 2008;64(2 suppl):S179-S185, discussion S185.
87. Chung KK, Lundy JB, Matson JR, et al. Continuous venovenous hemofiltration in severely burned patients with acute kidney injury: a cohort study. *Crit Care*. 2009;13(3):R62.
88. Vinsonneau C, Allain-Launay E, Blayau C, et al. Renal replacement therapy in adult and pediatric intensive care: recommendations by an expert panel from the French Intensive Care Society (SRLF) with the French Society of Anesthesia Intensive Care (SFAR) French Group for Pediatric Intensive Care Emergencies (GFRUP) the French Dialysis Society (SFD). *Ann Intensive Care*. 2015;5(1):58.
89. Karvellas CJ, Farhat MR, Sajjad I, et al. A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. *Crit Care*. 2011;15(1):R72.
90. Modem V, Thompson M, Gollhofer D, et al. Timing of continuous renal replacement therapy and mortality in critically ill children. *Crit Care Med*. 2014;42(4):943-953.
91. Gaudry S, Hajage D, Schortgen F, et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. *N Engl J Med*. 2016;375(2):122-133.
92. Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. *JAMA*. 2016;315(20):2190-2199.
93. Wald R, Adhikari NKJ, Smith OM, et al. Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. *Kidney Int*. 2015;88(4):897-904.

32 Critical Care in the Severely Burned: Organ Support and Management of Complications

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Introduction

Approximately 4000 burn victims die each year from complications related to thermal injury.[1,2] Burn deaths generally occur in a bimodal distribution, either immediately after the injury or weeks later due to multisystem organ failure (MOF), a pattern covered in Chapter 30. Recent reports reveal a 50% decline in burn-related deaths and hospital admissions in the United States over the previous 20 years.[2] In 1949, Bull and Fisher reported 50% mortality rates for children aged 0–14 years with burns of 49% of total body surface area (TBSA), 46% TBSA for patients aged 15–44, 27% TBSA for those aged between 45 and 64, and 10% TBSA for those 65 and older.[3] These dismal statistics have improved, with the latest studies reporting a 50% mortality for greater than 95% TBSA burns in children 14 years and under, 75% TBSA burns in adults, and around 30% TBSA in the elderly.[4] Therefore, a healthy young patient with almost any size burn should be expected to live, and the prospects for the older demographic are improving with modern wound treatment and critical care techniques.

Burned patients generally die from one of two causes: early deaths resulting from "burn shock" and immolation, or MOF leading to late deaths. With the advent of vigorous fluid resuscitation protocols in the severely burned, irreversible burn shock has been replaced by sepsis and the ensuing MOF as the leading cause of death associated with burns in those who do not die at the scene by a margin of 2 to 1.[4] Those with a risk of mortality who do not die precipitously will be treated by what is termed *critical care*, a service performed in specialized units containing the equipment, supplies, and personnel to institute intensive monitoring and life-sustaining organ support to promote recovery.

Critical illness in burned patients is most commonly beset by sepsis. In a pediatric burn population with massive burns of greater than 80% TBSA, 17.5% of the children developed sepsis, defined as bacteremia with clinical signs of infection.[5] Mortality in the whole group was 33%, most of whom succumbed to MOF. Some were bacteremic and "septic," but the majority were not. These findings highlight the observation that the development of severe critical illness and MOF often associate with infection, but they are by no means required to develop this syndrome. What is requisite is an inflammatory focus, which is the massive skin injury in severe burns requiring inflammation to heal.

It is postulated that the progression of patients to MOF exists in a continuum with the systemic inflammatory response syndrome (SIRS).[6] Nearly all burn patients meet the criteria for SIRS as defined by the consensus conference of the American College of Chest Physicians and the Society of Critical Care Medicine.[7] It is therefore not surprising that severe critical illness and MOF are common in burned patients.

Patients who develop dysfunction of various organs, such as the cardiopulmonary system, renal system, and gastrointestinal system, can be supported to maintain homeostasis until the organs repair themselves or a chronic support system can be established. Critical care may be loosely defined as the process of high-frequency physiologic monitoring coupled with short response times for pharmacologic and procedural interventions. Entire textbooks and many of the preceding chapters in this book are dedicated to critical care. This chapter will focus on synthesizing a critical care system for burn injury, including the organization of specialized burn intensive care units (BICUs) and organ-specific management.

Burn Intensive Care Unit Organization

PHYSICAL PLANT

Optimally, a BICU should exist within a designated burn center, ideally verified by the American Burn Association (ABA), and in conjunction with a recognized trauma center, thus providing the capability to treat both thermal and nonthermal injuries. This unit, however, need not be physically located in the same space as that designated for nonburned trauma patients. In fact, the requirement for the care of wounds in burned patients necessitates additional equipment, such as shower tables and overhead warmers, so a separate space dedicated to the severely burned should be standard. This space may be located in a separate hospital with established guidelines for transfer or a specialized unit.[8]

The optimal number of beds in the unit should be calculated by the incidence of moderate to severe burns in the referral area, which in the United States is approximately 20 per 100,000 people per year. The Committee on Trauma of the American College of Surgeons and the ABA recommend that 100 or more patients should be admitted to this facility yearly, with an average daily census of three or more patients to maintain sufficient experience and acceptable access to specialized care.[8]

Box 32.1 Assigned Burn Unit Personnel

- Experienced burn surgeons (burn unit director and qualified surgeons)
- Dedicated nursing personnel
- Physical and occupational therapists
- Social workers
- Dietitians
- Pharmacists
- Respiratory therapists
- Phychiatrists and clinical psychologists
- Prosthetists

Box 32.2 Consultants for the Burn ICU

- General surgery
- Plastic surgery
- Anesthesiology
- Cardiothoracic surgery
- Neurosurgery
- Obstetrics/gynecology
- Ophthalmology
- Orthopedic surgery
- Otolaryngology
- Urology
- Radiology
- Pediatrics
- Psychiatry
- Cardiology
- Gastroenterology
- Hematology
- Pulmonology
- Nephrology
- Neurology
- Pathology
- Infectious disease

Box 32.3 Equipment for a Fully Equipped Burn ICU

Standard

- Monitors (heart rate, electrocardiography, blood pressure, cardiac output, oxygen saturation, temperature)
- Scales
- Ventilators
- Advanced cardiac life support (ACLS) cardiac cart
- Laboratory support (blood gas analysis, hematology, chemistry, microbiology)

Specialty

- Fiberoptic bronchoscopes
- Fiberoptic gastroscopes/colonoscopes
- Dialysis equipment (peritoneal dialysis and hemodialysis)
- Portable plain radiography
- Computed tomography/fluoroscopy/angiography
- Indirect calorimeters

Most moderate to severe burns with hospital admission will require intensive monitoring for at least the day of admission during the resuscitative phase. Thereafter approximately 20% will undergo prolonged cardiopulmonary monitoring for inhalation injury, burn shock, cardiopulmonary compromise, renal dysfunction, and the development of SIRS and MOF. In these severely burned patients, the average length of stay in the BICU is approximately 1 day per % TBSA burned. Using an average of 25 days admission for a severely burned patient (20% of the burns, 4/100,000 per capita) and 2 days for those not so severely injured (80%, 16/100,000 per capita), this suggests 132 BICU inpatient days per 100,000 persons in the catchment area. Thus a 10-bed BICU should serve a population of 3,000,000 sufficiently when considered independently. Space provided should be at least 3,000 sq ft, including patient beds and support space for nursing/charting areas, office space, wound care areas, and storage.[8]

Multiply-resistant bacteria and fungi are commonly encountered in the BICU owing to the presence of open wounds. To prevent transmission of these organisms to other patients, isolation of burned patients from all other patients is recommended and should be considered when designing units for this purpose. Single rooms with negative-pressure ventilation are advisable. In addition, strict guidelines for contact precautions in wound care and interventions, and hand-washing are standard.

PERSONNEL

A BICU functions best by using a team approach among surgeons/intensivists, nurses, laboratory support staff, respiratory therapists, occupational and physical therapists, mental health professionals, prosthetists, dietitians, and pharmacists (Box 32.1). The unit should have a designated medical director, ideally a burn surgeon, to coordinate and supervise personnel, quality management, and resource utilization. The medical director will usually work with other qualified surgical staff to provide sufficient care for the patients. It is recommended that medical directors and each of their associates be well versed in critical care techniques and that each physician care for at least 50 patients per year to maintain skills.[8] In teaching hospitals, three to four residents or other qualified medical providers should be assigned to the 10-bed unit described. A coverage schedule should be devised to provide 24-hour prompt responses to problems.

Nursing personnel should consist of a nurse manager with at least 2 years of intensive care and acute burn care experience and 6 months of management responsibilities. The rest of the nursing staff in the BICU should have documented competencies specific to the care of burned patients, including critical care and wound care.[8] Owing to the high intensity of burn intensive care, at least five full-time equivalent nursing providers are required per BICU bed to provide sufficient 24-hour care. Additional personnel are required for respiratory care, occupational and physical therapy, and other support. A dedicated respiratory therapist for the burn unit at all times is optimal.

Owing to the nature of critical illness in burned patients, complications may arise that are best treated by specialists not generally in the field of burn care (Box 32.2). As such, these specialists should be available for consultation when the need arises. Given the regularity with which burn surgeons encounter subspecialty problems, such as corneal injuries, routine injuries are often managed directly by the burn surgeon without additional consultation.

EQUIPMENT

The equipment needs of the BICU include those items common to all ICUs, but some of which are specialized (Box 32.3). Each BICU bed must be equipped with monitors to

measure heart rate, continuous electrocardiography, noninvasive blood pressure, invasive arterial and venous blood pressures, end tidal carbon dioxide monitoring, and right heart cardiac output using dilution techniques or data derived from arterial pressure tracings. Arterial blood oxygen saturation measurement is also required, but continuous mixed venous saturation monitoring or the technical equivalent is optional. Equipment to measure weight and body temperature should be standard. Oxygen availability with at least two vacuum pumps must be present for each bed.

Ventilator equipment must also be available for all beds. The availability of a number of types of ventilator is optimal, including conventional ventilators with the capability to deliver both volume-targeted and pressure-targeted modes, as well as high-frequency ventilators that are oscillatory and/or percussive in design. An emergency cardiac cart containing advanced cardiac life support (ACLS) medications and a battery-powered electrocardiograph/defibrillator must be present in the unit. Infusion pumps to deliver continuous medications and intravenous/intraarterial fluids must also be readily available. A laboratory providing blood gas analysis, hematology, and blood chemistry should be located on site. Point-of-care blood analysis for glucose, arterial blood gas, and basic chemistries is strongly advised.[9,10] Microbiologic support to complete frequent, routine bacterial and fungal cultures and sensitivities must also be present, as well as virology.

Available specialty equipment should include various sizes of fiberoptic bronchoscopes for the diagnosis and treatment of pulmonary disorders, as well as personnel competent with these techniques. Fiberoptic gastroscopes and colonoscopes for gastrointestinal complications are also necessary for diagnosis, bleeding control, decompression, and difficult feeding access. For renal support, equipment to provide intermittent and/or continuous renal replacement should be present. Portable radiographic equipment for standard chest/abdominal/extremity radiographs must be immediately available. Equipment for computed tomography (CT), fluoroscopy, and angiography should be available. Indirect calorimeters to measure metabolic rate are strongly advised. Overhead warmers and central heating with individualized ambient temperature controls must be available for each room as a specialized requirement.[8]

Hemodynamic Monitoring in the Burn Intensive Care Unit

Most burned patients follow an anticipated course of recovery, which is monitored in the BICU by measuring physiologic parameters. Experienced clinicians assess these physiologic measures in a repeated and sequential fashion to discern when potential interventions may be initiated to improve outcomes. Often no intervention will be necessary from the unit's standard care protocol as the patient is following the anticipated course. At other times this is not the case, and procedural or pharmacologic intervention is beneficial. Physiologic monitoring is then used further to determine the adequacy of the interventions. The following is a survey of monitoring techniques used in the BICU.

CARDIOVASCULAR MONITORING

Arterial Lines

Hemodynamic monitoring is directed at assessing the results of resuscitation and maintaining organ and tissue perfusion. Currently used measures are only estimates of tissue perfusion because the measurement of oxygen and nutrient transfer to cells cannot be made directly at the bedside. Instead global physiologic measures of central pressures still serve as the principal guides.

Measurement of arterial blood pressure is the mainstay for the assessment of tissue perfusion. In critical illness, this measurement can be made using cuff sphygmomanometers; however in practice this technique is not useful because the measurement is episodic and placement of these cuffs on burned extremities is problematic. Diastolic pressures can also be artificially elevated in the elderly and obese. Instead continuous monitoring for hemodynamic instability through the use of intraarterial catheters is generally preferable when the patient is in the BICU for a prolonged period. Lines are typically placed in either the radial or the femoral artery. The radial artery is the preferred site for critically ill patients because of safety, with the dual arterial supply to the hand as backup should a complication arise. However it has been shown that radial artery catheters are inaccurate in the measurement of central blood pressure when vasopressors are used[11] and are notoriously inaccurate in children because of greater vascular reactivity.[12] Furthermore femoral cannulation sites are often unburned due to the insulation provided by undergarments, and they do not preclude mobilization with physical therapy or rehabilitation goals.[13] For these reasons, we recommend femoral arterial blood pressure measurement in most burned patients.

For arterial catheters, systolic, diastolic, and mean arterial pressures (MAPs) should be displayed continuously on the monitor screen. Either systolic or MAP can be used to determine adequacy of pressure, although a MAP of greater than 70 mm Hg is considered a more accurate descriptor of normal tissue perfusion on the whole. Reasons for this include the finding that, as the arterial pressure wave traverses proximally to distal, the systolic pressure gradually increases and the diastolic pressure decreases; the MAP determined by integrating areas under the curve, however, remains constant. The adequacy of the waveform must also be determined, with a diminished waveform indicative of catheter damping, requiring catheter replacement. Care must be taken to ensure that the diminished waveform is not true hypotension, which can be determined using a manual or cycling sphygmomanometer. Exaggerated waveforms with elevated systolic pressure and additional peaks in the waveform (generally only two are found) may be a phenomenon known as "catheter whip," which is the result of excessive movement of the catheter within the artery. Typically this problem is self-limited, but care must be taken not to interpret normal systolic blood pressure values with evidence of catheter whipping as unexceptional because the effect generally overestimates pressures. Again, use of MAP as the principal guideline for the assessment of blood pressure is optimal, as effects of catheter whip or other problems with intraarterial monitoring are then diminished.

Complications associated with arterial catheters include distal ischemia associated with vasospasm and thromboembolism, catheter infection, and arterial damage/pseudoaneurysm during insertion and removal. Although these complications are uncommon, the results can be devastating. Physical evidence of ischemia in the distal hand or foot should prompt immediate removal of the catheter and elevation of the extremity. If improvement in ischemic symptoms is not seen promptly (within an hour), angiography and intervention must be considered. Should thromboembolism be found, the clot can be removed with operative embolectomy or clot lysis at the discretion of the treating physician. If, during angiography, extensive arterial damage is found with ischemia, operative repair may be indicated. Consideration for anticoagulation must be made while balancing the risk of hemorrhage from open wounds versus the benefit of tissue salvage.

Evidence of catheter infection hallmarked by purulence and surrounding erythema should instigate removal of the catheter, which often will suffice. With continued evidence of infection, antibiotics and incision and drainage of the site should be entertained. Great caution must be exercised to avoid arterial bleeding if an incision is made over the catheter site. If a pseudo-aneurysm is encountered after arterial catheterization and removal without signs of distal ischemia, injection of thrombin[14] or compression with a vascular ultrasound device until no further flow is seen in the pseudo-aneurysm will often alleviate the problem without operative intervention.[15]

Cardiac Output Measurement

Pulmonary artery catheters placed percutaneously through a central vein (internal jugular, subclavian, or femoral) and "floated" into the pulmonary artery through the right heart have been used extensively in hemodynamic monitoring in BICUs. By measuring the back pressure through the distal catheter tip "wedged" into an end-pulmonary branch, an estimate of left atrial pressure can be measured. In addition, dyes or isotonic solutions injected into a proximal port can be used to determine cardiac output from the right heart. These data are used to estimate preload delivery to the heart, cardiac contractility, and afterload against which the heart must pump, which then directs therapy at restoration of hemodynamics. These catheters are used in BICUs under conditions of unexplained shock, hypoxemia, renal failure, and monitoring of high-risk patients.

The use of pulmonary artery catheters, however, has come under scrutiny from reports indicating no benefit from their use. A study of 5735 critically ill adults in medical and surgical ICUs showed an increase in mortality and use of resources when pulmonary artery catheters were used. Most of these patients had medical conditions. The authors of this report suggested that their results should prompt a critical evaluation of the use of pulmonary artery catheters under all conditions.[16] This was followed by a clinical trial in the United Kingdom demonstrating no benefit from the use of pulmonary artery catheters in a general ICU setting.[17] A more recent evaluation of the usefulness of these devices has demonstrated that, with proper training and in the appropriate setting, they can provide data not available through other modalities.[18] Over the past years, the use of pulmonary artery catheters has significantly diminished except in special circumstances, such as unexpected response to treatment, as in volume replacement for oliguria. Even in this condition, new technology based on arterial waveform analysis gives an estimate of cardiac output and end-diastolic volume, which generally gives enough information to guide appropriate therapy.[19] However, in the appropriate patients, pulmonary artery catheters may still play a valuable role.

Arterial Waveform Analysis

Multiple devices have been developed over the past decade using arterial waveform analysis to continuously measure cardiac output as well as to estimate preload. Stroke volume variation provides a good estimate of the fluid responsiveness of shock with only arterial access.[20] The transpulmonary thermodilution technique provides an even more complete hemodynamic dataset without the use of a pulmonary artery catheter. Using only a central line and central arterial line, thermodilution allows monitoring of preload with global end-diastolic volume index, intrathoracic blood volume, continuous cardiac output, and extravascular lung water index. Numerous studies have shown that these volumetric indices represent preload more precisely than urine output or cardiac filling pressures.[21] In a study involving 54 burned children, Herndon et al. determined pulse index continuous cardiac output (PiCCO) to be the superior measurement for cardiac parameters to transthoracic echocardiography and an objective cardiovascular monitor to guide goal-directed fluid resuscitation.[22]

Echocardiography

Transesophageal echocardiography has been used for a number of years as an intraoperative monitor in high-risk cardiovascular patients. It has not been used extensively in other critically ill patients because of the lack of available expertise and paucity of equipment. Since this device can be used as a diagnostic tool for the evaluation of hemodynamic function, it stands to reason that it could be used to monitor critically ill, severely burned patients. A report documented the use of transesophageal Doppler measurements of cardiac output in a series of severely burned patients and showed that intravascular volume and cardiac contractility are significantly diminished the first day after burn in spite of high-volume resuscitation.[23]

Echocardiography has also been studied as a means to supplement urine output monitoring. Investigators in China examined whether esophageal Doppler monitoring of heart function might be an improvement by studying 21 patients with massive burns (79 ± 8% TBSA burned) who were resuscitated with a goal of 1.0 mL/kg per hour. They found that cardiac output was predictably low after injury and increased linearly with time by increases in preload and contractility and decreased afterload. However changes in cardiac output were most closely associated with increased cardiac contractility and decreased afterload rather than increases in preload. Additionally urine output was not closely associated with cardiac output.[24] Held et al. evaluated 11 adult burn patients with a mean TBSA of 37% and found that changes in volume status on echocardiography preceded changes in urine output and vital signs, and they were able to titrate inotropes and vasopressors in elderly patients.[25]

These results call into question the validity of urine output as the primary measure of the adequacy of resuscitation. A similar study by investigators in Sweden probing the role of cardiac function, as measured by echocardiography, and myocyte damage, as measured by troponin abundance in the serum, showed that half of their patients had myocardial damage during resuscitation universally associated with some temporary cardiac wall motion abnormality. However systolic function was not adversely affected.[26] Bedside echocardiographic equipment and skills are increasingly common in BICUs and are an increasingly common means of hemodynamic monitoring in critical care.[27] However the intermittent nature of this procedural assessment allows it to only serve as a useful adjunct to add clarity to a difficult clinical scenario and prevents echocardiography from supplanting continuous monitoring modalities, such as thermodilution or waveform analysis. We look forward to further work regarding the optimal method of assessment of resuscitation; for the present, however, urine output remains the standard, and other measures are useful adjuncts.

Laboratory Estimates of Perfusion

Mixed venous saturation is the gold standard for the measurement of total tissue perfusion but has fallen out of favor because it requires a pulmonary artery catheter.[28] As such, peripheral surrogates, such as base deficit and serum lactate, have become the standard values followed to monitor shock. These can be measured in minutes using point-of-care techniques and rapid guide interventions.

The base deficit is a value calculated using the Henderson-Hasselbalch equation based on the relationship between pH, pCO_2, and serum bicarbonate:

$$pH = 6.1 + \log(HCO_3^-)/(pCO_2)(0.03)$$

It is the stoichiometric equivalent of base required to return the pH to 7.40. Base deficit is routinely calculated on blood gas analysis and provides a reasonable estimate of the degree of tissue anoxia and shock at the whole-body level, particularly in hemorrhagic shock. A rising base deficit indicates increasing metabolic acidosis and may stratify risk of mortality in patients after major trauma.[29] The same can be said for the use of base deficit in resuscitation of burned patients.[30,31] These studies showed a correlation between higher base deficit and increased mortality, and some have suggested that this value is a better monitor of resuscitation than the time-honored monitors of urine output and arterial blood pressure.[32] Recent studies of burned patients showed the base deficit was higher in nonsurvivors during resuscitation, although the authors could not identify a specific boundary for the effect.[33,34] Despite its utility as an indicator of shock, base deficit remains a nonspecific indicator of metabolic acidosis and may be elevated with many confounding conditions other than shock, including hyperchloremia, uremia, and alcohol, cocaine, and methamphetamine use. Interpretation can be difficult under these circumstances.

Lactate is another common measure used to determine the adequacy of tissue perfusion. Under acute low-flow conditions, cells transition from primarily aerobic metabolism to anaerobic metabolism for energy production (i.e., adenosine triphosphate [ATP]). A by-product of anaerobic metabolism is lactic acid. Under ischemic conditions, plasma lactate concentration will increase, leading to a decrease in pH. Measurement of lactate is commonly performed to determine the adequacy of generalized perfusion; increases suggest ischemia. Investigators showed that lactate does increase, along with base deficit, in burned patients during resuscitation, and higher levels are associated with poorer outcomes.[34] Later in the course, however, lactate concentrations must be used with some caution because elevated levels do not necessarily indicate ischemia. Under hypermetabolic conditions common in the severely burned, pyruvate dehydrogenase activity is sufficiently inefficient that lactate levels might be elevated without ischemia. Isolated elevations of lactate should then be interpreted with caution and confirmation of ischemia or shock by physical or other laboratory findings sought.

Multisystem Organ Failure

MOF is largely a creation of our success in critical care enabling previously moribund patients to survive long enough for organ failure to develop. Often particular organ systems are allowed to fail to maintain overall patient survival (e.g., performing an excision and grafting procedure that leads to renal failure to remove a septic burn which would otherwise be lethal). The topic of MOF is more thoroughly covered in Chapter 30, but we will briefly summarize it here.

HUMORAL MEDIATORS

Humoral inflammatory factors elaborated from the burn wound and the resultant immune, adrenal, and sympathetic activation mediate the development of SIRS.

A number of theories have been developed to explain the progression to MOF (Box 32.4). In the infection theory, as organisms proliferate out of control, endotoxins and exotoxins are released that cause the initiation of a cascade of inflammatory mediators through activation of pathogen-activated molecular pathway (PAMP) receptors, such as Toll-like receptors 2, 4, and 9,[35] as well as the recruitment of inflammatory cells. These pathways can result in organ damage and progression toward MOF if unchecked.

MOF can also be initiated by inflammation from the presence of necrotic tissue, and open wounds can incite a similar inflammatory mediator response to that seen with endotoxins. Evidence suggests that this response is due to activation of the cytokine cascade through damage-associated molecular pathways (DAMPs), which might be

Box 32.4 Theories for the Development of Multiple Organ Failure

- Infectious causes
- Macrophage theory
- Microcirculatory hypothesis
- Endothelial–leukocyte interactions
- Gut hypothesis
- Two-hit theory

antigens associated with liberated mitochondria from our own cells.[37] Four of these cytokines, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, and IL-8, are most strongly associated with sepsis and MOF in burns.[36] The primary support of this theory is that many patients, including those burned, can develop MOF without identified infection. Regardless, it is known that a cascade of systemic events is set in motion, either by invasive organisms or from open wounds, that initiates SIRS and may progress to MOF, thus supporting early burn excision and grafting.

Another theory implicates prolonged tissue hypoxia and the subsequent generation of toxic free radicals during reperfusion as the primary mediator of end-organ damage. As discussed in Chapter 8 on burn edema, this free radical damage can be ameliorated with high-dose intravenous vitamin C during resuscitation.[38] From in vitro models and in vivo animal models, we know tissues that were in shock initially and subsequently reperfused produce oxygen free radicals known to damage a number of cellular metabolism processes. It was found that free radical scavengers, such as superoxide dismutase, improve survival in animal models, but these results have not yet been established in humans.[42] Endogenous natural antioxidants, such as vitamins C and E, are low in burned patients, suggesting that therapeutic interventions may be beneficial.[43]

The final two theories revolve around the role of the gut in the generation of organ failure and the "two-hit" theory of MOF. For years, investigators have implicated the gut as the "engine" of organ failure, which is associated with loss of gut barrier function and translocation of enteric bacteria and/or their toxic metabolites. Bacterial translocation has been shown to occur after burn in patients.[45] No studies have clearly shown whether bacterial translocation is the cause of SIRS/MOF, probably because investigators have as yet been unable to control bacterial translocation effectively during shock in humans; thus, a cause-and-effect relationship cannot be established. The "two-hit" theory ascribes a summation of insults to the development of MOF. Each of the insults alone is inadequate to cause the response, but one or more can "prime" the inflammatory response system just described, such that another normally insignificant injury causes the release of toxic mediators ending in MOF.

It is likely that some part of all of these theories is a cause for MOF in burned patients; probably the relative contribution is unique in each patient. Therefore a single solution is unlikely, and this should be kept in mind when devising strategies to improve care and outcomes.

COURSE OF ORGAN FAILURE

Generally, MOF will begin in the renal and/or pulmonary systems and progress in a systematic fashion through the liver, gut, hematologic system, and central nervous system. The development of MOF does not inevitably lead to mortality, however. Efforts to support failed organs until they recover are justified.

Critical Care Interventions

Critical care of a burn patient in the modern era is predicated upon seven key factors:

- Sufficient goal-directed fluid resuscitation
- Early burn excision and grafting
- Aggressive antimicrobial and source control of sepsis
- Aggressive and sufficient nutritional support
- Active warming
- Aggressive physical, occupational, and respiratory therapy
- Aggressive and continuous support of organ failures

Sufficient fluid resuscitation of an acute burn wound is thoroughly covered in Chapter 9 on fluid resuscitation. Various formulas to predict fluid requirement, balances between crystalloid versus colloid, and resuscitation endpoints have been advocated. Early in resuscitation it is critical to provide sufficient volume to maintain preload and perfusion in the setting of fluid losses into burn edema and distributive shock while avoiding over-resuscitation, with the resultant costs such as heart failure, liver failure, and compartment syndromes.[46]

Early burn excision and grafting has been discussed thoroughly in Chapter 12 on operative management. The overriding principle is to remove inflammatory and diseased burned tissue to break the hyperinflammatory state underlying burn shock. Early grafting reduces the inflammatory load on the patient, fluid loss, heat loss, the area susceptible to infection, and the total length of critical care. Collectively it reduces the exposure time available for MOF to occur.

Furthermore, the blood loss associated with large-scale early excision often results in a functional plasma exchange.[47] Plasma exchange has been shown to be effective in reducing burn resuscitation, ostensibly by removing the inflammatory and oxidative humoral mediators underlying burn shock. Klein et al. reviewed 44 plasma exchanges in patients reaching twice Parkland with albumin or fresh frozen plasma and found a 40% reduction in fluid resuscitation.[48] In a plasma exchange protocol triggered at 1.2 times Parkland, Neff et al. found a 24% increase in MAP, 400% increase in urine output, and 25% reduction in resuscitation rate, with a reduction in lactic acid as well.[49] In 37 patients undergoing plasma exchange with a mean TBSA of 48.6%, hourly fluid, base deficit, lactate, and hematocrit all improved and were associated with decreased resuscitation volume and increased urine output.[48] Collectively these data support the notion that plasma exchange improves burn shock; however there are thus far no studies directly linking plasma exchange resulting from intraoperative blood loss with improvements in burn outcome demonstrated in early burn excision.

Chapter 11 on infection control well defines the critical nature of early surgical source control and appropriate antimicrobials, but generally emphasizes that meticulous aseptic technique, excision of infected or devitalized tissue, coverage with viable grafts, topical antimicrobials, culture surveillance, and systemic antimicrobials when appropriate are critical components.[50] Similarly, Chapters 28 and 29 on nutrition support and hypermetabolism, respectively, effectively discuss the critical need for enteral feeding and nutritional support, physical therapy, and the requirement to keep patients warm. The remainder of this chapter is directed toward organ-specific critical care support.

TOXICOLOGICAL BURN CRITICAL CARE

Many toxins can affect the burn-injured patient, particularly with occupational injuries. Specific therapies for all toxins are beyond the scope of this chapter and require appropriate decontamination, antidotes, and consultation with material data safety sheets and poison control centers for known exposures if beyond the burn physician's comfort. However the most common toxins are cyanide and carbon monoxide.[51] Cyanide can be elaborated from the combustion of various plastics, and significant exposure can result from smoke inhalation. Mounting evidence indicates that cyanide toxicity is clinically significant in inhalation injuries, being found at clinically significant levels in up to 76% of inhalation injury patients. Few clinical labs return blood cyanide labs in a clinically useful time scale, so surrogate markers of less than 15% TBSA with smoke inhalation, Glasgow Coma Scale (GCS) under 14, abnormal hemodynamics, and/or a lactate level of greater than 10 are known sensitive indicators of cyanide toxicity of greater than 1.0 mg/L. In these cases, empiric therapy is recommended with hydroxycobalamin.[52] It is the first-line antidote for cyanide toxicity and has a very mild side effect profile of transient hypertension, bradycardia, and urine discoloration. Hydroxycobalamin is also a nitric oxide scavenger and effectively reduces the hypotension often seen in burn shock.[52]

As a common product of combustion, carbon monoxide (CO) should be considered in any inhalation injury, enclosed fire, or patient with altered mental status. Patients with carboxyhemoglobin (COHb) levels above 25% should be mechanically ventilated on 100% FIO_2, which reduces the half-life from 4 hours to 1 hour. There are rare indications for hyperbaric oxygen (HBO) because it can reduce the CO half-life to 15 minutes, particularly in the setting of pregnancy or seizures. HBO is only indicated in the burn setting if it can be immediately employed in conjunction with definitive burn care in specialized centers. For cases where instituting HBO unnecessarily delays burn care, mechanical ventilation can bring COHb to safe levels prior to HBO's institution, and appropriate burn care should take precedence.[53]

NEUROLOGICAL BURN CRITICAL CARE

The main aspects of neurologic management of burn patients are pain control, sedation, delirium management, and management of acute stress disorder or posttraumatic stress disorder (PTSD). Furthermore there can be a need for seizure treatment or prophylaxis, management of the traumatic brain injury, or drug and alcohol withdraw protocols, which can occur concomitantly with the burn injury and are beyond the purview of this chapter. An important component of neurological care is early mobilization; physical/occupational therapy should be performed unless firmly contraindicated.[13]

Pain control is the most common neurologic intervention in the burn patient. Basal pain management with narcotics such as morphine is administered as needed to maintain comfort, while taking care to avoid oversedation that can prevent achieving physical therapeutic goals. Methadone can help by providing basal pain coverage and weaning of narcotics.[51] Interventions required for the patient to heal, such as physical therapy or wound care, will create a certain amount of pain that cannot be fully alleviated without preventing the patient's progress.[54] The burn team must assess the patient's pain management and use their experience to carefully balance short-term analgesia with long-term recovery and function.

Additional analgesics of short duration should be used for painful procedures, such as extensive wound care or staple removal. Often additional narcotics, such as fentanyl or additional morphine, are sufficient. For more extensive procedures ketamine is a safe, effective, and recommended agent. Several large series support ketamine use in nurse-driven protocols. In a series of 522 painful procedures in pediatric burn patients, only 2.9% required intervention such as airway repositioning, zero intubations in lengths from 1 to 105 minutes and weights from 2 to 111 kilograms.[55] A meta-analysis of 8282 ketamine sedations from 32 ED studies demonstrated no intubations. There was a 0.8% rate of transient apnea and 0.3% rate of laryngospasm; however all were resolved with positioning and/or bag valve masking.[56] In these studies, trained nurses typically performed the sedation. Ketamine has a favorable safety profile relative to benzodiazepine and narcotics due to its lack of respiratory depression and its cardiovascular stimulating effects.[54] Care should be taken to prevent emergence delirium in adult patients.

Sedation in the BICU is more complicated, requiring the balance of short-term sedative goals and apparent patient comfort with the intermediate costs of delirium and decreased therapy participation, as well as with long-term neuropsychiatric costs. The first goal is to minimize sedation administered, which is accomplished best with the use of a sedation scale and avoiding continuous benzodiazepine infusions. The use of the Richmond Agitation Sedation Scale has been shown to decrease mean duration of ventilator and sedation consumption.[57]

Benzodiazepines have reduced utility due to increased delirium and length of mechanical ventilation. Propofol, ketamine, and remifentanil have been increasingly used as alternatives to the formerly standard benzodiazepine-based therapies.[58] When compared directly to midazolam, patients sedated with the α-adrenergic agonist dexmedetomidine have required less sedation and have less hypotension. This sedative can be considered more effective, as well as being less of a risk in terms of hypotension.[59] Benzodiazepines are associated with an increased risk of agitation and delirium, and benzodiazepine and propofol are associated with more ventilator-associated events than dexmedetomidine. Dexmedetomidine is associated with less time to extubation and higher rates of bradycardia, but this is generally well tolerated in burn patients due to their hyperdynamic state and tachycardia.[60] The less expensive oral equivalent, clonidine, is a common adjuvant to sedation working on a similar α-adrenergic mechanism as dexmedetomidine; it is currently under meta-analysis for that role.[61] Ketamine infusion has been shown to be safe and effective in continuous BICU sedation as well.[62]

Psychiatric and psychological care is a critical component of BICU care. Standard psychological therapies and interventions are important factors of burn care.[63] The critical care team can help prevent delirium and PTSD by

avoiding benzodiazepine, minimizing sedation, treating pain first, limiting sleep disturbances, encouraging mobility, reorientation, and avoiding prolonged infusion of sedatives.[64] Despite our best efforts, many patients in the BICU experience delirium and agitation. Haloperidol remains in use in critical agitation and delirium settings and has documented safety in pediatric and adult burn populations.[65] Atypical antipsychotics have gained a substantial role in basal coverage of delirium and agitation and are safe and effective. The BICU team must remember to discontinue these medications when patient are no longer delirious; 84.2% of patients started in the BICU continued use after discharge from BICU, and 28.6% continued following discharge from the hospital.[66]

CARDIOVASCULAR BURN CRITICAL CARE

Treatment of cardiovascular responses after burn requires an understanding of cardiovascular physiology and the effects of treatment. One of the hallmarks of serious illness is the direct link between cardiac performance and patient performance. Cardiac compensation to burn injury is hyperdynamic to meet hypermetabolic needs, maintain perfusion of injured vascular beds, and compensate for the vasoplegia associated with burn shock. As such, patients often require supraphysiologic cardiac output to compensate for their systemic pathology.[67] The four determinants of cardiac function and hence tissue perfusion are:

- Ventricular preload or end-diastolic muscle fiber length
- Myocardial contractility or strength of the heart muscle
- Ventricular afterload, or the degree of resistance against which the heart must pump
- Heart rate and rhythm

A thorough comprehension of the effects of each of these components on heart function is necessary to initiate effective treatments for burned patients with cardiovascular abnormalities.

Preload

Preload is the force that stretches the cardiac muscle prior to contraction. This force is composed of the volume that fills the heart from venous return. Due to the molecular arrangement of actin and myosin in muscle, the more the incoming venous volume stretches the muscle, the further it will contract. This is best demonstrated on a Frank–Starling curve (Fig. 32.1), first described by Otto Frank in a frog heart preparation in 1884; Ernest Starling extended this observation to the mammalian heart in 1914. The relationship demonstrated in the Frank–Starling curve justifies the use of preload augmentation by volume resuscitation to increase cardiac performance. However when the end-diastolic volume becomes excessive, cardiac function can decrease; probably the muscle fibers overstretch and pull the contractile fibers past each other, thereby reducing the contact required for contractile force. The preload necessary to reduce cardiac function in experimental settings is in excess of 60 mm Hg, which is rarely encountered in patients.

Preload is estimated clinically by central venous pressure, pulmonary artery wedge pressure, echocardiography, or transpulmonary thermodilution. These measures can be used to optimize preload, balancing vascular volume loading and cardiac performance against interstitial and pulmonary edema.

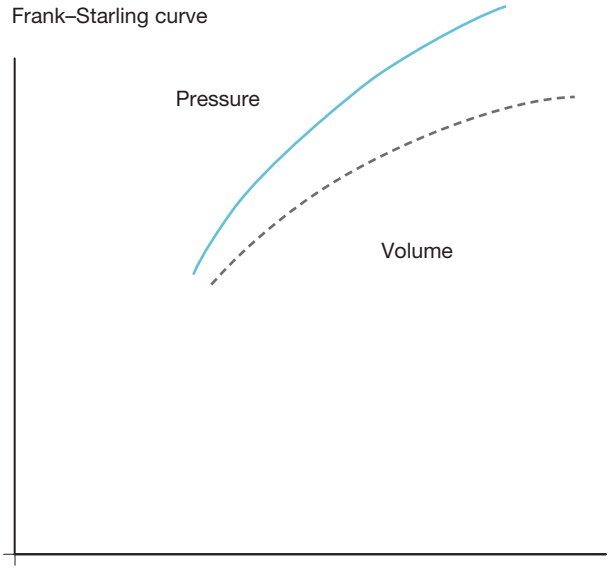

Fig. 32.1 Frank–Starling curve. The solid line depicts the pressure–volume relationship of the heart, showing that as pressure to the heart (preload) increases, the volume pumped by the heart increases. Immediately after burn, contractility diminishes, shifting the curve downward (*dashed line*). It still must be noted that, with this change, the volume pumped by the heart still increases with increased pressure (preload), validating the use of increased atrial pressure as a means of increasing cardiac output after severe burn.

Cardiac Contractility

The force with which the heart contracts is referred to as cardiac contractility. It is directly related to the number of fibers contracting, their preload and afterload. Contractility is diminished in patients with low preload or high afterload, in coronary artery disease with loss of myocardium from infarction and ischemia, in burned patients during the acute resuscitation due to myocardial depressant factor, in septic shock with Takotsobu cardiomyopathy, or in severely malnourished patients. Calculating the left ventricular stroke work from pulmonary artery catheter-derived values provides the best estimate of cardiac contractility and can be determined with the following formula:

$$\mathrm{LVSW} = \mathrm{SV}(\mathrm{MAP} - \mathrm{PCWP}) \times 0.0136$$

where LVSW is left ventricular stroke work, SV is the stroke volume (cardiac index ÷ heart rate), and PCWP is pulmonary capillary wedge pressure. In current practice, the contractility is usually tracked with arterial waveform continuous cardiac output monitoring or echocardiography.

Afterload

Afterload is the force impeding or opposing ventricular contraction and, in conjunction with cardiac output, creates blood pressure. This force is equivalent to the tension developed across the wall of the ventricle during systole. Clinically afterload is measured by arterial resistance as an estimate of arterial compliance. Arterial resistance is

measured as the difference between inflow pressure (mean arterial) and outflow pressure (venous) divided by the flow rate (cardiac output):

$$SVR = (MAP - CVP)/CO$$

where SVR is systemic vascular resistance, CVP is central venous pressure, and CO is cardiac output. Pulmonary artery catheters, arterial waveform analysis, or echocardiography calculates this value.

Heart Rate and Rhythm

For the heart to function properly, the electrical conduction system must be intact to provide rhythmic efficient contractions to develop sufficient force to propel blood through the circulatory system. For example, if the heart rate approaches 200 beats/min, the heart will have insufficient time to fill completely, thereby reducing myocardial fiber stretch and heart function. Also, if frequent premature ventricular contractions are present, the heart will not perform optimally, for similar reasons. Heart rate and rhythm are monitored continuously as routine in every critically ill patient using electrocardiography. A combination of sympathetic and adrenergic tone, combined with high atrial stretch, can predispose burn patients to atrial arrhythmias, such as atrial fibrillation (AF). Judicious fluid and electrolyte management, β-blockade, rate control, and the appropriate use of antiarrhythmics are cornerstones of treatment. An important note: mortality is higher in BICU patients after developing AF.[68]

Effects of Burn on Cardiac Performance

Severe burns affect cardiac performance in a plethora of ways. The first is to reduce preload to the heart through volume loss into burned and nonburned tissues. It is for this reason that volumes predicted by resuscitation formulas must be used to maintain blood pressure and hemodynamics. In addition, severe burn induces myocardial depression characterized by a decrease in tension development, and velocities of contraction and relaxation. CO is then reduced. These effects are most evident early in the course of injury during resuscitation; however they are followed shortly thereafter by a hyperdynamic phase of increased CO, primarily caused by a decrease in afterload through vasodilation and an increase in heart rate.

Hemodynamic Therapy: Preload Augmentation. When hypotension or other signs of inadequate cardiac function (i.e., decreased urine output) are encountered, the usual response is to augment preload by increasing intravascular volume. This is a sound physiologic approach based on the Frank–Starling principle and should be the first therapy for any patient in shock. Intravascular volume can be increased using either crystalloids or colloids to increase the CVP and PCWP to a value between 10 and 20 mm Hg. Preload goals can also be stroke volume variation below 12% or global end-diastolic volume index between 680 and 800 mL/m^2.[69] The adequacy of this therapy can be monitored by the restoration of arterial blood pressure, a decrease in tachycardia, and a urine output of greater than 0.5 mL/kg per hour.

Some caution must be exercised when augmenting preload for hemodynamic benefit in burned patients. Excessive volume administration may lead to significant interstitial edema and volume overload, with the development of peripheral and pulmonary edema. These changes can lead to conversion of partial-thickness burns to full-thickness injuries in the periphery and cause significant respiratory problems, liver failure, and compartment syndrome. Once hemodynamics are restored, fluid overload can be treated with spontaneous diuresis, pharmacologic diuresis, dialysis, or even therapeutic phlebotomy if required.

Hemodynamic Therapy: Inotropes and Vasopressors. If preload optimization is insufficient to improve hemodynamics, patients may require inotropes to increase cardiac output and/or vasopressors to increase afterload. Inotrope classes include phosphodiesterase inhibitors, digoxin, and adrenergic agonists. Phosphodiesterase inhibitors like milrinone increase contractility and decrease afterload without increasing myocardial oxygen demand by raising intracellular cyclic adenosine monophosphate (cAMP) levels to increase myocyte calcium (Ca^{2+}) levels. Digoxin increases contractility and decreases heart rate without increasing myocardial oxygen demand by inhibiting the sodium/potassium (Na^+/K^+) pump and increasing intracellular Ca^{2+}. Dobutamine is a commonly used inotrope with effects limited to β-adrenergic stimulation, thereby increasing CO and causing vasodilation. Dobutamine can be associated with increased heart rate and does increase myocardial oxygen demand. The associated vasodilation may be useful in perfusing peripheral vascular beds, as in threatened skin. The data support dobutamine reducing extravascular lung water and decreasing SVR index with increasing cardiac index and urine output, despite the global end-diastolic volume index (GEDI) being unchanged.[70]

Catecholamines, the most commonly used medication to augment blood pressure, are considered "inoconstrictors" because they have both inotropic and vasoconstrictive properties. One caveat regarding the use of these inoconstrictors is that myocardial oxygen consumption increases, which may affect the ischemic areas of the heart. However the hypotension being treated by the catecholamines will also compromise myocardial oxygen delivery substantially, so this consideration should not preclude their use by an experienced critical care burn physician. Epinephrine is the catecholamine of choice because it provides a greater proportion of its increase in blood pressure from inotropy rather than vasoconstriction. However norepinephrine is the preferred pressor in septic shock; its greater reliance on vasoconstriction versus inotropy can compromise dermal vascular beds critical to wound healing and survival in a burn patient, particularly in the setting of inadequate preload. Dopamine has generally fallen out of favor due to tachyphylaxis and tachycardias.[71] Therefore we consider epinephrine the preferred catecholamine.

Pure vasoconstrictors have a very limited role in burn care because concomitant inotropic support is advisable due to the patient's hyperdynamic state. Agents with primary effects on the α-adrenergic receptor can be used to induce vasoconstriction and increase blood pressure. Norepinephrine is often considered in this group, although 40% of its increase in blood pressure is due to α-mediated vasoconstriction, whereas 60% is from increased CO.[72,73]

Phenylephrine is a pure α-agonist, and can decrease CO and perfusion.[72,73] These agents are effective in septic shock or neurogenic shock to increase vascular tone.[74] However, in burned patients, it is believed that these agents will cause vasoconstriction of the skin and splanchnic circulation, thereby redistributing blood flow. This can cause grafts to fail and conversion of partial-thickness skin injuries to full-thickness, as well as resulting in ischemic injury to the gut. Additionally norepinephrine in both physiologic and pharmacologic doses suppressed wound macrophage efficiency in a cAMP-mediated manner via the adrenergic receptor. This may be part of the benefit provided by β-blockers.[75] The physiology of catecholamines was discussed in Chapter 23 on hormonal, adrenal, and sympathetic responses to burn injury.

Another pure vasoconstrictive agent used with great popularity is vasopressin. A very potent vasoconstrictor, it is mediated through its own receptor independent of the adrenergic receptors. Levels of vasopressin have been shown to be low in septic shock, and physiologic replacement at 0.02–0.044 U/kg per minute without titration is used in some burn units to increase MAP to good effect. Some investigators found that the use of vasopressin in this setting increased blood pressure, decreased heart rate, and spared norepinephrine dosing when used concomitantly.[76] In these physiologic replacement doses, there is believed to be minimal effect on splanchnic or dermal flow. Although there was a trend toward reduced renal failure with the administration of vasopressin, the VANISH trial failed to conclusively demonstrate reduced renal failure rates in septic patients treated with vasopressin compared to norepinephrine.[74] In an animal model, Li et al. found that adding a small physiologic dose of vasopressin to norepinephrine improved mitochondrial function and all measures of hemodynamics, as well as tissue and splanchnic perfusion.[77] In a series studying 30 septic burn patients treated with vasopressin plus norepinephrine, reduction of total norepinephrine dosing was shown. However one patient died from upper gastrointestinal necrosis; this patient presented with increased peripheral ischemia and donor site conversion, as well as skin graft failure. These data again support concerns regarding the use of pure vasoconstrictive agents when treating burn patients.[76]

Very rarely methylene blue, as a pure vasoconstrictor, may prove beneficial in treating refractory vasoplegia. It is a potent nitric oxide synthase inhibitor and, in case reports, has been shown to successfully reverse refractory vasoplegia following severe burn and thus should be in the armamentarium.[78,79]

Use of vasopressors and ionotropes in burn patients is an indispensible component of burn care. Balancing risks and benefit profiles of various medications in an individual patient's physiology is the purview of an experienced, trained burn critical care surgeon.

Effects of β-Blockade on Cardiac Performance After Severe Burn

One response to severe burn is a dramatic increase in catecholamine production; this has been linked to a number of metabolic abnormalities including increased resting energy expenditure, muscle catabolism, and altered thermoregulation. A nonspecific β-blocker, propranolol, has been used to reduce heart rate and myocardial work in severe burns.[80] Propranolol administration also reduces peripheral lipolysis[81] and muscle catabolism,[82] which are additional benefits. Wurzer et al. demonstrated that propranolol reduced cardiogenic stress by reducing cardiac index and MAP in severely burned, injured children without reducing peripheral oxygen delivery or increasing lactic acidosis events or organ dysfunction.[83] Further trials are in progress to define the benefits of β-blockade as well as its interaction with other anabolic medications such as oxandrolone. Regardless β-blockade is becoming an increasingly standard component of burn care.

PULMONARY BURN CRITICAL CARE

Lungs can be injured from inhalation injury, infection, inflammatory mediators, heart failure, or a sequela of critical care interventions, such as fluid overload or ventilator injury. Minor pathology can be treated with supplemental oxygen, diuresis, bronchodilators, or mucolytics. However mechanical ventilation is an essential treatment to manage pulmonary failure.

Mechanical ventilation in the severely burned generally occurs for three reasons: airway control during the resuscitative phase, airway management for smoke inhalation, and support during acute respiratory distress syndrome (ARDS). The first indication is for airway control early in the course, with the development of massive whole-body edema associated with the great resuscitative volumes required to maintain euvolemia. In this situation, the need for mechanical ventilation is not due to lung failure per se, but rather to maintain the airway until the whole-body edema is resolved. Once this occurs, usually 2–3 days into the course, extubation can be accomplished with minimal sequela. Ventilator management during this phase is routine. The second indication is airway management early in the course of smoke inhalation, which is a direct toxic injury to the airways and alveoli resulting in mucosal sloughing, loss of mucociliary escalator function, airway narrowing and edema, loss of surfactant, weakening of cartilaginous support of the airways, and fibrinous exudation into the airways.[53] Chapter 16 on inhalation injury comprehensively covers this issue. The third indication is the development of hypoxemia or hypercarbia due to a high alveolar-arterial (A-a) gradient, shunting, ventilation/perfusion (VQ) mismatching, poor compliance, or high resistance. Severe burns are known to be associated with hypoxemia and the development of ARDS. The clinical manifestations are dyspnea, severe hypoxemia, and decreased lung compliance, with radiographic evidence of diffuse bilateral pulmonary infiltrates.

Indications for Intubation

Intubation entails passing an endotracheal tube from either the nose or the mouth through the pharynx and into the trachea. This tube is subsequently connected to a mechanical ventilator to induce inspiration and passive exhalation. In burned patients indications for intubation are, in general, to improve oxygenation and ventilation or to maintain a compromised airway, such as in a severe inhalation injury or obtunded patient (Table 32.1).

Table 32.1 Clinical Indications for Intubation

Criteria	Value
PaO_2 (mmHg)	<60
$PaCO_2$ (mmHg)	>50 (acutely)
P/F ratio	<200
Respiratory rate	>40
Respiratory/ventilatory failure	Impending
Upper airway edema	Severe

It is important to intubate appropriate patients prior to respiratory arrest. It should be considered, however, that in a large study series more than 33% of burn patients were extubated within 1 day of intubation for transfer to a burn center without reintubation. These patients were subjected to risk without reward, and loss of an endotracheal tube in a heavily sedated or paralyzed patient is potentially fatal.[84]

Securing an endotracheal tube (ETT) to a burned and/or edematous face can be challenging. In a large survey of burn centers, ETTs were reported secured with linen nonadhesive tape in 59% of cases, manufactured devices in 48%, and orthodontically in 24%.[85] Our center has used nasal intubation with a septal tie for 20 years without accidental extubation or septic sinusitis.

Tracheotomy can provide a long-term durable airway with less patient discomfort. In a survey of American burn centers, the average tracheostomy was performed at 2 weeks; however there is a consensus that there are indications for earlier tracheostomy.[85] Interestingly, however, in a study of 600 adult medical ICU patients, Terragni et al. found that early tracheotomy did not result in significant improvement in ventilator-associated pneumonia, although the duration of ventilator-assisted respiration was reduced, as was ICU time.[86]

Pulmonary Physiology

There has been a proliferation of management strategies for pulmonary failure with an alphabet soup of ventilator modes. However the physiology of human lungs remains constant regardless of the proliferation of devices. Maintaining a broad physiologic view allows optimal matching of the ventilator's actions to the patient's needs. Lungs have three main functions:

- Ventilation
- Oxygenation
- Expectoration

Ventilation. Ventilation allows the elimination of carbon dioxide (CO_2), as measured on arterial blood gas by the $PaCO_2$. The ventilator accomplishes this with minute ventilation (V_{min}) minus dead space ventilation (V_d). In general, $PaCO_2$ varies inversely with V_{min}, so this value must be considered when making ventilator adjustments to alter $PaCO_2$. V_{min} is equal to tidal volume multiplied by respiratory rate. Therefore, $PaCO_2$ can be adjusted downward by increasing either tidal volume or respiratory rate. In general, the respiratory rate should be set between 10 and 20 breaths/min and tidal volume at 6 mL/kg ideal body weight initially. In a normal patient, V_{min} is 100 cc/kg per minute, but with the high CO_2 production seen in burn patients the needed minute ventilation can increase two- to fourfold. Adjustments can then be made in minute ventilation to optimize $PaCO_2$, which is usually 40 mm Hg but can be higher in patients with pre-existing chronic obstructive pulmonary disease (COPD) or smoking habits.[87] When making these adjustments, it should be noted that the respiratory rate cannot be increased above 40 breaths/min in those who are not neonates, and tidal volume should be minimized to avert ventilator-induced lung injury (VILI).

As respiratory rates increase in an attempt to increase minute ventilation while complying with low tidal volumes, the fraction of dead space can also increase, further impeding ventilator function. In these cases, decreasing the minute ventilation will increase CO_2 elimination. Dead space ventilation–perfusion abnormalities can be monitored with volumetric capnography performed bedside to measure physiological and alveolar dead space.[88] This can be a useful adjunct for ventilator management. Volumetric capnography accounts for total CO_2 exhaled, unlike late expiratory end-tidal CO_2 ($EtCO_2$) monitoring, which assumes an A-a gradient of only 2–3 mm Hg, inappropriate in many critical care patients. $EtCO_2$ monitoring has utility in monitoring trends or in the setting of a low gradient, as seen in traumatic head injuries. However in critically ill burn patients, the A-a gradient can be in a state of flux, calling into question values received from the $EtCO_2$ monitor and making volumetric capnography more appealing. Factors affecting the A-a gradient include CO, airway dead space, airway resistance, and metabolic rate; each of these may change in a severely burned patient, particularly those with inhalation injury. For these reasons, $EtCO_2$ monitoring is ill-advised in burned patients for the estimation of $PaCO_2$. Serial blood gas examination is a more reliable monitor.

The ARDSnet studies have well documented that ventilatory injuries to the lung can induce ARDS and have an appreciable effect on morbidity and mortality. Volutrauma occurs when an excess of volume over-distends the lungs, injuring compliant alveoli. Volumes are preferentially directed to compliant and uninjured alveoli because noncompliant alveoli have too long a time-constant to accept the volume. As healthy alveoli are sequentially injured, a positive feedback is established, and the injury continues to worsen. This is the principle underlying low tidal volume (LTV) ventilation. Use of positive end expiratory pressure (PEEP) can facilitate maintaining more compliant alveoli and reduce atelectotrauma by reducing alveolar collapse as well as preserving the lung in a more compliant portion of the pressure volume loop.[89] Furthermore having more nitrogen in the ventilated gas maintains a stenting function because it is not absorbed out of the airways as is oxygen.[90] When plateau airway pressures are greater than 30 mm Hg the ventilated lung is relatively noncompliant, indicative of ARDS or pulmonary edema, which subject the lung to barotrauma similarly. In this situation, "permissive hypercapnia" is a strategy that can be used to reduce barotrauma. This strategy seeks to limit peak and plateau airway pressures by reducing tidal volumes to allow for respiratory acidosis ($PaCO_2$ >45 mm Hg, arterial pH <7.30). This strategy was used to some extent in the trial investigating the

efficacy of pressure-limited ventilation on improving outcomes in critically ill ventilated patients.[91]

LTV ventilation has been shown in the ARDSnet trials to be protective against ARDS, but it can also compromise ventilatory function and CO_2 elimination. Burn patients represent unique challenges in mechanical ventilation and ARDS given the reduced compliance due to eschar, chest wall and pulmonary edema due to resuscitation, the unique physiology from inhalation injury, and the increased CO_2 production due to hypermetabolic response. Furthermore the work of breathing progressively increases at lower tidal volumes.[92] LTV protocols have been proved ineffective in the burn population: 33% of burn patients failed to meet oxygenation and ventilation requirements, increasing to approximately 67% in inhalation patients.[85]

Sousse et al. analyzed pulmonary outcomes in 932 burned pediatric patients with inhalation injury over 28 years, stratifying for tidal volume. Their findings, starkly divergent from ADRSnet predictions, demonstrated high tidal volume (15 +/− 3 mL/kg) was associated with significantly decreased ventilator days, maximum PEEP, and significantly increased maximum peak inspiratory pressure; ARDS was significantly decreased, but pneumothorax increased. They concluded that high tidal volumes might interrupt the sequences of events leading to lung injury following inhalation injury.[93]

Another school of thought holds that surrogate markers, such as airway pressures, should be used to avoid ARDS. By this logic, when tidal volumes were lowered, patients with more compliant lungs did poorly, whereas patients with less compliant lungs did well.[94] Regardless, lung-protective strategies are notoriously difficult to institute in the burn population, and some lung injury often must be accepted to assure overall patient survival.

Oxygenation. Like the adequacy of ventilation, oxygenation has been classically determined using the Pa_{O_2} in arterial blood. Arterial oxygenation is calculated using three factors: mean alveolar pressure of oxygen (MAP-O_2), the A-a gradient, and VQ mismatching. MAP-O_2, as determined by the ventilator, is the area beneath the pressure/time curve multiplied by the fraction of inspired oxygen (F_{IO_2}). Increasing the FiO_2 has limited ability to improve oxygenation because F_{IO_2} in excess of 60 is considered pulmonary toxic for prolonged time courses.[95] However increasing MAP-O_2 profoundly improves oxygenation, often quite safely. This can be accomplished by increasing the PEEP or the inspiratory time during which the airways are maintained at inspiratory pressure for longer, thereby enlarging the area under the curve. However as more time is maintained in inspiration, less is available for exhalation and ventilation. Thus hypercarbia and acidosis can limit the maintenance of high MAP-O_2.[96] These implications will be discussed in further detail in the ventilator mode section.

The A-a gradient is a function of the diffusion membrane separating air from blood. This is affected by pulmonary edema. A-a gradient issues are best managed by reducing pulmonary edema with diuresis, improving cardiac performance using inotropes, and allowing time for the lungs to heal their diffusion membrane by repopulating the type-1 pneumocytes.

VQ mismatching occurs as deoxygenated blood is shunted through poorly ventilated lungs and hypoxic vasoconstriction becomes dysregulated in the pulmonary vasculature. This is treated first by improving the aeration of the lung using pulmonary toileting, recruitment maneuvers, and open lung techniques to aerate long time constant aveoli.[97] Furthermore inhaled pulmonary vasodilators, such as nitric oxide or prostaglandins, can vasodilate aerated beds and improve VQ matching.[98] Finally prone positioning can also improve VQ matching, as well as posterior aeration.[99] In a survey of American burn centers, ARDS was managed through fluid restriction/diureses and enteral nutrition, as well as by neuromuscular blockade. In severe ARDS, prone positioning was used in 33% of centers and extracorporeal membrane oxygenation (ECMO) in 18%.[85]

Oxygen is principally delivered to tissues on hemoglobin, so, in general, a Pa_{O_2} value of 60 mm Hg is considered sufficient because it equates to a saturation of approximately 92%. Pulse oximetry effectively measures oxygenation and can be used to guide ventilator management. Falsely measuring methemoglobin and carboxyhemoglobin as oxygen-saturated hemoglobin, which is common initially in patients with smoke inhalation injury, highlights the shortcoming of this technique. Otherwise this is a very accurate method to determine the oxygen content in arterial blood because 97% of oxygen is carried to the tissues via hemoglobin. This assertion has been corroborated by in vitro studies showing the accuracy of pulse oximetry to within 2–3% of oxyhemoglobin levels.[100] The major limitations of this technique lie in its insensitivity to changes in pulmonary gas exchange. Because of the shape of the oxyhemoglobin dissociation curve, when the Sa_{O_2} exceeds 90% and the Pa_{O_2} is greater than 60 mm Hg, the curve is flat, and changes in Pa_{O_2} can move considerably with little variation in Sa_{O_2}. Regardless it is presumed that an Sa_{O_2} value of greater than 92% is indicative of adequate oxygenation. That the oxygenation saturation measurement is a continuous direct measure immediately available whereas blood gas measurement of Pa_{O_2} is intermittent is an advantage that should not be overlooked.

A commonly used parameter to assess the adequacy of oxygenation is the ratio of Pa_{O_2} to F_{IO_2} (P/F ratio). It is an easily calculated surrogate for the A-a gradient.[101] As such, the P/F ratio is one of the criteria utilized to diagnose ARDS in the Berlin definition (Table 32.2). ARDS is defined as bilateral opacities not explained by effusion, collapse of nodules occurring within 1 week of a clinical insult not fully explained by cardiac failure, or fluid overload associated with a P/F ratio of less than 300. ARDS is stratified to mild, with a P/F between 200 and 300; moderate, between 100 and 200; and severe, below 100.[101]

However, not incorporating MAP, a key determinant in oxygenation, is a major flaw when utilizing the P/F ratio. Thus two patients on two different levels of ventilator support (one on minimal PEEP, the other on maximal) are indistinguishable based on this parameter, although they are clearly disparate when using the A-a gradient. To account for this variable, the oxygenation index (OI) may be used:[102]

$$\text{Oxygenation index (OI)} = (\text{Mean airway pressure } (mmH_2O) \times FiO_2)/PaO_2$$

Table 32.2 Berlin Definition—ARDS

Onset within one week of onset of injury or illness	
Bilateral lung opacities not explained by effusion, atelectasis, or nodules	
Respiratory failure without cardiac failure or fluid overload	
Diminished oxygenation	
Mild	200 < P/F < 300
Moderate	100 < P/F < 200
Severe	P/F < 100

P/F = partial pressure arterial oxygen/fraction of inspired oxygen

This parameter is particularly helpful in determining a patient's oxygenation status in relation to the level of ventilator support: the higher the number, the worse the level of oxygenation. Generally, an OI of greater than 20 should be a cause for concern.

Expectoration. The final aspect of pulmonary physiology necessary for consideration in pulmonary critical care is expectoration. The injured lung must clear its secretions, damaged mucosa, pathogens, and aspirated material. In the case of an inhalation injury, there is the transudate of fibrinous material and sloughing of injured mucosa that must be cleared in the setting of a compromised mucociliary escalator. Chest physiotherapy, mucolytics, suctioning, and particular ventilator modes aid in the expectoration of the lungs.[103]

A commonly used technique to treat inhalation injury is the combination of nebulized heparin and N-acetylcysteine with albuterol and pulmonary toileting.[104] The goal is that the heparin will prevent coagulation of the transudated plasma, which comes through the injured pulmonary capillaries. The N-acetylcysteine serves as a mucolytic agent and allows expectoration, along with the sloughed mucosa, during physiotherapy and suctioning.

In a meta-analysis of five studies comprising 286 patients, inhaled heparin was found to reduce ventilator days and resulted in more patients alive at day 28 with lower lung injury scores, although methodological issues were noted.[105] However, in a follow-up analysis of those studies, individual patient data provided no convincing evidence regarding any benefit of heparin nebulization in intubated and ventilated ICU patients, although none of these patients had inhalation burn injuries.[105] In a review of inhalation-injured patients, Kashefi found a nebulized heparin and N-acetylcysteine/albuterol protocol did not reduce mortality or duration of mechanical ventilation, but did increase pneumonia rates.[106] Conversely Sood and Waldroth more recently published a case-control study of 72 inhalation-injured patients and found that a 7-day course of nebulized heparin with N-acetylcysteine and albuterol decreased mean ventilator days from 14 to 7 and increased ventilator-free days. There was no change in mortality, pneumonia rates, or bleeding in their study. In this series of inhalation-injured patients, nebulized heparin was found to be safe and effective.[104] This efficacy is consistent with our own clinical experience.

Mechanical Ventilation

Mechanical ventilation is an essential component of burn pulmonary critical care. Mechanical ventilatory support allows life to be sustained with lungs that would otherwise inexorably lead to death. It is important that the use of mechanical ventilation provide the minimal interruption to burn care, including both wound care and physical therapy. The safety of mobilization of mechanically ventilated patients is well documented, including out-of-bed mobilization of intubated patients (Fig. 32.2).[13]

The principal clinical difference between mechanical ventilation and spontaneous ventilation is the effect of positive pressure, as opposed to normal physiologic negative pressure. The use of positive pressure improves ventilation by recruiting alveoli and increasing functional residual capacity (i.e., the number and volume of open alveoli at the end of expiration), thus improving VQ mismatch and reducing shunting of blood past nonventilated lung areas (Fig. 32.3). Positive pressure ventilation also allows maintenance of higher MAP-O_2 to overcome high A-a gradients. Adverse effects of positive-pressure ventilation lie in its propensity to produce trauma to the airways (barotrauma) and its effects on intrathoracic pressure, which can impede venous return to the heart, thus reducing cardiac output.

In a survey of American burn centers, pressure support ventilation and volume assist control were the most common *starting* ventilator modes for all burn patients; however 53% of centers report using an open lung technique such as high-frequency percussive ventilation (HFPV), high-frequency oscillation ventilation (HFOV), or airway pressure release ventilation (APRV) in the setting of inhalation injury.[85]

When oxygenation begins to decline, initial maneuvers are to increase the F_{IO_2} to greater than 40%, possibly to 100%. Concentrations of oxygen greater than 60% are considered toxic to airway epithelium over the course of hours; other means to increase oxygenation should be employed.[95] As discussed earlier, treating hypoxia is first accomplished by increasing the MAP-O_2 by raising the level of PEEP incrementally until the desired level of oxygenation is reached while keeping the F_{IO_2} to less than 60%. Once a level of 15–20 mm Hg of PEEP is reached, other means of increasing MAP-O_2 will need to be employed. These consist of ventilator modes, including inverse ratio ventilation, HFOV, HFPV, and APRV.

After MAP-O_2 is maximized, therapies are directed at improving VQ mismatching with inhaled nitric oxide or prone positioning. ECMO has been used with success in burn patients when the lungs are too injured to perform life-sustaining gas exchange. This must be done with caution given the need for anticoagulation and the limitation imposed in the ability to mobilize the patient, both of which can compromise other critical aspects of burn care.[107]

Ventilator Modes. Regardless of the mode (Fig. 32.4), the basic pulmonary physiology principles balancing ventilation, oxygenation, and expectoration against VILI lung injury are the purview of a skilled burn surgeon and respiratory therapist.

RESPIRATORY CONSIDERATIONS	IN-BED EXERCISES	OUT-OF-BED EXERCISES
Intubation		
Endotracheal tube[a]		
Tracheostomy tube		
Respiratory parameters		
Fraction of inspired oxygen		
≤ 0.6		
> 0.6		
Percutaneous oxygen saturation		
≥ 90%		
< 90%[b]		
Respiratory rate		
≤ 30 bpm		
> 30 bpm		
Ventilation		
Mode HFOV		
PEEP		
≤ 10 cmH_2O		
> 10 cmH_2O		
Ventilator dysynchrony[c]		
Rescue therapies		
Nitric oxide		
Prostacyclin		
Prone positioning[d]		

Fig. 32.2 Respiratory considerations for in-bed and out-of-bed exercises. *Green circle* indicates low risk for adverse event. *Yellow triangle* indicates potential risk and consequences of an adverse event but may be outweighed the potential benefits of mobilization. *Red octagon* indicates a significant potential risk of an adverse event, and mobilization should only be carried out with specific consideration by senior staff nurse or physical therapist. (From Hodgson CL, Stiller K, Needham DM, et al. Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults. *Crit Care.* 2014;18[6]:658.)

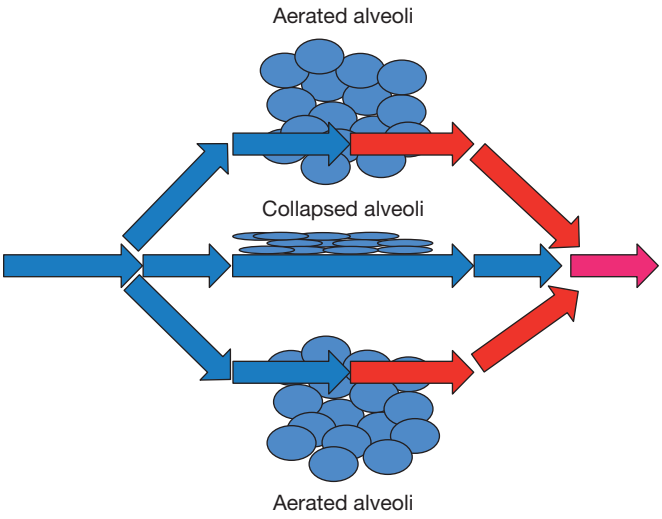

Fig. 32.3 A schematic of intrapulmonary shunting. Blood comes into the lung and then divides into capillaries and passes close to alveoli, where gas exchange occurs. In the case of alveolar collapse, the passing blood does not undergo gas exchange and thus returns to the pulmonary vein unchanged (low oxygen concentration, blue color). This then mixes with oxygenated blood from the aerated alveoli (high oxygen concentration, red color) to return to the heart and the periphery. In effect, more collapsed lung equates to less oxygenation through this process.

Volume-control mode delivers a preset tidal volume regardless of patient effort and is typically used only under general anesthesia due to ventilator–patient *dyssynchrony*; it takes all respiratory control away from the patient (Fig. 32.5). Assist-control mode differs by allowing the patient to demand additional breaths with a ventilator-preset minimum rate. All breaths are delivered at a prescribed volume, irrespective of any patient attempts for a larger or smaller breath. Some patients find this mode uncomfortable due to the inability to control their volume and require greater sedation than they would under other modes.

Volume-cycled ventilation delivers a set volume of air regardless of pressure required. In the case of poor lung compliance, such as ARDS, this mode could lead to excessive ventilator pressures and significant airway injury. For this reason, *time-cycled pressure control ventilation* was developed; this delivers inspiration at a given flow rate to a preset pressure. The breath is terminated at a set cycle time, not on the basis of volume of flow, as with volume-controlled ventilation. Therefore pressure control has the advantage of limiting inspiratory pressure despite changes in compliance. It has the disadvantage of a variable tidal volume during dynamic changes in lung compliance, which can lead to inadequate or excessive minute ventilation if compliance respectively worsens or improves.

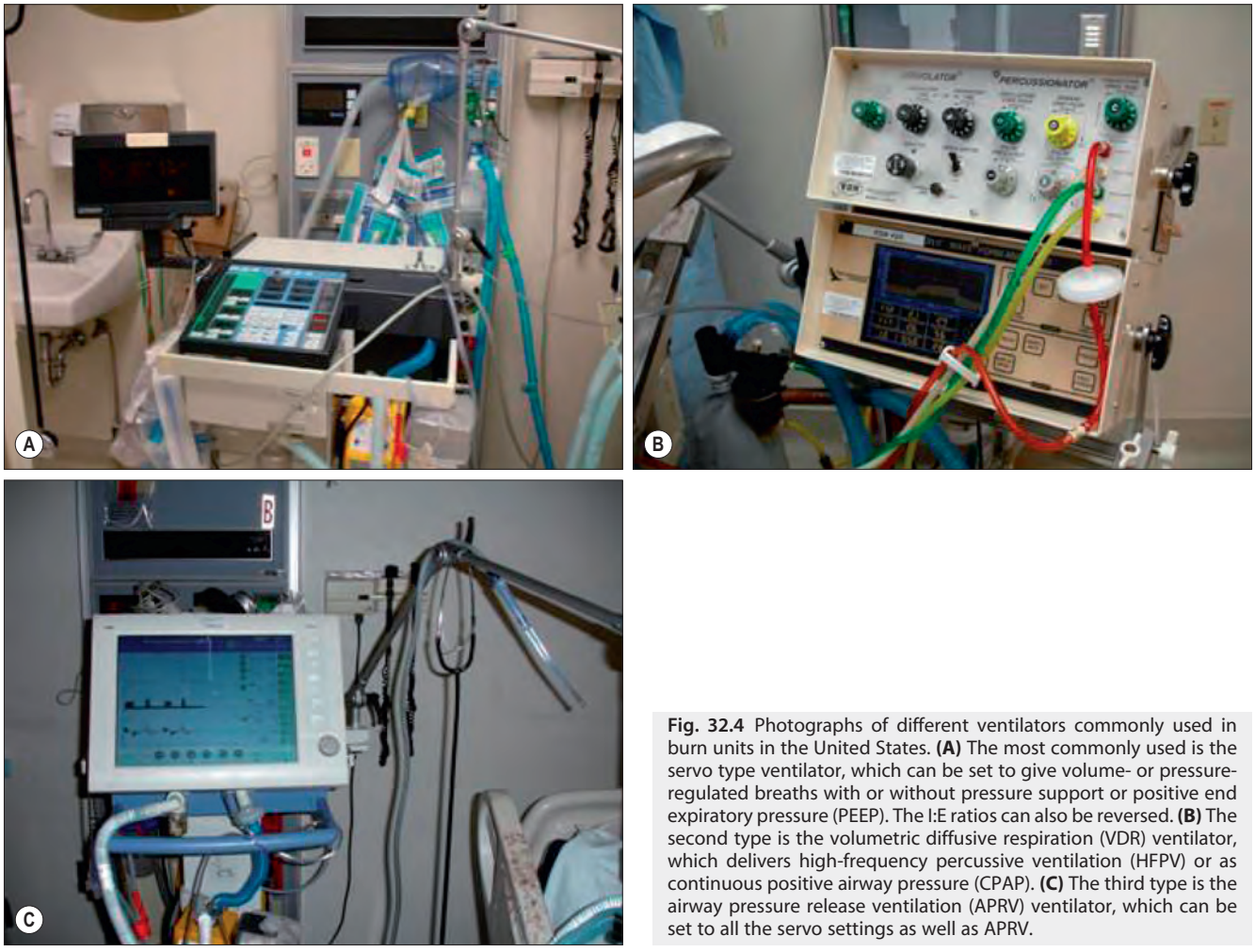

Fig. 32.4 Photographs of different ventilators commonly used in burn units in the United States. **(A)** The most commonly used is the servo type ventilator, which can be set to give volume- or pressure-regulated breaths with or without pressure support or positive end expiratory pressure (PEEP). The I:E ratios can also be reversed. **(B)** The second type is the volumetric diffusive respiration (VDR) ventilator, which delivers high-frequency percussive ventilation (HFPV) or as continuous positive airway pressure (CPAP). **(C)** The third type is the airway pressure release ventilation (APRV) ventilator, which can be set to all the servo settings as well as APRV.

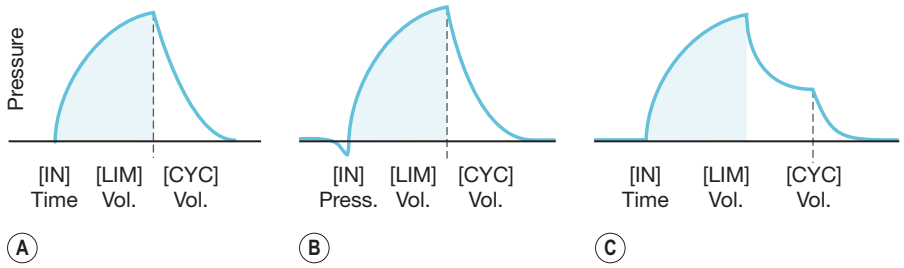

Fig. 32.5 Airway pressure curves illustrating the three mechanical functions: *IN*, initiation of the cycle; *LIM*, the preset limit (i.e., pressure or volume) imposed on the positive pressure cycle; *CYC*, the function (i.e., time or volume) ending the cycle. Each mechanical function is governed by one of four physical factors: volume, pressure, flow, and time. **(A)** A time-initiated, volume-limited mode. **(B)** A pressure-initiated (sub-baseline pressure produced by the patient's effort to breathe), volume-limited mode. **(C)** A time-initiated, volume-limited, time-cycled mode that extends inspiration beyond the time that the volume is delivered. A plateau is reached after flow has stopped but before the ventilator cycles into exhalation. (From Shapiro BA, Lacmak RM, Care RD, et al. *Clinical application of respiratory care*. St. Louis, MO: Mosby Year Book; 1991.)

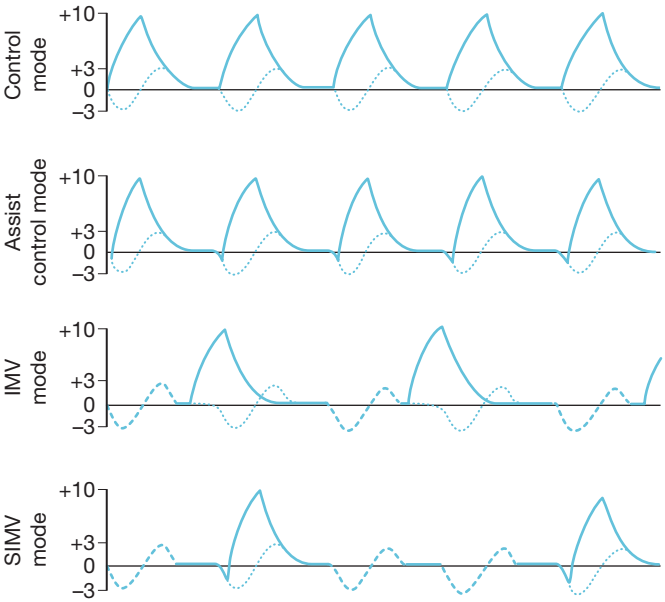

Fig. 32.6 Airway pressure tracings of four volume-cycled modes. The thick solid lines represent ventilator breaths. The thick dotted lines are spontaneous breaths. The thin dotted lines illustrate the spontaneous breathing pattern in the absence of ventilator breaths. *IMV*, intermittent mandatory ventilation; *SIMV*, synchronized intermittent mandatory ventilation. (From Shapiro BA, Lacmak RM, Care RD, et al. *Clinical application of respiratory care*. St. Louis, MO: Mosby Year Book; 1991.)

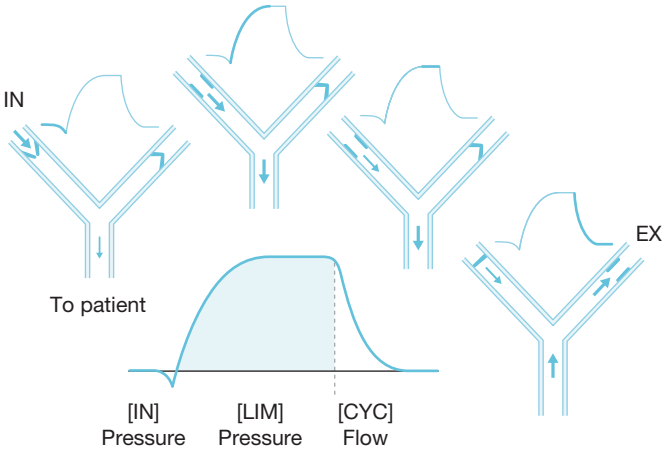

Fig. 32.7 Schematic illustration of pressure support ventilation. *IN*, initiation by spontaneous breath; *LIM* limit (pressure); *CYC*, cycle (derived from decreasing inspiratory flow); *EX*, expiration. (From Shapiro BA, Lacmak RM, Care RD, et al. *Clinical application of respiratory care*. St. Louis, MO: Mosby Year Book; 1991.)

Intermittent mandatory ventilation (IMV) allows spontaneous ventilation interspersed with volume-cycled or time-cycled pressure control mechanical ventilation. The addition of synchronization, in synchronized intermittent mandatory ventilation (SIMV), avoids placing a mechanical breath on top of a spontaneous patient breath, greatly improving this mode. It was hoped that maintaining some patient work in breathing would preserve respiratory strength while mechanical ventilation was required and that this mode would support weaning to progressively increasing patient effort while reducing mechanical support, although outcome data did not support a role in weaning (Fig. 32.6).

Pressure-support ventilation (also known as continuous positive airway pressure [CPAP]) is a patient-triggered pressure-limited flow-cycled ventilatory mode (Fig. 32.7). Each pressure support breath is triggered by patient negative-pressure effort and allows the patient to control his or her minute ventilation. This is a very comfortable mode for patients and effective for weaning; however it is not compatible with decreased respiratory drive. Care must be taken to ensure the patient does not develop progressive atelectasis with resultant decreases in compliance.

Inverse ratio ventilation (IRV) increases the MAP-O_2 thereby improving oxygenation in the setting of high A-a gradients. Conventional ventilation uses the time of inspiration and expiration at a ratio of 1 : 4 or 1 : 2, providing the greater time for expiration, as it is generally a passive process. IRV reverses this to give a longer inspiratory time (1 : 1 or 2 : 1) by using rapid inspiratory flow rates and decelerating flow patterns during the inspiratory phase. The prolonged inspiratory pressure increases MAP-O_2 dramatically to drive oxygen across a large diffusion membrane. Similarly to PEEP, this prolonged pressure recruits alveoli with long time constants. In severe lung disease, ventilation in the lung is unequal due to peribronchial narrowing. Thus some underventilated alveoli are actually open but unable to efficiently exchange gases, thereby increasing the intrapulmonary shunt and reducing arterial oxygenation. IRV can improve on this by selective air-trapping (intrinsic

PEEP) in these compromised air spaces. This can be done in either a volume-cycled or time-cycled pressure ventilation mode, but pressure-controlled ventilation is most commonly used to reduce peak airway pressures. Some studies show no benefit of IRV compared to conventional volume ventilation in terms of oxygenation.[108] These studies demonstrate some slight improvements in ventilation ($PaCO_2$). Furthermore this mode is not well tolerated by patients because they are unable to spontaneously breathe and thus tend to require heavy sedation. For these reasons, IRV cannot be recommended except in the setting of ARDS refractory to other therapies.

APRV delivers continuous positive airway pressure with a time-cycled pressure-release phase (to allow for expiration). Similar to IRV, it maintains high pressures within the airways for most of the respiratory cycle, thus allowing for very high MAP-O_2 to overcome high A-a gradients, recruitment of long time constant alveoli, and improved VQ matching. Unlike IRV, the patient can breathe spontaneously over the high and low pressures enabling greater patient comfort and synchrony, minimal sedation, and augmented minute ventilation. These characteristics allow for an open lung with extensive alveolar recruitment and thereby improved VQ mismatching.[109] This mode is best utilized in patients permitted to breathe spontaneously with negative pressure induced by diaphragmatic contraction, which aids in lung recruitment of areas previously atelectatic. This contrasts conventional positive-pressure ventilation, where positive pressure within the bronchus through the volume of air distributes preferentially down the path of least resistance to areas of the lung already well aerated, predisposing them to over-distension and barotrauma. Theoretically APRV is the ideal lung-protective strategy.

APRV gained popularity in the late 1990s and is becoming the preferred mode of ventilation in many centers, particularly in the setting of inhalation injuries. This open lung technique allows effective expectoration during the "dump" exhalation phases. Small prospective trials suggest APRV associates with fewer ventilator days, improved gas exchange, decreased atelectasis, improved hemodynamic performance, and decreased sedative administration compared to conventional modes in nonburned populations.[97] Some recent data in trauma patients refute this, although that paper suffered from a significant lack of statistical power.[109] Nonetheless this mode is being increasingly used in burn units around the world, but no prospective trials have yet been reported.

HFOV maximizes MAP-O_2 by maintaining airways at MAP-O_2 and delivering subtidal, high-frequency oscillatory breaths otherwise described as "CPAP with a wiggle." It is believed to maintain open alveoli by recruiting collapsed portions of diseased lung and applying the equivalent of CPAP used during conventional ventilation and driving oxygen into the blood with a high A-a gradient. HFOV maintains a maximal MAP-O_2 with a limited peak pressure while there is neither opening nor closing of alveoli. Thus this is a "lung-protective" mode preventing atelectotrauma, volutrauma, and barotrauma. Ventilation and CO_2 elimination are achieved via eddy currents mixing the air throughout the ventilator circuit, but poor CO_2 elimination is a major limitation of HFOV.[96] Because there is no exhalation, expectoration is minimal unless special maneuvers are employed.[110] A randomized prospective trial in adult patients with ARDS demonstrated that HFOV resulted in brief improvements in oxygenation, although mortality and complication rates were not different.[111] One center reported early success in reversing profound hypoxemia in burned patients with ARDS while facilitating early excision and grafting with intraoperative use.[112] However this same group recently showed that, in burned patients with inhalation injury, this method often failed secondary to hypercapnia rather than hypoxia.[113] HFOV appears to be effective in improving oxygenation in burned patients with inhalation injury, but the data without inhalation injury are murkier. In the recent OSCILLATE and OSCAR trials in unburned populations, no benefit and potential harm with HFOV was found.[85]

HFPV is a pressure-limited, time-cycled mode of ventilation delivering subtidal pressure-limited breaths at a high frequency (400–800 beats/min) superimposed on a conventional inspiratory and expiratory pressure-controlled cycle (10–30 breaths/min). The purported advantages are mobilizing airway secretions, casts permitting better expectoration and pulmonary toilet, and providing adequate gas exchange at lower airway pressures. First reported in 1989, HFPV has been tested primarily in burned patients with inhalation injury.[114] In this study, HFPV was used as a salvage therapy in one group of burned patients with inhalation injury and as the primary therapy in another. Improvements in oxygenation and a lower rate of pneumonia were observed. A subsequent study documented improvements in mortality in burned patients with inhalation injury treated with HFPV compared to historical controls.[115] Other outcomes in this study were significant decreases in the work of breathing and lower inspiratory pressures in addition to improvements in oxygenation and the pneumonia rate. This method of ventilation is advocated in the treatment of inhalation injury because it facilitates expectoration, particularly compared to HFOV.

In severely burned ventilated patients, a randomized controlled trial tested the effects of a low tidal volume conventional ventilator strategy against an HFPV ventilator strategy. This study found differences in improved oxygenation early in the course but no differences in mortality or other outcomes. However it demonstrated the need for ventilator "rescue" in only the HFPV group, defined as the need for changing ventilator modes due to inadequate oxygenation or ventilation despite maximizing the mode. Thus the data support HFPV in this population (e.g., less rescue indicated).[116] At a minimum, these data show HFPV as a useful tool in the burned patient population.

Nitric oxide (NO) is used to improve VQ mismatch in the setting of refractory hypoxemia. It is a short-lived gaseous product of endothelial cells that is a powerful local vasodilator. As a gas, this product can be delivered through the endotracheal tube to areas of ventilated lung where it can provide localized pulmonary vasodilation. Thus areas of ventilated lung can receive more blood flow to reduce intrapulmonary shunting and improve oxygenation. This compound has been used extensively to beneficial effect in neonates and children with hypoxemic respiratory failure. It has also been used in ventilated burned children to improve oxygenation.[98] Although NO therapy has received considerable attention as a potential therapeutic option in

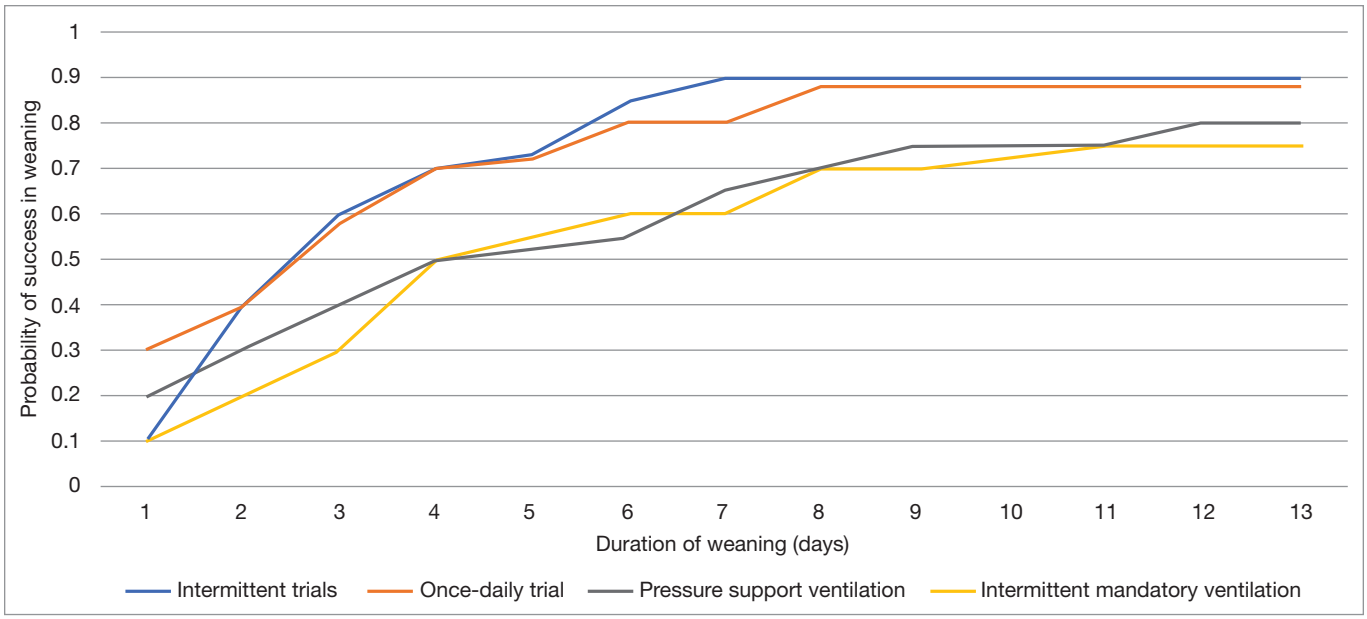

Fig. 32.8 The probability of successful weaning with intermittent mandatory ventilation, pressure support ventilation, intermittent trials of spontaneous breathing, and once-daily trials of spontaneous breathing (Kaplan–Meier curves). After adjustments for baseline characteristics (Cox proportional hazards model), the rate of successful weaning with a once-daily trial of spontaneous breathing was 2.83 times higher than that with intermittent mandatory ventilation ($P < 0.006$) and 2.05 times higher than that with pressure support ventilation ($P < 0.04$). (From Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. *The N Engl J Med.* 1995;332(6):345-350.)

severe pulmonary disease, no reports to date have documented improved mortality or other clinical outcomes in spite of improvements in oxygenation. *Inhaled prostaglandins* have a similar effect via an alternate mechanism. Some centers prefer using prostaglandins due to cost. Epoprostenol has been shown to be noninferior to inhaled nitric oxide with regards to ventilator-free days in ARDS.[117] Inhaled NO and aerosolized epoprostenol consistently improve oxygenation but have not yet been demonstrated to impact survival ventilator-free days or attenuation of disease severity. [118] Epoprostenol has also been successfully used in cases of inhalation injury with a nebulized heparin protocol.[119]

Weaning From Mechanical Ventilation. Regardless of the mode of ventilation, almost all patients surviving the initial insult will eventually need to be weaned off the ventilator. Clinicians continue to debate the advantages of weaning patients with various forms of mechanical ventilation. Some prefer using pressure support ventilation (PSV) with or without SIMV because of the ease with which the level can gradually be reduced. Others advocate that intermittent trials with abrupt cessation of ventilator support while also maintaining endotracheal intubation ("t-tube trials") result in more rapid weaning.[120] Between weaning trials it is important to provide sufficient support to re-recruit alveoli and prevent progressive atelectasis and the resultant loss of compliance, all of which make weaning more difficult. Weaning from ventilation depends on the rate at which the patient recovers from the condition requiring mechanical ventilation and the aggression of the clinician driving the weaning process. In practice, either method of weaning from the ventilator (gradually with pressure support or intermittently with t-tube or PSV trials) will be successful (Fig. 32.8).

The standard of care has shifted to perform protocolized daily sedation interruptions, spontaneous breathing trials, and assessment from extubation. This protocol has been shown to decrease ventilator days and mortality in randomized controlled trials (RCTs). An RCT has demonstrated one life saved for every seven patients treated with a spontaneous breathing trial protocol.[121] There is an argument that decreased sedation applied in these protocols increases self-extubation, which was found in the study. However the reintubation rate was not different, indicating that patients who were able to self-extubate tended to not require further intubation. Thus, in this study, self-extubation was a good weaning parameter.[121]

Monitoring of Mechanical Ventilation. For patients on mechanical ventilation, sedatives and paralytics for the endotracheal tube or other conditions often impair the normal physiologic regulation of ventilation and oxygenation. For these reasons, monitoring of ventilation and oxygenation by the clinician is required utilizing serial examination, chest X-ray, blood gas analysis, continuous SaO_2, and, preferably, $EtCO_2$.

LIMITING VENTILATOR-INDUCED LUNG INJURY. Mechanical ventilatory support is employed to provide supraphysiologic conditions to injured lungs otherwise unable to sustain life. Ultimately ventilator weaning is predicated on these lungs healing sufficiently to allow them to again sustain the patient's life without the supraphysiologic conditions the ventilator creates, such as positive pressure. Care must be taken to balance the systemic needs of the patient for gas exchange with the injurious nature of mechanical

ventilation in a supraphysiologic manner. VILI is the result of injurious ventilator settings that lead to a combination of barotrauma, volutrauma, atelectrauma (repeated opening and closing of alveoli), and chemotrauma (paracrine inflammatory effects). VILI is a common complication of mechanical ventilation and results in pneumothorax, pneumomediastinum, subcutaneous emphysema, interstitial emphysema, or pneumatoceles.[122]

In a volume-cycled mode, large tidal volumes, along with elevated peak and plateau pressures, have been implicated in inducing VILI. It is conceivable that limiting airway pressures may reduce morbidity. Early reports showed no clear benefit of pressure-limited ventilation, which was demonstrated by giving lower tidal volumes more frequently to maintain minute ventilation and accepting a higher $Paco_2$ value and lower arterial pH.[123]

This "permissive hypercapnia" is a compromise in the acceptance of a recoverable compensated systemic pathology to allow less injurious ventilation and hopefully permit the lungs to heal.[91] Criticism of these trials rests in their low enrollment and lack of power to show differences. As an answer to this critique, a large multicenter trial documented improved survival and increased ventilator-free days during the first 28 days in the ICU in patients with ARDS treated with low tidal volumes (6 mL/kg predicted body weight) versus traditional tidal volumes (12 mL/kg predicted body weight). In fact, the data safety committee halted the study early because the benefits incurred to the treated group were so clinically significant.[124] Suspected reasons for the improvements seen in this trial contrary to prior trials was the number of subjects enrolled as well as the defined protocol to limit both tidal volumes (volutrauma) and plateau pressures of less than 30 cm H_2O (barotrauma). Interestingly, this trial demonstrated decreased inflammatory markers, specifically IL-6, in the low tidal volume arm, suggesting a third possible mechanism of benefit (chemotrauma).

Theoretically the low tidal volume strategy subscribes to the theory of ARDS, which dictates that small healthy regions of lung exist adjacent to diseased and collapsed areas. In the conventionally treated group, higher tidal volumes and pressure are distributed only to open healthy alveoli; therefore the barotrauma of high pressures is delivered to this "healthy" lung, thereby increasing the damage there and worsening outcomes.[125]

In burned patients, decreased chest wall compliance, presence of smoke inhalation injury to the upper airways, and massive fluid administration coupled with increased CO_2 production due to hypermetabolism are just a few variables that make effective gas exchange challenging while optimally minimizing VILI. Prospective trials comparing modes of ventilation to minimize VILI are lacking in burn literature, making it difficult to ascertain which approach is best suited to this population. In 61 burned patients, one study showed no statistically significant differences between a pressure-limited strategy and a conventional strategy for mortality, pulmonary complications, or incidence of pneumothoraces.[126] In the trial comparing HFPV (a pressure-limited strategy) to an ARDSnet-based conventional strategy, a lower incidence of barotrauma was seen in the HFPV group. However there was no difference in inflammatory markers between the two modalities.[116]

It stands to reason that pressure-limited ventilation strategies (either conventional or high frequency) might be of benefit in burned patients in sufficiently powered studies. One outcome that should certainly be accounted for is the need for adjunctive therapies (rescue treatments), as implied earlier. Given current data, the best balance is struck by an experienced physician with a firm understanding of pulmonary physiology continuously weighing the systemic needs of the patient against the capabilities of available interventions and their potential pulmonary harm.

Epidemiology, Pathophysiology, and Treatment of ARDS. ARDS occurs as a result of injury to the lung, which can be direct through smoke inhalation or pneumonia or indirect through mediators associated with sepsis (Table 32.3). Until recently, most studies of ARDS reported mortality rates between 40% and 60%. Now, in trauma patients, the most recent mortality rate for ARDS was 14%; in addition, the incidence of ARDS fell by 50% in a matched patient population.[127] Thus we conclude that the incidence has gone down. What changed is the method of management, indicating that reducing the risk of further harm is the most effective treatment for this condition.

ARDS occurs because of damage to the endothelium and lung epithelium. It is speculated that the products of inflammation, such as cytokines, endotoxin, complement, and coagulation system products, induce the changes characteristic of ARDS.[122] The acute phase of ARDS is marked by an influx of protein-rich edema fluid into the air spaces as a consequence of increased permeability of the alveolar–capillary barrier (Fig. 32.9). The importance of endothelial injury and increased vascular permeability leading to the formation of pulmonary edema is well established. Epithelial injury is also of great importance. In fact, the degree of alveolar epithelial injury is an important predictor of outcome.

Neutrophils play a role in the pathogenesis of ARDS. Histologic studies of lung specimens obtained early in the course demonstrate marked accumulation of neutrophils in the alveolar fluid. However it must be stated that ARDS develops in patients with profound neutropenia, and some animal models of ARDS are neutrophil independent, implying that neutrophils may be nothing more than bystanders in the inflammatory process.[128]

The effects of ventilator injury on the development and progression of ARDS are now firmly established. Previous

Table 32.3 ARDS Risk Factors

Direct	Indirect
Pneumonia	Nonpulmonary sepsis
Aspiration of gastric contents	Major injury
Inhalation injury	Pancreatitis
Pulmonary contusion	Severe burns
Pulmonary vasculitis	Noncardiogenic shock
Drowning	Drug overdose
	Transfusion-related acute lung injury

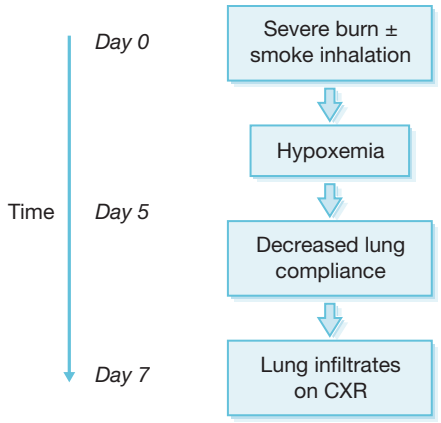

Fig. 32.9 Typical timeline for progression to acute respiratory distress syndrome (ARDS). Patients are typically intubated for airway compromise and operative intervention. At day 4 or 5 after severe burn, oxygenation will deteriorate, requiring higher inspired concentrations of oxygen. These measures will soon fail with the introduction of decreased lung compliance requiring higher inspired airway pressures. Only then will infiltrates begin to appear on the chest X-ray.

studies focused on the potentially damaging effects of high oxygen concentrations on lung epithelium and a prolonged F_{IO_2} of greater than 60% should be avoided.[129] Evidence suggests that mechanical ventilation at high pressures injures the lung,[124] causing increased pulmonary edema in the uninjured lung and enhanced edema in the injured lung.[130] Alveolar overdistension and cyclic opening and closing of alveoli associated with high ventilator pressures are also potentially damaging to the lung. High F_{IO_2} may predispose to this atelectrauma by displacing nitrogen from the alveoli. Nitrogen is then not absorbed and can serve as a stent maintaining airway patency.[90]

After the development of ARDS, some patients have a rapid recovery over a few days. Others progress to fibrotic lung injury; the alveolar space fills with mesenchymal cells, extracellular proteins, and new blood vessels. The finding of fibrosis on histologic analysis correlates with increased mortality.[131]

In nonfatal cases of ARDS, the lung heals by the proliferation of type II epithelial cells, which begin to cover the denuded basement membrane and differentiate into type I epithelial cells, restoring normal alveolar architecture, and increasing the fluid transport capacity of the alveolar epithelium. Alveolar edema is resolved by active transport of sodium from the distal airspace into the interstitium by intact alveoli. Soluble protein is removed primarily by diffusion between alveolar cells, while insoluble protein is eliminated by endocytosis and transcytosis by alveolar epithelial cells and phagocytosis by macrophages.

The severely burned are unique among patients who develop ARDS. Direct injury to the lung from smoke inhalation can cause respiratory insufficiency and relative hypoxia due to increased capillary permeability and interstitial edema increasing the A-a gradient, while ciliary dysfunction embarrasses expectoration. A few days later, the damaged and necrotic respiratory mucosa begin to slough, causing bronchial plugging and atelectasis, further worsening the clinical condition. However it is not typically until 4–8 days into the course of injury that severe hypoxemia and ARDS develop in burned patients, a scenario not unlike that in other types of patients who develop ARDS, such as after abdominal sepsis or multiple blunt trauma. While smoke inhalation is understandably associated with the development of ARDS, this affiliation is related to the inflammation corresponding to the injury in addition to that rendered by the burn wound. In fact, it was shown that the degree of inhalation injury was not associated with the development of ARDS in burned patients.[132] It may be, then, that smoke inhalation and ARDS are actually two distinct conditions that are related. Indeed, the preponderance of pathology in smoke inhalation is to the airways beginning proximally and decreasing in effect as you move more distally into the lung away from the source of smoke. Conversely the preponderance of damage in ARDS is alveolar, beginning distally and decreasing as it proceeds proximally.

Treatment of ARDS. Until the healing processes just described can be accomplished, the treatment of ARDS is largely supportive. A careful search for potential underlying causes should ensue, including attention to possibly treatable sources such as unexcised or open burn wounds, invasive burn wound infection, intraabdominal infections, pneumonia, line sepsis, or cholangitis, to name a few. Treatment of the inciting cause of ARDS and careful ventilator management aimed to limit further VILI while maintaining life-sustaining gas exchange are the core of ARDS treatment protocol. An improved understanding of the pathogenesis of ARDS has led to the assessment of several novel treatment strategies, including changes in mechanical ventilation strategies, fluid management, surfactant therapy, NO treatments, and antiinflammatory strategies.

The most appropriate method of mechanical ventilation for ARDS has been controversial for some time, although the picture is becoming clearer; the ARDSnet study provided much of this clarity.[124] They reported a 22% decline in mortality in patients with ARDS treated with tidal volumes of 6 mL/kg compared to those treated with conventional volumes of 12 mL/kg. In this study, peak airway pressures could not exceed 30 cm H_2O in the lower tidal volume group, and a detailed protocol was used to adjust the F_{IO_2} and PEEP. These results differed from those of smaller previous studies showing no improvement with pressure-limited ventilation. Potential reasons for the discrepancy between the National Institutes of Health (NIH) study and the others are as follows: the NIH study had the lowest tidal volume of the three studies and respiratory acidosis was allowed in the NIH study, with sodium bicarbonate treatment if necessary to maintain homeostasis. Furthermore the NIH study had more patients and so may have been more sufficiently powered to show differences between treatment groups.

The implementation and utility of low tidal volume protocols have been limited, likely due to the unique pathology of burn patients with hypermetabolism requiring greater gas exchange and inhalation injury requiring greater airway support and expectoration. In one study, one-third of burn patients failed to meet oxygenation and ventilation requirements when treated with low tidal volumes, and two-thirds failed when there was an inhalation injury.[85] Counter to the ARDSnet data, in a review of 28 years of 932 burned

pediatric patients with inhalation injury and stratifying for tidal volume, high tidal volume (15 +/− 3 mL/kg) was associated with significantly fewer ventilator days. This effect could reflect an interruption of events leading to lung injury following inhalation injury but could also evince the capacity of pediatric lungs to heal given their preserved stem cell function and ability to form airways de novo.[93]

PEEP has clearly been shown to benefit patients with ARDS; however the optimum level has been contentious. The best effects of PEEP are to increase functional residual capacity or the number of open alveoli at the end of expiration, as well as increase MAP-O_2 and thus oxygenation. However the use of prophylactic PEEP therapy in patients at risk for ARDS showed no benefit for the treatment group compared to controls.[89]

A study of PEEP therapy aimed at raising the level of PEEP above the lower inflection point on pressure–volume curves, thereby preventing alveolar closure, in conjunction with low tidal volumes and pressure-controlled IRV showed improved mortality compared to a control group managed with conventional ventilation.[133] Drawbacks to this study were the unusually high mortality (71%) in the control group; improvements in mortality for the treatment group compared to controls could only be determined at hospital day 28, which was not appreciated at hospital discharge.

Inhaled NO and prostaglandins are potent pulmonary vasodilators with effects localized to ventilated areas of the lung, thus directing more blood to the functional areas of the lung. The conceivable result, then, is to diminish the fraction of blood shunted through the lungs without oxygenation, thereby improving pulmonary venous oxygenation and reducing VQ mismatching. Observational studies suggest that inhaled NO might be beneficial in the treatment of ARDS by improving oxygenation without increased ventilatory pressures and reducing barotrauma. However randomized trials testing this hypothesis have, as of yet, been disappointing. In the most recent large study, inhaled NO therapy did not reduce mortality or the duration of mechanical ventilation. Improvements in oxygenation were seen, but the effects were not sustained.[134] The reported experience with this modality in burns is only anecdotal.

Prone positioning is another modality commonly used in BICUs for refractory hypoxemia, aimed to reduce VQ mismatch. This is based on the rationale that dependent areas of the lung in ARDS have the most blood flow and the most edema, thereby leading to a greater mismatch of blood flow and aerated lung and a greater shunting of blood past unaerated areas; hence blood returns to the heart unoxygenated. By placing the patient in the prone position for a prescribed period, the previously aerated lung now receives a greater portion of blood flow as directed by gravity. This approach almost always results in improved oxygenation, but, as with NO, has not been shown to be of benefit for mortality in prospective trials.[135] However two recent meta-analyses have demonstrated significant mortality benefit in those with severe hypoxemia.[99,136] Thus it appears that in certain subpopulations VQ mismatch therapies may be considered after carefully balancing risk versus benefit.

Ultimately if the lungs are too injured to provide the sufficient gas exchange required to maintain life, even with the support of mechanical ventilation and techniques aimed to minimize VQ mismatch, mechanical circulatory support must be considered. ECMO can be employed either in a venovenous method to only supplement gas exchange or in an arteriovenous method to also supplement cardiac function. Its use has the benefit of maximizing gas exchange while allowing total lung rest without need for further injurious ventilation techniques. There has been limited experience globally and no large trials to document any benefit to date. In a small series investigating ECMO, 60% of burned patients in the series survived and had significant improvements within 96 hours of ECMO administration.[137] This intervention must be regarded with great trepidation, given the need for anticoagulation and that cannulation prevents standard burn care and rehabilitation. This therapy can be life-saving, but it should be considered carefully and utilized only in the appropriate candidate. Often it is preferable to balance an injurious but survivable ventilation strategy with the other burn care needs of the patient.

Last, glucocorticoids have been used in the treatment of ARDS because of the inflammatory nature of the disease. There have been several trials with contradictory and equivocal data. To add fuel to the fire, the most recent large trial of glucocorticoid treatment of early severe ARDS showed an improvement in ventilator days and MOF scores.[138] Others have shown the benefit of glucocorticoids when used to good effect in the later fibroproliferative phases of the disease.[139] It is probable that some population with ARDS exists in which glucocorticoid treatment is of benefit, but we do not think it is burns. This type of therapy may be treacherous in burned patients at risk for invasive burn wound infection but might be considered upon complete burn wound closure. If steroids are used, high-dose vitamin A can be tried to ameliorate the wound-healing complications.[140]

GASTROINTESTINAL SYSTEM BURN CRITICAL CARE

Pathophysiologic Changes in the Gut After Burn

The gut, including the stomach, intestines, liver, and pancreas, plays six critical roles after burn injury: absorption of nutrients, mucosal barrier to invasive microbes, elimination of hydrophobic wastes, clearance of lactate, production of acute-phase proteins and coagulation factors, and an endocrine function able to drive toward anabolism. The gastrointestinal response to burn injury is highlighted by mucosal atrophy, changes in digestive absorption, and increased intestinal permeability. Changes in gut blood flow are related to changes in permeability. Intestinal blood flow was shown to decrease in nonresuscitated animals, a change associated with increased gut permeability at 5 hours post burn.[141] This effect was abolished at 24 hours. Systolic hypotension has been shown to occur in the immediate hours after burn in animals with a 40% TBSA full-thickness injury.

Clinical Changes in the Gut After Burn

Given these changes in the gut from burn, it is commonplace to observe some evidence of gut dysfunction after burn, as evidenced by feeding intolerance and mucosal ulceration and bleeding, particularly in the stomach and

duodenum.[5] Enteral feeding is an important means of providing nutrition to burned patients and has led to a decrease in mortality, but on occasion the gut will not cooperate. Reduced motility and ileus are common, as is diarrhea, at times requiring parenteral nutrition to meet caloric needs. At present there is no specific treatment for burn-induced ileus, but early enteral feeding prevents some of these potential complications.

The best management for the gut and the patient in total is sufficient enteral nutrition. Ascertaining the amount and type of nutrition is the subject of Chapter 28 on nutritional support. It is worth noting here that feeding the gut promotes mucosal barrier function, nourishes the patient, and promotes bile flow, elimination of hydrophobic wastes, and an anabolic hormonal release from the gut and pancreas.[142,143] In determining the amount to feed, measurement of resting energy expenditure is superior to equations used to estimate caloric needs, such as the World Health Organization (WHO), Schodield-HW, and Harris-Benedict equations and, as such, should be used to calculate feeding goals.[144]

Stress ulceration of the stomach and duodenum, on the other hand, can be prevented effectively with antacid therapy. In the 1970s, stress ulceration leading to life-threatening hemorrhage was common. The mechanism of injury corresponds to an imbalance between protective factors, such as mucus production, protective prostaglandin output, and bicarbonate secretion, and injurious factors, such as decreased blood flow and acid production. Gastric ulcers developed in the watershed zones between capillary beds, which are worsened by gastric acid-induced injury. With today's use of standard critical care techniques, including gastric acid suppression and expeditious wound closure, upper gastrointestinal bleeding is relatively rare. When it occurs, treatment is congruent with standard upper gastrointestinal bleeding protocols through identification of the bleeding source and control with local techniques or surgery when required.

Abdominal compartment syndrome has proved a significant risk. This is associated with massive volume resuscitation, inducing generalized edema in a relatively limited abdominal compartment. It eventuates in decreased gut blood flow and renal blood flow causing oliguria and bowel ischemia.[145] The tragedy is that the early sign of this condition is low urine output, which is commonly addressed by more intravenous fluid, which only worsens the case. The associated physical finding is abdominal distension. An estimate of intraabdominal pressure can be obtained by pressure monitoring of the bladder; pressures of greater than 30 torr are concerning and should instigate further investigation. Treatments are aimed at reducing intraabdominal pressures through drainage, sedation, and paralysis, or decompressive laparotomy if needed.[146] Unfortunately those with burns of greater than 40% TBSA are at highest risk for abdominal compartment syndrome and have a mortality rate approaching 100% when treated with decompressive laparotomy.[87] Therefore the best treatment for this condition is prevention through judicious resuscitation, as discussed in Chapters 8 and 9 on burn edema and resuscitation, respectively.

The liver also plays a critical role in the recovery from burn injury. Acute liver failure is a rare occurrence in burn injured patients and is more thoroughly discussed in Chapters 30 and 31 on MOF and the liver, respectively. It is related to ICU common causes such as preexisting cirrhosis, drug toxicity, or viral activation, but also to burn-specific issues such as hepatic steatosis, right heart failure, and/or fluid overload. High central venous pressures (CVPs) compromise the pressure gradient from the portal system that provides 75% of the oxygen delivery to the liver, thus creating an ischemic injury.[147] Treatment is to first remove hepatotoxic medications and reduce CVP to improve hepatic perfusion, then begin symptomatic treatment including monitoring and treating elevated ICP; treating hemodynamic failure, respiratory failure, and hypoglycemia; and replacing clotting factors.[148]

Pancreatitis also occurs, though rarely subsequent to burn injury. Its etiology tends to be ischemic in nature, with an incidence of 0.17% demonstrated in a pediatric series. It is associated with elevated mortality and thus should be taken seriously. It is diagnosed with elevated amylase or lipase in conjunction with abdominal pain, feeding intolerance, or radiographic signs. Treatment is feeding distal to the ligament of Trietz and, should this fail to abate the pancreatitis, bowel rest is advisable with parenteral feedings.[149]

RENAL BURN CRITICAL CARE

Pathophysiology

Acute kidney injury (AKI) is a potentially lethal complication of burns. Of note, AKI has supplanted the prior term (acute renal failure [ARF]). Despite substantial technical developments in dialysis to replace the function of the kidneys, mortality meets or exceeds 50% for all critically ill patients who develop ARF.[150] Interestingly mortality associated with AKI undergoing hemodialysis for frank renal failure in the critically ill has not improved significantly in more than 40 years. The same can be said for renal failure requiring dialysis, specifically in the severely burned. The cause of death in these critically ill patients was not uremia because of advances in dialysis, but primarily sepsis and cardiovascular and pulmonary dysfunction.[151]

With the advent of early aggressive resuscitation after burn, the incidence of renal failure coincident with the initial phases of recovery has diminished significantly in the severely burned. However another period of risk for the development of renal failure 2–14 days after resuscitation is still present and is likely related to the development of sepsis.[152] Transient hypotension, nephrotoxic medications such as antibiotics, hypovolemia from insensible fluid losses, and rhabdomyolysis are all also significant etiologies of AKI in the BICU.[153]

AKI, usually in the form of acute tubular necrosis (ATN), is characterized by deterioration of renal function over a period of hours to days, resulting in the failure of the kidney to excrete nitrogenous waste products and maintain fluid and electrolyte homeostasis. It may be caused by a number of factors interfering with glomerular filtration and tubular resorption. In burned patients, the causes can be generally narrowed to renal hypoperfusion, nephrotoxic insults from pharmacologic treatments (e.g., aminoglycosides or intravenous contrast agents), or sepsis.[153] Ischemic renal failure

is the more common of the three causes and is induced by hypoperfusion from an imbalance between vasoconstrictive and vasodilatory factors acting on the small renal vessels during low-flow states. Decreased flow to the renal cells directly alters endothelial cell function, reducing the production of and response to vasodilatory substances. The renal medulla is the portion of the kidney most sensitive to hypoxia, and the damage is initially to the renal tubular cells. The outer medulla and proximal tubules have high oxygen requirements, and the resulting ischemia causes swelling of tubular and endothelial cells, with necrosis, apoptosis, and inflammation evident on a histologic examination. These changes lead to further vascular congestion and decreased blood flow, resulting in more cell loss and further decrements in renal function. Characteristic tubular casts can be seen on urine microscopy that is diagnostic for ATN.

After the initiating event, tubular function and glomerular filtration rate (GFR) decrease to reduce urine production. The progression of AKI is commonly divided into three phases: initiation, maintenance, and recovery; it can be oliguric (urine output <400 mL/day) or nonoliguric (urine output >400 mL/day) in nature. Patients with nonoliguric AKI have a better prognosis than oliguric AKI patients, probably due in large measure to the decreased severity of the insult and the fact that many have drug-associated nephrotoxicity or interstitial nephritis.[151]

Once AKI is established, pharmacologic improvement of renal blood flow will not reverse the injury. Agents such as dopamine, which was commonly used in the past to dilate renal arterioles and increase renal blood flow via dopamine receptors, have been shown to be mostly ineffective.[154] Recently the potent dopamine-1 receptor agonist fenoldopam has garnered some interest as an agent to improve renal perfusion and outcomes. A meta-analysis of randomized controlled trials demonstrated that low-dose fenoldopam (0.03–0.09 μg/kg per minute) may be of benefit in reducing the need for renal replacement therapy and hospital mortality when used in septic patients with either established AKI or at high risk for AKI in a mixed ICU population.[155] Its use in this setting has been reported in a noncontrolled study in burned patients, with improvement in renal function (increased urine output and decreased serum creatinine) and without any hypotension at the low dose.[156] Further work will need to be done in the burn population to fully determine its efficacy.

Diuretic therapies, such as mannitol and loop diuretics, have been used extensively in patients with AKI to increase urine flow and protect the kidney from further ischemic damage. Mannitol can reduce cellular swelling in the proximal tubule and increase intratubular flow, thus potentially decreasing intratubular obstruction and further renal dysfunction. Mannitol has been previously recommended along with vigorous volume replacement and sodium bicarbonate for the treatment of early myoglobinuric acute kidney injury. However recent evidence suggests a lack of benefit and a need to reevaluate this practice.[157] Loop diuretics also increase intratubular flow rates and can convert an oliguric state to a nonoliguric state, thereby facilitating clinical management of renal failure. While patients with nonoliguric AKI are generally easier to manage from a volume standpoint, there is no evidence that conversion from an oliguric to a nonoliguric state improves outcomes.

Table 32.4 Laboratory Tests to Distinguish Prerenal from Intrinsic Renal Failure

Examination	Prerenal	Intrinsic Renal
Urine osmolality (mmol/kg)	>400	<400
Urinary sodium (mEq/dL)	<20	>40
FENa (%)*	<1	>2

*FENa, fractional excretion of sodium, calculated as (U/PNa/U/PCr) × 100, where U is urinary concentration, and P is plasma concentration. Na is sodium and Cr is creatinine.

The initial care of patients with AKI is focused on reversing the underlying cause and correcting fluid and electrolyte imbalances. Renal failure is heralded by a decrease in urinary output. Volumes of urine of less than 1 mL/kg per hour may indicate the onset of AKI. This failure may be due to a prerenal cause, which is typically due to decreased renal blood flow from hypoperfusion, or intrinsic renal causes, which are associated with medications, rhabdomyolysis, or sepsis. Differentiation between these etiologies can be made with laboratory examinations (Table 32.4). Prerenal etiologies are associated with concentrated urine (urine osmolarity >400 mmol/kg), decreased urinary sodium concentrations, and decreased fractional excretion of sodium. Intrinsic renal causes will be associated with a more dilute urine with higher sodium concentrations. These tests should be performed before diuretics are administered because this treatment will increase urinary sodium and decrease urine osmolality even in prerenal conditions. In general, urine osmolarity and urinary sodium concentrations are primarily used for these determinations because of the ease of measurement. In terms of clinical utility, renal dysfunction is often a mixture of prerenal and intrinsic causes, making treatment decisions difficult.

Should these tests reveal a prerenal cause, volume optimization should ensue to prevent further renal ischemia, although in the fluid overloaded patient with heart failure inotropes may be necessary. Physical examination and invasive monitoring, if deemed appropriate, should guide this volume replacement. The decision to administer or remove fluids may prove difficult, however, because both strategies have detrimental consequences if followed inappropriately. Although volume replacement is ineffective in restoring renal function once tubular necrosis is established, it remains the most effective prophylactic strategy, and so is generally the place to start at the onset of renal failure.

Owing to the wide variation in the definition of AKI, reporting an accurate incidence, as well as resultant outcomes, has been problematic. In an effort to resolve this and standardize the classification of AKI, the Acute Dialysis Quality Initiative (ADQI) developed and reported the Risk, Injury, Failure, Loss of function, End-stage (RIFLE) renal disease criteria.[158] More recently, the Acute Kidney Injury Network (AKIN) proposed a modified version of the RIFLE system because of a number of identified limitations. These revised criteria are intended to simplify the definition and make it more clinically applicable. According to the AKIN

criteria, stage 1 AKI is delineated by "an abrupt (within 48 hours) reduction of kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dL, a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 mL/kg per hour for more than 6 hours)." Stages 2 and 3 are the same as RIFLE—Injury and Failure, respectively.[159]

In burned patients, investigators showed that the incidence and outcomes of greater than 20% TBSA burned patients with AKI using RIFLE criteria was 24% (12% Risk, 8% Injury, and 5% Failure). Associated mortality was 14%, which increased directly with each RIFLE class (7% normal, 13% Risk, 40% Injury, and 83% Failure). Renal dysfunction occurred within 7 days in 55% of affected patients and completely recovered in all survivors; pulmonary dysfunction was present in all. Sepsis was a possible aggravating factor in acute kidney injury in 48%. They concluded that AKI is common after severe burn, develops within days of injury, and parallels other organ dysfunction.[160] These data confirm earlier studies showing that the development of renal failure is associated with dismal outcomes. Minor dysfunction does not necessarily correlate to progression and mortality, giving hope to therapies designed to maintain renal function after severe burn.

Another study examined the incidence of renal dysfunction in burned patients, defined by serum creatinine levels of greater than 1.4 mg/dL. Thirty-nine percent of patients admitted to the BICU developed renal insufficiency, of which 33% underwent renal replacement therapy. Associated mortality in those with renal insufficiency was 44%. Those who developed renal insufficiency within 5 days of thermal injury had a higher mortality than those with later onset. Of interest, all survivors regained normal renal function later in their course.[153] The next study investigated early markers of renal dysfunction and found that elevations in urinary microalbumin and malondialdehyde (both three- and fourfold) were present in all burn patients with eventual renal dysfunction.[161] These may come to be indicators of risk for injury that can be acted upon early to prevent progression to more severe degrees of failure and thereby improve outcomes.

The last study investigated the role of continuous venovenous hemofiltration (CVVH) in the treatment of renal dysfunction after severe burn. Investigators compared a population of patients treated with high-volume CVVH (at least 50 mL/kg per hour) compared to nontreated historical controls and found that both 28-day and mortality improved by 50% with this therapy.[162] A multicenter RCT comparing early high-volume CVVH (70 mL/kg per hour) to standard care is under way in this high-risk population (ClinicalTrials.gov Identifier: NCT01213914).

After ensuring adequate volume status, every effort should be made to prevent other causes of renal injury. All nephrotoxins should be discontinued or avoided. Hyperkalemia may develop and can be treated with resins, glucose and insulin, and sodium bicarbonate in the presence of metabolic acidosis. Medications eliminated through the kidney should be adjusted. Once the diagnosis of AKI is established, consideration can be given to diuretic therapy or the early initiation of CVVH, especially if it is determined that the patient is volume overloaded. Reducing the volume of fluid given can also alleviate volume overload in burned patients. These patients have increased insensible losses from the wounds that can be roughly calculated at 3750 mL/m^2 TBSA wound plus 1500 mL/m^2 TBSA total. Reducing the infused volume of intravenous fluids and enteral feedings below the expected insensate losses may alleviate some of these problems.

However it is important to continue sufficient nutritional delivery to the patient and balance this against the renal function, utilizing diuretics and even dialysis to ensure an excessive nutrient debt does not develop. Reducing potassium administration in enteral feedings and giving oral bicarbonate solutions can minimize electrolyte abnormalities. Almost invariably, severely burned patients require exogenous potassium because of the heightened aldosterone response resulting in potassium wasting. Therefore hyperkalemia is rare, even with some renal insufficiency. Indeed, spironolactone is generally a wise adjuvant to loop diuretics in burn patients due to this potassium wasting.

Intermittent dialysis remains a viable replacement therapy for severe AKI in the hemodynamically normal ICU patient, although this is changing. The indications for dialysis are edema and volume overload, electrolyte abnormalities not amenable to other treatments, or refractory acidosis. In recent years, continuous renal replacement therapies (CRRT) have emerged as another option for critically ill patients with AKI. The advantages of continuous over intermittent treatment include more precise fluid and metabolic control, increased hemodynamic stability, and the enhanced ability to remove injurious cytokines. Additionally many BICU surgeons perform CRRT without use of nephrologists or dialysis nurses, thus making the timely application of CRRT practical as a component of burn critical care. Disadvantages constitute the need for heightened surveillance, heavy resource and nursing utilization, and slower overall clearance compared to intermittent dialysis.

Peritoneal dialysis (PD) is another option for AKI in burned patients.[163] Catheters can be placed at the bedside with near-continuous exchanges to improve electrolyte and volume overload problems. The capital required for this treatment is minimal and surgeons unable to perform CRRT can easily place a catheter and begin PD. Hypertonic solutions are used to remove fluid volume, and the concentrations of potassium and bicarbonate are modified to produce the desired results. The dwell time is usually 30 min, followed by 30 min of drainage. This treatment can be repeated in cycles until the problem is resolved. For maintenance, 4–6 such cycles a day with prolonged dwell times (1 h) is usually sufficient during the acute phase. This treatment is known to be useful in burned patients but has not received a significant amount of study.

HEMATOLOGIC BURN CRITICAL CARE

Burn patients are subject to major blood loss due to phlebotomy and surgery. As such, they can suffer intravascular hemolysis in burn wounds. They also suffer hematopoietic suppression or modulation from inflammation and adrenergic causes. Coagulation factors and platelets can be consumed, creating a consumptive coagulopathy. Resultantly transfusion is a standard component of burn critical care.

The threshold for transfusion in the euvolemic patient has been lowered over the past decades through sequential studies. Concomitantly the indication for transfusion in the setting of active hemorrhage has been expanded. In a landmark study in the *New England Journal of Medicine,* Holst et al. demonstrated in septic shock a transfusion threshold of 7 mg/dL.[164] Lelubre et al. subsequently showed this to be a safe threshold in burn patients, although they did note a 5.9% rate of protocol suspension for myocardial ischemia in 1.2% of burn patients or life-threatening bleeding in 3.7%.[165] Palmieri and Greenhalgh similarly demonstrated that restrictive blood transfusion does not adversely impact outcomes and causes significant savings.[166] In a series of greater than 60% TBSA burned children with inhalation injury, Jeschke and Herndon determined high transfusion patients (>20 units PRBC/>5 FFP) had their risk of sepsis increase from 8% to 58%, and they concluded that the immunocompromising effect of blood transfusion may be the etiologic factor.[167] Collectively these data support the practice of restrictive transfusion in the euvolemic burn patient without active hemorrhage.

In patients undergoing active hemorrhage, those who are at risk of or are in hemorrhagic shock, transfusion is critical. This occurs commonly during burn excision or in the postoperative resuscitation. These patients should be actively and rapidly transfused, as would be done in any trauma, with a goal of maintaining euvolemia, hemoglobin, clotting factors, normal pH, and temperature. U.S. Army data have demonstrated that whole blood transfusion is associated with improved survival compared to resuscitation with blood components for hemorrhagic shock. However whole blood is not yet available in the civilian world; groups are working to develop a civilian equivalent with storage stability at 4°C for 15 days.[168]

The current standard is to transfuse blood components in a 1 : 1 ratio of red cells to plasma. Pidcoke et al. did find the amalgamated transfusate samples administered to burn and soft tissue excision patients produced abnormally weak clots and have inferior platelet functions, thus concluding the transfusates were not hemostatic.[169] Regardless, given the currently available products, these component-based therapies are the standard of care.

In addition to meticulous and rapid techniques, epinephrine, thrombin, and direct pressure, antifibrinolytic therapy has also been used to limit intraoperative hemorrhage during burn excision. In the CRASH-2 trial, tranexamic acid (TXA) was shown in a double-blind RCT to reduce all-cause mortality and severe blood loss in traumatic bleeding.[170–172] However TXA use has only been defined topically in one burn case study, although a clinical trial is currently examining its parenteral value in burn wounds.[33]

Finally, transfusions of albumin or fresh frozen plasma (FFP) are key components of resuscitation, both in the acute burn setting and also in the critical care setting. As discussed extensively in Chapter 8 on burn edema, large-volume resuscitation with crystalloid damages the endovascular glycocalyx, thereby encouraging edema. This damage is limited with colloidal resuscitation, particularly plasma.[173] In select patients where interstitial or pulmonary edema is of significant concern, resuscitation with plasma transfusion may thus be indicated.

Burn wounds create a hypercoagulable environment due to the procoagulant effects created by the release of subendothelial collagen and also of tissue thromboplastin leading to a high risk of venothromboembolism (VTE). Data from a University of Michigan study demonstrated a substantial incidence of deep venous thrombosis (DVT) in 23% of their burned population with TBSA of less than 30%.[174] Several methods have been advocated to reduce the incidence of complications, including DVTs and capillary thrombosis, from this hypercoagulable state. One treatment, first proposed by Leyvraz, maintains a prothrombin time (PTT) of 1.2 times normal values using a sliding scale unfractionated heparin protocol.[175] This can be achieved via either a subcutaneous route or IV route; our institution prefers to use the intravenous route with monitoring of the PTT, starting with a dose of 5 units/kg per hour. Other methods include standard prophylaxis with low-molecular-weight heparin (LMWH).[176] The altered pharmacokinetics of burn patients benefit from factor Xa monitoring to assure prophylactic anticoagulation with LMWH. In a meta-analysis of RCTs involving 7226 ICU patients, those receiving any heparin-based VTE compared with placebo demonstrated reduced rates of DVT (relative risk [RR] 95%; confidence interval [CI] 0.41–0.63) and pulmonary embolism (PE) (RR 0.28–0.97), but not symptomatic DVT (RR 0.59–1.25), major bleeding (RR 0.56–1.21), or mortality (RR 0.78–1.02). LMWH was more effective compared to unfractionated heparin reducing rates of PE (RR 0.39–1.00) and symptomatic PE (RR 0.34–0.97), but not DVT (RR, 0.74–1.08), symptomatic DVT (RR 0.60–1.25), major bleeding (RR 0.75–1.26), or mortality (RR 0.82–1.04).[177] Overall, specifically in patients not actively hemorrhaging or where prophylaxis is contraindicated, VTE prophylaxis should be addressed.

ENDOCRINE BURN CRITICAL CARE

The role of the endocrine system in burn injury was thoroughly addressed previously in Chapter 23, so here we will focus on the practical critical care implications. Hyperglycemia and insulin resistance are common in the critically ill, and the burned patient is no exception. In 2001, Greet van den Berge reported in a landmark trial that intensive insulin treatment with continuous infusions of insulin aimed at normalizing blood glucose levels between 80 and 110 mg/dL reduced bloodstream infections and acute kidney injury and improved mortality.[178] This study was among the first to show some benefit of a treatment for all critically ill patients. Since this study, most intensivists throughout the world have targeted glucose control in a more normal range through the use of insulin. This may have other beneficial effects because investigators have shown an anabolic benefit of insulin treatment in burned patients in terms of muscle mass.[179] Intensive insulin treatment significantly decreases sepsis and infections, as well as reducing organ dysfunctions, thereby reducing IL-6 and acute-phase proteins. There was a trend toward reduced mortality; however the study was not sufficiently powered for this outcome.[180]

The particular range to which glucose should be controlled has not been firmly established, however, as the latest large-scale study on glucose control in the ICU did not

find a benefit to keeping glucose in the normal range, but rather indicated a higher range might have been even more beneficial.[181] The caveat to this analysis is that, on a post-hoc basis, injured patients had better outcomes with a normal glucose range rather than higher. However a growing body of evidence has demonstrated that hypoglycemic episodes (<60 mg/dL) cause increased length of stay, more infections, sepsis, MOF, and mortality.[182] Interestingly these negative outcomes and mortalities were not an acute result of the hypoglycemia, thus indicating there are lasting negative effects of transient and even successfully treated hypoglycemias. As such, the Society of Critical Care Medicine tolerates higher blood glucoses, in the 150–180 mg/dL range.[71] Methods to balance the benefits of euglycemia with the risks of hypoglycemia remain an active area of study in critical care.

In another landmark trial, cortisol levels were found to be low in many critically ill patients, and a mortality benefit accrued with physiologic replacement with hydrocortisone.[183] This study highlighted that hypocortisolemia is, at the very least, associated with septic shock and hypotension, and that replacement with hydrocortisone at 50 mg every 6 h improves outcomes. The same was seen in burned patients in the ICU.[184,185] This occurs despite the demonstrated fact that burn patients are in a hyperadrenal state.[186] It must be noted, however, that the benefits seem to be limited to those with relative adrenal insufficiency assessed by corticotropin stimulation, as seen in the follow-up CORTICUS trial.[187] Regardless, in the case of hypotension unrelated to hypovolemia in burn patients, cortisol levels and adrenal stimulation can be performed to determine whether relative adrenal insufficiency exists.

Venet et al. performed a placebo-controlled, double-blind RCT testing hydrocortisone in BICU patients suffering from refractory shock, defined as greater than 0.5 μg/kg per minute of norepinephrine. They found a significant reduction of norepinephrine treatment duration. Of note, 78% of these patients had a negative corticotropin stimulation test. They concluded low-dose hydrocortisone in burn patients with refractory shock reduces vasopressor administration.[188] These data thus obviate the value of cortisol stimulation tests. In a subsequent study, Winter et al. demonstrated that a hydrocortisone bolus of 100 mg followed by a 0.48 mg/kg per hour infusion improved norepinephrine dosing in burn survivors, but not in nonsurvivors.[185]

Burn surgeons are typically reticent to risk the negative wound healing and immunosuppressive complications of glucocorticoids. However, in the setting of refractory shock, a trial of steroids can prove diagnostic and therapeutic. Furthermore high-dose vitamin A can be utilized to ameliorate the wound-healing complications.[140]

INFECTIOUS DISEASE BURN CRITICAL CARE

Sepsis is a leading cause of mortality in burn patients and is the subject of Chapter 11. Sepsis has two potential causes: infection or inflammation without infection. Reliable detection of those patients with some component of infection is crucial. Our difficulty in severe burns is delineating this because traditional screening indicators for infection, such as temperature and white blood cell count, are unreliable because of the massive hypermetabolism and inflammation associated with recovery and healing.[189,190] The current standard for diagnosis is a high index of suspicion and frequent culturing of wounds, lines, blood, airways, urine, and any other potential source. Suspicion must as well be maintained for invasive yeast and molds, viruses (most especially herpetic viruses), and, of course, bacteria.

Potential does exist for elevations in procalcitonin (PCT) to be associated with a higher risk of infection, this being linked to pathogen infection presumably through PAMPs rather than DAMPs. An interesting study from Iran examined the role of white blood cells, sedimentation rate, C-reactive protein, and PCT in diagnosing sepsis in the severely burned. The authors found that PCT was the only test with any distinguishing capacity and accuracy.[191]

In a recent meta-analysis of 566 patients from nine trials of sepsis in burn patients, PCT demonstrated a sensitivity of 0.74 and a specificity of 0.88.[192] In a subsequent study, a protocol was instituted utilizing PCT to determine duration of antibiotic therapy in 46 burn BICU patients. Antibiotic duration was significantly reduced without relapse of infection, increase in mortality or organ failure, or increase in length of stay.[193] PCT has not yet become a standard of care; however data continue to support its utility in the burn population.

Prevention of Organ Failure

This brief outline of the potential pathophysiology and causes of burn-induced critical illness and MOF demonstrates the complexity of the problem. Prevention of organ failure is the subject of Chapter 30. Because different cascade systems are involved in the pathogenesis, it is currently impossible to pinpoint a single mediator or system that initiates the event. Thus because the mechanisms of progression are not well known and specific treatments cannot be accurately devised, it seems that prevention is the best solution. Current recommendations are to prevent the development of organ dysfunction and provide optimal support to avoid the conditions that promote its onset. In burned patients this can be accomplished most reliably through expeditious wound closure, rapid mobilization of the patient, and prompt identification of and treatment of early infections.

Conclusion

Burn critical care is predicated on seven key factors: sufficient goal-directed fluid resuscitation; early burn excision and wound coverage; aggressive antimicrobial and source control of sepsis; aggressive nutritional support; active warming; aggressive physical, occupational, and respiratory therapy; and aggressive and continuous support of organ failures until such time as the patient can heal. This care has reduced mortality over the past three decades, in large part through the development of specialized units for the care of burned patients. These units are equipped with the personnel and equipment to deliver state-of-the-art care. Better understanding of the processes of critical illness and MOF has led to effective prevention strategies and treatment modalities. Further advances in the understanding of

the mechanisms of the progression from SIRS to MOF might engender new breakthroughs that can be expected to further improve the outcomes of burned patients.

Complete references available online at www.expertconsult.inkling.com

Further Reading

Chung KK, Wolf SE, Renz EM, et al. High-frequency percussive ventilation and low tidal volume ventilation in burns: a randomized controlled trial. *Crit Care Med*. 2010;38:1970-1977.

Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41(2):580-637.

Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126-134.

Hodgson CL, Stiller K, Needham DM, et al. Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults. *Crit Care*. 2014;18(6):658.

Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med*. 2014;371(15):1381-1391.

MacLennan L, Moiemen N. Management of cyanide toxicity in patients with burns. *Burns*. 2015;41(1):18-24.

McIntire A, Harris SA, Whitten JA, et al. Outcomes following the use of nebulized heparin for inhalation injury (HIHI Study). *J Burn Care Res*. 2017;38(1):45-52.

Ren H, Li Y, Han C, Hu H. Serum procalcitonin as a diagnostic biomarker for sepsis in burned patients: a meta-analysis. *Burns*. 2015;41(3):502-509.

Venet F, Plassais J, Textoris J, et al. Low-dose hydrocortisone reduces norepinephrine duration in severe burn patients: a randomized clinical trial. *Crit Care*. 2015;19:21.

Wurzer P, Branski LK, Jeschke MG, et al. Transpulmonary thermodilution versus transthoracic echocardiography for cardiac output measurements in severely burned children. *Shock*. 2016;46(3):249-253.

References

1. Brigham PA, McLoughlin E. Burn incidence and medical care use in the United States: estimates, trends, and data sources. *J Burn Care Rehabil*. 1996;17(2):95-107.
2. Control CfD. WISQARS; 2010. wwwcdcgov/injury/wisqars/Home.
3. Bull JP, Squire JR. A study of mortality in a burns unit: standards for the evaluation of alternative methods of treatment. *Ann Surg*. 1949;130(2):160-173.
4. Miller SF, Bessey PQ, Schurr MJ, et al. National burn repository 2005: a ten-year review. *J Burn Care Res*. 2006;27(4):411-436.
5. Wolf SE, Jeschke MG, Rose JK, et al. Enteral feeding intolerance: an indicator of sepsis-associated mortality in burned children. *Arch Surg*. 1997;132(12):1310-1313, discussion 1313-1314.
6. Baue AE, Durham R, Faist E. Systemic inflammatory response syndrome (SIRS): multiple organ dysfunction syndrome (MODS): multiple organ failure (MOF): are we winning the battle? *Shock*. 1998;10(2):79-89.
7. Muckart DJ, Bhagwanjee S. American College of Chest Physicians/Society of Crit Care Med. Consensus Conference definitions of the systemic inflammatory response syndrome and allied disorders in relation to critically injured patients. *Crit Care Med*. 1997;25(11):1789-1795.
8. Trauma ACoSCo. Guidelines for the operation of burn units. In: *Resources for the Optimal Care of the Injured Patient*. Chicago: American College of Surgeons; 2006:55-62.
9. Inoue S, Egi M, Kotani J, et al. Accuracy of blood-glucose measurements using glucose meters and arterial blood gas analyzers in critically ill adult patients: systematic review. *Crit Care*. 2013;17(2):R48.
10. Larsson A, Greig-Pylypczuk R, Huisman A. The state of point-of-care testing: a European perspective. *Ups J Med Sci*. 2015;120(1):1-10.
11. Galluccio ST, Chapman MJ, Finnis ME. Femoral-radial arterial pressure gradients in critically ill patients. *Crit Care Resusc*. 2009;11(1):34-38.
12. Park MK, Robotham JL, German VF. Systolic pressure amplification in pedal arteries in children. *Crit Care Med*. 1983;11(4):286-289.
13. Hodgson CL, Stiller K, Needham DM, et al. Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults. *Crit Care*. 2014;18(6):658.
14. Cope C, Zeit R. Coagulation of aneurysms by direct percutaneous thrombin injection. *AJR Am J Roentgenol*. 1986;147(2):383-387.
15. Chatterjee T, Do DD, Mahler F, et al. A prospective, randomized evaluation of nonsurgical closure of femoral pseudoaneurysm by compression device with or without ultrasound guidance. *Catheter Cardiovasc Interv*. 1999;47(3):304-309.
16. Connors AF Jr, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *JAMA*. 1996;276(11):889-897.
17. Harvey S, Stevens K, Harrison D, et al. An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial. *Health Technol Assess*. 2006;10(29):iii-iv, ix-xi, 1-133.
18. Barnett CF, Vaduganathan M, Lan G, et al. Critical reappraisal of pulmonary artery catheterization and invasive hemodynamic assessment in acute heart failure. *Expert Rev Cardiovasc Ther*. 2013;11(4):417-424.
19. Boldt J, Papsdorf M. Fluid management in burn patients: results from a European survey-more questions than answers. *Burns*. 2008;34(3):328-338.
20. Lavrentieva A, Kontakiotis T, Kaimakamis E, et al. Evaluation of arterial waveform derived variables for an assessment of volume resuscitation in mechanically ventilated burn patients. *Burns*. 2013;39(2):249-254.
21. Peeters Y, Lebeer M, Wise R, et al. An overview on fluid resuscitation and resuscitation endpoints in burns: Past, present and future. Part 2 - avoiding complications by using the right endpoints with a new personalized protocolized approach. *Anaesthesiol Intensive Ther*. 2015;47(Spec No):s15-s26.
22. Wurzer P, Branski LK, Jeschke MG, et al. Transpulmonary thermodilution versus transthoracic echocardiography for cardiac output measurements in severely burned children. *Shock*. 2016;46(3):249-253.
23. Papp A, Uusaro A, Parviainen I, et al. Myocardial function and haemodynamics in extensive burn trauma: evaluation by clinical signs, invasive monitoring, echocardiography and cytokine concentrations. A prospective clinical study. *Acta Anaesthesiol Scand*. 2003;47(10):1257-1263.
24. Wang GY, Ma B, Tang HT, et al. Esophageal echo-Doppler monitoring in burn shock resuscitation: are hemodynamic variables the critical standard guiding fluid therapy? *J Trauma*. 2008;65(6):1396-1401.
25. Held JM, Litt J, Kennedy JD, et al. Surgeon-performed hemodynamic transesophageal echocardiography in the burn intensive care unit. *J Burn Care Res*. 2016;37(1):e63-e68.
26. Bak Z, Sjoberg F, Eriksson O, et al. Cardiac dysfunction after burns. *Burns*. 2008;34(5):603-609.
27. Funcke S, Sander M, Goepfert MS, et al. Practice of hemodynamic monitoring and management in German, Austrian, and Swiss intensive care units: the multicenter cross-sectional ICU-CardioMan Study. *Ann Intensive Care*. 2016;6(1):49.
28. van Beest P, Wietasch G, Scheeren T, et al. Clinical review: use of venous oxygen saturations as a goal – a yet unfinished puzzle. *Crit Care*. 2011;15(5):232.
29. Kincaid EH, Miller PR, Meredith JW, et al. Elevated arterial base deficit in trauma patients: a marker of impaired oxygen utilization. *J Am Coll Surg*. 1998;187(4):384-392.
30. Wolf SE, Rose JK, Desai MH, et al. Mortality determinants in massive pediatric burns. An analysis of 103 children with > or = 80% TBSA burns (> or = 70% full-thickness). *Ann Surg*. 1997;225(5):554-565, discussion 565-569.
31. Kaups KL, Davis JW, Dominic WJ. Base deficit as an indicator or resuscitation needs in patients with burn injuries. *J Burn Care Rehabil*. 1998;19(4):346-348.
32. Jeng JC, Lee K, Jablonski K, Jordan MH. Serum lactate and base deficit suggest inadequate resuscitation of patients with burn injuries: application of a point-of-care laboratory instrument. *J Burn Care Rehabil*. 1997;18(5):402-405.
33. Andel D, Kamolz LP, Roka J, et al. Base deficit and lactate: early predictors of morbidity and mortality in patients with burns. *Burns*. 2007;33(8):973-978.
34. Cochran A, Edelman LS, Saffle JR, et al. The relationship of serum lactate and base deficit in burn patients to mortality. *J Burn Care Res*. 2007;28(2):231-240.
35. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994;149(3 Pt 1):818-824.
36. Zhang Q, Raoof M, Chen Y, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature*. 2010;464(7285):104-107.
37. Jeschke MG, Chinkes DL, Finnerty CC, et al. Pathophysiologic response to severe burn injury. *Ann Surg*. 2008;248(3):387-401.
38. Kremer T, Harenberg P, Hernekamp F, et al. High-dose vitamin C treatment reduces capillary leakage after burn plasma transfer in rats. *J Burn Care Res*. 2010;31(3):470-479.
39. Reference deleted at revises
40. Reference deleted at revises
41. Reference deleted at revises
42. van Bebber IP, Lieners CF, Koldewijn EL, et al. Superoxide dismutase and catalase in an experimental model of multiple organ failure. *J Surg Res*. 1992;52(3):265-270.
43. Traber DL, Traber MG, Enkhbaatar P, et al. Tocopherol as treatment for lung injury associated with burn and smoke inhalation. *J Burn Care Res*. 2009;30(1):164-165.
44. Reference deleted at revises
45. Deitch EA. Intestinal permeability is increased in burn patients shortly after injury. *Surgery*. 1990;107(4):411-416.
46. Peeters Y, Vandervelden S, Wise R, et al. An overview on fluid resuscitation and resuscitation endpoints in burns: past, present and future. Part 1 – historical background, resuscitation fluid and adjunctive treatment. *Anaesthesiol Intensive Ther*. 2015;47(Spec No):s6-s14.
47. Chicarilli ZN, Cuono CB, Heinrich JJ, et al. Selective aggressive burn excision for high mortality subgroups. *J Trauma*. 1986;26(1):18-25.
48. Klein MB, Edwards JA, Kramer CB, et al. The beneficial effects of plasma exchange after severe burn injury. *J Burn Care Res*. 2009;30(2):243-248.
49. Endorf FW, Dries DJ. Burn resuscitation. *Scand J Trauma Resusc Emerg Med*. 2011;19:69.
50. Herndon DN, Parks DH. Comparison of serial debridement and autografting and early massive excision with cadaver skin overlay in the treatment of large burns in children. *J Trauma*. 1986;26(2):149-152.

51. Toon MH, Maybauer MO, Greenwood JE, et al. Management of acute smoke inhalation injury. *Crit Care Resusc*. 2010;12(1):53-61.
52. MacLennan L, Moiemen N. Management of cyanide toxicity in patients with burns. *Burns*. 2015;41(1):18-24.
53. Dries DJ, Endorf FW. Inhalation injury: epidemiology, pathology, treatment strategies. *Scand J Trauma Resusc Emerg Med*. 2013;21:31.
54. Richardson P, Mustard L. The management of pain in the burns unit. *Burns*. 2009;35(7):921-936.
55. Owens VF, Palmieri TL, Comroe CM, et al. Ketamine: a safe and effective agent for painful procedures in the pediatric burn patient. *J Burn Care Res*. 2006;27(2):211-216, discussion 217.
56. Green SM, Roback MG, Krauss B, et al. Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: an individual-patient data meta-analysis of 8,282 children. *Ann Emerg Med*. 2009;54(2):158–168.e151–154.
57. Yousefi H, Toghyani F, Yazdannik AR, et al. Effect of using Richmond Agitation Sedation Scale on duration of mechanical ventilation, type and dosage of sedation on hospitalized patients in intensive care units. *Iran J Nurs Midwifery Res*. 2015;20(6):700-704.
58. Mohrien KM, Jones GM, MacDermott JR, et al. Remifentanil, ketamine, and fospropofol: a review of alterative continuous infusion agents for sedation in the critically ill. *Crit Care Nurs Q*. 2014;37(2):137-151.
59. Fagin A, Palmieri T, Greenhalgh D, et al. A comparison of dexmedetomidine and midazolam for sedation in severe pediatric burn injury. *J Burn Care Res*. 2012;33(6):759-763.
60. Dexmedetomidine for sedation in the ICU or PICU: a review of cost-effectiveness and guidelines. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2014 Dec. CADTH Rapid Response Reports.
61. Jing Wang G, Belley-Cote E, Burry L, et al. Clonidine for sedation in the critically ill: a systematic review and meta-analysis (protocol). *Syst Rev*. 2015;4:154.
62. Benken ST, Goncharenko A. The future of intensive care unit sedation: a report of continuous infusion Ketamine as an alternative sedative agent. *J Pharm Pract*. 2016;[Epub ahead of print].
63. Stoddard FJ Jr, Ryan CM, Schneider JC. Physical and psychiatric recovery from burns. *Surg Clin North Am*. 2014;94(4):863-878.
64. Porhomayon J, El-Solh AA, Adlparvar G, et al. Impact of sedation on cognitive function in mechanically ventilated patients. *Lung*. 2016;194(1):43-52.
65. Brown RL, Henke A, Greenhalgh DG, et al. The use of haloperidol in the agitated, critically ill pediatric patient with burns. *J Burn Care Rehabil*. 1996;17(1):34-38.
66. Kram BL, Kram SJ, Brooks KR. Implications of atypical antipsychotic prescribing in the intensive care unit. *J Crit Care*. 2015;30(4):814-818.
67. Branski LK, Herndon DN, Byrd JF, et al. Transpulmonary thermodilution for hemodynamic measurements in severely burned children. *Crit Care*. 2011;15(2):R118.
68. Yoshida T, Fujii T, Uchino S, et al. Epidemiology, prevention, and treatment of new-onset atrial fibrillation in critically ill: a systematic review. *J Intensive Care*. 2015;3(1):19.
69. Michard F, Alaya S, Zarka V, et al. Global end-diastolic volume as an indicator of cardiac preload in patients with septic shock. *Chest*. 2003;124(5):1900-1908.
70. Zhou M, Dai J, Du M, et al. Effect of dobutamine on extravascular lung water index, ventilator function, and perfusion parameters in acute respiratory distress syndrome associated with septic shock. *Artif Cells Nanomed Biotechnol*. 2016;44(5):1326-1332.
71. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41(2):580-637.
72. Hollenberg SM. Inotrope and vasopressor therapy of septic shock. *Crit Care Nurs Clin North Am*. 2011;23(1):127-148.
73. Johnston WE. Applied cardiac physiology. *Refresh Courses Anesthesiol*. 2012;40(1):73-79.
74. Gordon AC, Mason AJ, Thirunavukkarasu N, et al. Effect of early Vasopressin vs Norepinephrine on kidney failure in patients with septic shock: The VANISH randomized clinical trial. *JAMA*. 2016;316(5):509-518.
75. Gosain A, Muthu K, Gamelli RL, et al. Norepinephrine suppresses wound macrophage phagocytic efficiency through alpha- and beta-adrenoreceptor dependent pathways. *Surgery*. 2007;142(2):170-179.
76. Cartotto R, McGibney K, Smith T, et al. Vasopressin for the septic burn patient. *Burns*. 2007;33(4):441-451.
77. Li T, Fang Y, Zhu Y, et al. A small dose of arginine vasopressin in combination with norepinephrine is a good early treatment for uncontrolled hemorrhagic shock after hemostasis. *J Surg Res*. 2011;169(1):76-84.
78. Jaskille AD, Jeng JC, Jordan MH. Methylene blue in the treatment of vasoplegia following severe burns. *J Burn Care Res*. 2008;29(2):408-410.
79. Church JT, Posluszny JA, Hemmila M, et al. Methylene blue for burn-induced vasoplegia: case report and review of literature. *J Burn Care Res*. 2015;36(2):e107-e111.
80. Williams FN, Herndon DN, Kulp GA, et al. Propranolol decreases cardiac work in a dose-dependent manner in severely burned children. *Surgery*. 2011;149(2):231-239.
81. Aarsland A, Chinkes D, Wolfe RR, et al. Beta-blockade lowers peripheral lipolysis in burn patients receiving growth hormone. Rate of hepatic very low density lipoprotein triglyceride secretion remains unchanged. *Ann Surg*. 1996;223(6):777-787, discussion 787-789.
82. Herndon DN, Hart DW, Wolf SE, et al. Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med*. 2001;345(17):1223-1229.
83. Wurzer P, Branski LK, Clayton RP, et al. Propranolol reduces cardiac index but does not adversely affect peripheral perfusion in severely burned children. *Shock*. 2016.
84. Romanowski KS, Palmieri TL, Sen S, et al. More than one third of intubations in patients transferred to burn centers are unnecessary: proposed guidelines for appropriate intubation of the burn patient. *J Burn Care Res*. 2016;37(5):e409-e414.
85. Chung KK, Rhie RY, Lundy JB, et al. A survey of mechanical ventilator practices across burn centers in North America. *J Burn Care Res*. 2016;37(2):e131-e139.
86. Terragni PP, Antonelli M, Fumagalli R, et al. Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients: a randomized controlled trial. *JAMA*. 2010;303(15):1483-1489.
87. Savi A, Gasparetto Maccari J, Frederico Tonietto T, et al. Influence of FIO_2 on $PaCO_2$ during noninvasive ventilation in patients with COPD. *Respir Care*. 2014;59(3):383-387.
88. Verscheure S, Massion PB, Verschuren F, et al. Volumetric capnography: lessons from the past and current clinical applications. *Crit Care*. 2016;20(1):184.
89. Badet M, Bayle F, Richard JC, et al. Comparison of optimal positive end-expiratory pressure and recruitment maneuvers during lung-protective mechanical ventilation in patients with acute lung injury/acute respiratory distress syndrome. *Respir Care*. 2009;54(7):847-854.
90. Li Y, Tang R, Huang YZ, et al. [The value of nitrogen washout/washin method in assessing alveolar recruitment volume in acute lung injury patients]. *Zhonghua Nei Ke Za Zhi*. 2013;52(4):295-298.
91. Ni Chonghaile M, Higgins B, Laffey JG. Permissive hypercapnia: role in protective lung ventilatory strategies. *Curr Opin Crit Care*. 2005;11(1):56-62.
92. Kallet RH, Campbell AR, Dicker RA, et al. Effects of tidal volume on work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome. *Crit Care Med*. 2006;34(1):8-14.
93. Sousse LE, Herndon DN, Andersen CR, et al. High tidal volume decreases adult respiratory distress syndrome, atelectasis, and ventilator days compared with low tidal volume in pediatric burned patients with inhalation injury. *J Am Coll Surg*. 2015;220(4):570-578.
94. Deans KJ, Minneci PC, Cui X, et al. Mechanical ventilation in ARDS: One size does not fit all. *Crit Care Med*. 2005;33(5):1141-1143.
95. Kallet RH, Branson RD. Should oxygen therapy be tightly regulated to minimize hyperoxia in critically ill patients? *Respir Care*. 2016;61(6):801-817.
96. Greathouse ST, Hadad I, Zieger M, et al. High-frequency oscillatory ventilators in burn patients: experience of Riley Hospital for Children. *J Burn Care Res*. 2012;33(3):425-435.
97. Yoshida T, Rinka H, Kaji A, et al. The impact of spontaneous ventilation on distribution of lung aeration in patients with acute respiratory distress syndrome: airway pressure release ventilation versus pressure support ventilation. *Anesth Analg*. 2009;109(6):1892-1900.
98. Sheridan RL, Zapol WM, Ritz RH, et al. Low-dose inhaled nitric oxide in acutely burned children with profound respiratory failure. *Surgery*. 1999;126(5):856-862.

99. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. *Intensive Care Med*. 2010;36(4):585-599.
100. Tremper KK, Barker SJ. Pulse oximetry. *Anesthesiology*. 1989;70(1):98-108.
101. Fanelli V, Vlachou A, Ghannadian S, et al. Acute respiratory distress syndrome: new definition, current and future therapeutic options. *J Thorac Dis*. 2013;5(3):326-334.
102. National Heart Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network, Wiedemann HP, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564-2575.
103. Sheridan RL. Fire-related inhalation injury. *N Engl J Med*. 2016;375(5):464-469.
104. McIntire A, Harris SA, Whitten JA, et al. Outcomes following the use of nebulized Heparin for inhalation injury (HIHI Study). *J Burn Care Res*. 2016.
105. Glas GJ, Serpa Neto A, Horn J, et al. Nebulized heparin for patients under mechanical ventilation: an individual patient data meta-analysis. *Ann Intensive Care*. 2016;6(1):33.
106. Kashefi NS, Nathan JI, Dissanaike S. Does a nebulized Heparin/N-acetylcysteine protocol improve outcomes in adult smoke inhalation? *Plast Reconstr Surg Glob Open*. 2014;2(6):e165.
107. Soussi S, Gallais P, Kachatryan L, et al. Extracorporeal membrane oxygenation in burn patients with refractory acute respiratory distress syndrome leads to 28% 90-day survival. *Intensive Care Med*. 2016;42(11):1826-1827.
108. Zavala E, Ferrer M, Polese G, et al. Effect of inverse I:E ratio ventilation on pulmonary gas exchange in acute respiratory distress syndrome. *Anesthesiology*. 1998;88(1):35-42.
109. Maxwell RA, Green JM, Waldrop J, et al. A randomized prospective trial of airway pressure release ventilation and low tidal volume ventilation in adult trauma patients with acute respiratory failure. *J Trauma*. 2010;69(3):501-510, discussion 511.
110. Ntoumenopoulos G, Berry M, Camporota L. Effects of manually-assisted cough combined with postural drainage, saline instillation and airway suctioning in critically-ill patients during high-frequency oscillatory ventilation: a prospective observational single centre trial. *Physiother Theory Pract*. 2014;30(5):306-311.
111. Derdak S, Mehta S, Stewart TE, et al. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. *Am J Respir Crit Care Med*. 2002;166(6):801-808.
112. Cartotto R, Ellis S, Gomez M, et al. High frequency oscillatory ventilation in burn patients with the acute respiratory distress syndrome. *Burns*. 2004;30(5):453-463.
113. Cartotto R, Walia G, Ellis S, et al. Oscillation after inhalation: high frequency oscillatory ventilation in burn patients with the acute respiratory distress syndrome and co-existing smoke inhalation injury. *J Burn Care Res*. 2009;30(1):119-127.
114. Cioffi WG, Graves TA, McManus WF, et al. High-frequency percussive ventilation in patients with inhalation injury. *J Trauma*. 1989;29(3):350-354.
115. Cortiella J, Mlcak R, Herndon D. High frequency percussive ventilation in pediatric patients with inhalation injury. *J Burn Care Rehabil*. 1999;20(3):232-235.
116. Chung KK, Wolf SE, Renz EM, et al. High-frequency percussive ventilation and low tidal volume ventilation in burns: a randomized controlled trial. *Crit Care Med*. 2010;38(10):1970-1977.
117. Ammar MA, Bauer SR, Bass SN, et al. Noninferiority of inhaled Epoprostenol to inhaled nitric oxide for the treatment of ARDS. *Ann Pharmacother*. 2015;49(10):1105-1112.
118. Dzierba AL, Abel EE, Buckley MS, et al. A review of inhaled nitric oxide and aerosolized epoprostenol in acute lung injury or acute respiratory distress syndrome. *Pharmacotherapy*. 2014;34(3):279-290.
119. Dube KM, Ditch KL, Hills L. Use of nebulized heparin, nebulized N-acetylcysteine, and nebulized epoprostenol in a patient with smoke inhalational injury and acute respiratory distress syndrome. *J Pharm Pract*. 2016.
120. Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. *N Engl J Med*. 1995;332(6):345-350.
121. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126-134.
122. Curley GF, Laffey JG, Zhang H, et al. Biotrauma and ventilator induced lung injury: clinical implications. *Chest*. 2016;150(5):1109-1117.
123. Brower RG, Shanholtz CB, Fessler HE, et al. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. *Crit Care Med*. 1999;27(8):1492-1498.
124. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342(18):1301-1308.
125. Nieman GF, Gatto LA, Habashi NM. Impact of mechanical ventilation on the pathophysiology of progressive acute lung injury. *J Appl Physiol*. 2015;119(11):1245-1261.
126. Wolter TP, Fuchs PC, Horvat N, et al. Is high PEEP low volume ventilation in burn patients beneficial? A retrospective study of 61 patients. *Burns*. 2004;30(4):368-373.
127. Martin M, Salim A, Murray J, et al. The decreasing incidence and mortality of acute respiratory distress syndrome after injury: a 5-year observational study. *J Trauma*. 2005;59(5):1107-1113.
128. Azoulay E, Darmon M. Acute respiratory distress syndrome during neutropenia recovery. *Crit Care*. 2010;14(1):114.
129. Peek GJ, Clemens F, Elbourne D, et al. CESAR: conventional ventilatory support vs extracorporeal membrane oxygenation for severe adult respiratory failure. *BMC Health Serv Res*. 2006;6:163.
130. de Prost N, Roux D, Dreyfuss D, et al. Alveolar edema dispersion and alveolar protein permeability during high volume ventilation: effect of positive end-expiratory pressure. *Intensive Care Med*. 2007;33(4):711-717.
131. Tugrul S, Akinci O, Ozcan PE, et al. Effects of sustained inflation and postinflation positive end-expiratory pressure in acute respiratory distress syndrome: focusing on pulmonary and extrapulmonary forms. *Crit Care Med*. 2003;31(3):738-744.
132. Liffner G, Bak Z, Reske A, et al. Inhalation injury assessed by score does not contribute to the development of acute respiratory distress syndrome in burn victims. *Burns*. 2005;31(3):263-268.
133. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med*. 1998;338(6):347-354.
134. Taylor RW, Zimmerman JL, Dellinger RP, et al. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. *JAMA*. 2004;291(13):1603-1609.
135. Taccone P, Pesenti A, Latini R, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 2009;302(18):1977-1984.
136. Alsaghir AH, Martin CM. Effect of prone positioning in patients with acute respiratory distress syndrome: a meta-analysis. *Crit Care Med*. 2008;36(2):603-609.
137. Goretsky MJ, Greenhalgh DG, Warden GD, et al. The use of extracorporeal life support in pediatric burn patients with respiratory failure. *J Pediatr Surg*. 1995;30(4):620-623.
138. Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in early severe ARDS: results of a randomized controlled trial. *Chest*. 2007;131(4):954-963.
139. Meduri GU, Chinn AJ, Leeper KV, et al. Corticosteroid rescue treatment of progressive fibroproliferation in late ARDS. Patterns of response and predictors of outcome. *Chest*. 1994;105(5):1516-1527.
140. Phillips JD, Kim CS, Fonkalsrud EW, et al. Effects of chronic corticosteroids and vitamin A on the healing of intestinal anastomoses. *Am J Surg*. 1992;163(1):71-77.
141. Horton JW. Bacterial translocation after burn injury: the contribution of ischemia and permeability changes. *Shock*. 1994;1(4):286-290.
142. Xia X, Wang X, Li Q, et al. Essential amino acid enriched high-protein enteral nutrition modulates insulin-like growth factor-1 system function in a rat model of trauma-hemorrhagic shock. *PLoS ONE*. 2013;8(10):e77823.
143. Elke G, van Zanten AR, Lemieux M, et al. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. *Crit Care*. 2016;20(1):117.
144. Suman OE, Mlcak RP, Chinkes DL, et al. Resting energy expenditure in severely burned children: analysis of agreement between indirect calorimetry and prediction equations using the Bland-Altman method. *Burns*. 2006;32(3):335-342.

145. Oda J, Ueyama M, Yamashita K, et al. Hypertonic lactated saline resuscitation reduces the risk of abdominal compartment syndrome in severely burned patients. *J Trauma*. 2006;60(1):64-71.
146. Latenser BA, Kowal-Vern A, Kimball D, et al. A pilot study comparing percutaneous decompression with decompressive laparotomy for acute abdominal compartment syndrome in thermal injury. *J Burn Care Rehabil*. 2002;23(3):190-195.
147. Markell KW, Renz EM, White CE, et al. Abdominal complications after severe burns. *J Am Coll Surg*. 2009;208(5):940-947, discussion 947-949.
148. Wang DW, Yin YM, Yao YM. Advances in the management of acute liver failure. *World J Gastroenterol*. 2013;19(41):7069-7077.
149. Rivero HG, Lee JO, Herndon DN, et al. The role of acute pancreatitis in pediatric burn patients. *Burns*. 2011;37(1):82-85.
150. Chertow GM, Christiansen CL, Cleary PD, et al. Prognostic stratification in critically ill patients with acute renal failure requiring dialysis. *Arch Intern Med*. 1995;155(14):1505-1511.
151. Rennie TJ, Patton A, Dreischulte T, et al. Incidence and outcomes of acute kidney injury requiring renal replacement therapy: a retrospective cohort study. *Nephron*. 2016;133(4):239-246.
152. Jeschke MG, Barrow RE, Wolf SE, et al. Mortality in burned children with acute renal failure. *Arch Surg*. 1998;133(7):752-756.
153. Mustonen KM, Vuola J. Acute renal failure in intensive care burn patients (ARF in burn patients). *J Burn Care Res*. 2008;29(1):227-237.
154. Ichai C, Passeron C, Carles M, et al. Prolonged low-dose dopamine infusion induces a transient improvement in renal function in hemodynamically stable, critically ill patients: a single-blind, prospective, controlled study. *Crit Care Med*. 2000;28(5):1329-1335.
155. Morelli A, Ricci Z, Bellomo R, et al. Prophylactic fenoldopam for renal protection in sepsis: a randomized, double-blind, placebo-controlled pilot trial. *Crit Care Med*. 2005;33(11):2451-2456.
156. Simmons JW, Chung KK, Renz EM, et al. Fenoldopam use in a burn intensive care unit: a retrospective study. *BMC Anesthesiol*. 2010;10:9.
157. Brown CV, Rhee P, Chan L, et al. Preventing renal failure in patients with rhabdomyolysis: do bicarbonate and mannitol make a difference? *J Trauma*. 2004;56(6):1191-1196.
158. Bellomo R, Ronco C, Kellum JA, et al. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8(4):R204-R212.
159. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11(2):R31.
160. Steinvall I, Bak Z, Sjoberg F. Acute kidney injury is common, parallels organ dysfunction or failure, and carries appreciable mortality in patients with major burns: a prospective exploratory cohort study. *Crit Care*. 2008;12(5):R124.
161. Sabry A, El-Din AB, El-Hadidy AM, et al. Markers of tubular and glomerular injury in predicting acute renal injury outcome in thermal burn patients: a prospective study. *Ren Fail*. 2009;31(6):457-463.
162. Chung KK, Lundy JB, Matson JR, et al. Continuous venovenous hemofiltration in severely burned patients with acute kidney injury: a cohort study. *Crit Care*. 2009;13(3):R62.
163. Pomeranz A, Reichenberg Y, Schurr D, et al. Acute renal failure in a burn patient: the advantages of continuous peritoneal dialysis. *Burns Incl Therm Inj*. 1985;11(5):367-370.
164. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med*. 2014;371(15):1381-1391.
165. Lelubre C, Vincent JL, Taccone FS. Red blood cell transfusion strategies in critically ill patients: lessons from recent randomized clinical studies. *Minerva Anestesiol*. 2016;82(9):1010-1016.
166. Palmieri TL, Lee T, O'Mara MS, et al. Effects of a restrictive blood transfusion policy on outcomes in children with burn injury. *J Burn Care Res*. 2007;28(1):65-70.
167. Jeschke MG, Chinkes DL, Finnerty CC, et al. Blood transfusions are associated with increased risk for development of sepsis in severely burned pediatric patients. *Crit Care Med*. 2007;35(2):579-583.
168. Spinella PC, Pidcoke HF, Strandenes G, et al. Whole blood for hemostatic resuscitation of major bleeding. *Transfusion*. 2016;56(suppl 2):S190-S202.
169. Pidcoke HF, Isbell CL, Herzig MC, et al. Acute blood loss during burn and soft tissue excisions: An observational study of blood product resuscitation practices and focused review. *J Trauma Acute Care Surg*. 2015;78(6 suppl 1):S39-S47.
170. Munoz-Sanchez A, Murillo-Cabezas F. Tranexamic acid therapy decreases mortality of traumatic hemorrhagic shock]. *Med Intensiva*. 2011;35(5):286-287.
171. CRASH-2 Collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376(9734):23-32.
172. Tang YM, Chapman TW, Brooks P. Use of tranexamic acid to reduce bleeding in burns surgery. *J Plast Reconstr Aesthet Surg*. 2012;65(5):684-686.
173. Kozar RA, Peng Z, Zhang R, et al. Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock. *Anesth Analg*. 2011;112(6):1289-1295.
174. Wahl WL, Brandt MM, Ahrns KS, et al. Venous thrombosis incidence in burn patients: preliminary results of a prospective study. *J Burn Care Rehabil*. 2002;23(2):97-102.
175. Leyvraz PF, Richard J, Bachmann F, et al. Adjusted versus fixed-dose subcutaneous heparin in the prevention of deep-vein thrombosis after total hip replacement. *N Engl J Med*. 1983;309(16):954-958.
176. Faucher LD, Conlon KM. Practice guidelines for deep venous thrombosis prophylaxis in burns. *J Burn Care Res*. 2007;28(5):661-663.
177. Alhazzani W, Lim W, Jaeschke RZ, et al. Heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care Med*. 2013;41(9):2088-2098.
178. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. 2001;345(19):1359-1367.
179. Thomas SJ, Morimoto K, Herndon DN, et al. The effect of prolonged euglycemic hyperinsulinemia on lean body mass after severe burn. *Surgery*. 2002;132(2):341-347.
180. Jeschke MG, Kulp GA, Kraft R, et al. Intensive insulin therapy in severely burned pediatric patients: a prospective randomized trial. *Am J Respir Crit Care Med*. 2010;182(3):351-359.
181. Investigators N-SS, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283-1297.
182. Jeschke MG, Pinto R, Herndon DN, et al. Hypoglycemia is associated with increased postburn morbidity and mortality in pediatric patients. *Crit Care Med*. 2014;42(5):1221-1231.
183. Annane D, Sebille V, Bellissant E, Ger-Inf-05 Study Group. Effect of low doses of corticosteroids in septic shock patients with or without early acute respiratory distress syndrome. *Crit Care Med*. 2006;34(1):22-30.
184. Fuchs P, Groger A, Bozkurt A, et al. Cortisol in severely burned patients: investigations on disturbance of the hypothalamic-pituitary-adrenal axis. *Shock*. 2007;28(6):662-667.
185. Winter W, Kamolz L, Donner A, et al. Hydrocortisone improved haemodynamics and fluid requirement in surviving but not non-surviving of severely burned patients. *Burns*. 2003;29(7):717-720.
186. Norbury WB, Herndon DN, Branski LK, et al. Urinary cortisol and catecholamine excretion after burn injury in children. *J Clin Endocrinol Metab*. 2008;93(4):1270-1275.
187. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358(2):111-124.
188. Venet F, Plassais J, Textoris J, et al. Low-dose hydrocortisone reduces norepinephrine duration in severe burn patients: a randomized clinical trial. *Crit Care*. 2015;19:21.
189. Greenhalgh DG, Saffle JR, Holmes JHT, et al. American Burn Association consensus conference to define sepsis and infection in burns. *J Burn Care Res*. 2007;28(6):776-790.
190. Murray CK, Hoffmaster RM, Schmit DR, et al. Evaluation of white blood cell count, neutrophil percentage, and elevated temperature as predictors of bloodstream infection in burn patients. *Arch Surg*. 2007;142(7):639-642.
191. Barati M, Alinejad F, Bahar MA, et al. Comparison of WBC, ESR, CRP and PCT serum levels in septic and non-septic burn cases. *Burns*. 2008;34(6):770-774.
192. Ren H, Li Y, Han C, Hu H. Serum procalcitonin as a diagnostic biomarker for sepsis in burned patients: a meta-analysis. *Burns*. 2015;41(3):502-509.
193. Lavrentieva A, Kontou P, Soulountsi V, et al. Implementation of a procalcitonin-guided algorithm for antibiotic therapy in the burn intensive care unit. *Ann Burns Fire Disasters*. 2015;28(3):163-170.

33 Burn Nursing

DEBRA A. BENJAMIN and MARY JACO

Introduction

The bedside nurse caring for the severely burned patient is given more responsibility than in most types of serious illness. It is extremely important that the nurse be an integral part of the team of people caring for the burned patient.[1] This is as important when modern burn care began as it is today. Care begins with the immediate resuscitation of the patient in the emergency department and continues until discharge, through rehabilitation and surgical reconstruction, until the patient is completely recovered and reintegrated into society. During the acute hospitalization, the nurse caring for the burned patient spends more time with the patient than any other member of the burn team. Because of this, especially during the acute hospitalization, the nurse is the best person to notice changes in patient condition and status and must continuously keep various team members updated on changes. Physical changes can include fluid balances, cardiovascular changes, neurological status changes, and tolerance of nutritional feedings. The nurse may also be the best person to act as patient advocate for psychosocial needs such as pain control, anxiety, and the like.

Emergency Needs: Resuscitation and Pulmonary Priorities

One of the first priorities in caring for the burn patient after assuring that the patient's airway is secure is to address cardiovascular needs. After a patient receives a severe burn injury, a leakage of fluids into the area of the burn injury causes swelling and may prevent circulation to that and distal areas. Circumferential burns especially need to be monitored to ensure there that is adequate circulation to the surrounding tissues and areas distal to the burn. Pulses must be checked hourly, and any diminished or absent pulses should be reported to the physician immediately. Another complication is circumferential third-degree burns around the chest and neck, which often cause restrictive defects. The increased amount of edema, combined with decreased chest excursion, may greatly decrease tidal volume. This condition may progress and can become life threatening, in which case chest escharotomy may be necessary to release the constricting eschar. The procedure may be done at the bedside or in the operating room. Equipment includes sterile drapes, scalpel, and electrosurgical unit (to control bleeding).

As fluids shift from the cardiovascular system to the interstitial regions of the burn, there may be a subsequent drop in blood pressure and organ perfusion and a decrease in urine output. It is the responsibility of the nurse, who is always with the patient, to monitor the patient's vital signs and urine output and notify the physician of changes to ensure an adequate fluid and cardiovascular status. An adult should maintain a urine output of 0.5 cc/kg per hour and a child should maintain a urine output of 1.0 cc/kg per hour. Lower urine volume rates may indicate hypovolemia, which can lead to cardiovascular collapse. Resuscitation fluids are to be started as soon as the patient first comes in contact with medical personnel. This is normally accomplished with IV fluids using resuscitation formulas designed for adults or children, or through oral ingestion of fluids.[2] The goal is to provide adequate fluid resuscitation to maintain a normal cardiovascular status, perfusion of organs and tissues, and an adequate urine output.

Inhalation injury continues to be the most serious and life-threatening complication of burn injury. Early diagnosis and treatment greatly impact the outcome of care. Impaired gas exchange is a potential problem for patients who have face and neck burns and/or inhalation injury. Inhalation injury may include carbon monoxide poisoning, upper airway injury (heat injury above the glottis), lower airway injury (chemical injury to lung parenchyma), and restrictive defects (circumferential third-degree burn around the chest). Upper airway edema causes respiratory distress and is the primary concern during the initial 24- to 48-hour postburn phase. Tracheobronchitis, atelectasis, bronchorrhea, pneumonia, and adult respiratory distress syndrome (ARDS) may occur during the acute postburn stage either related or unrelated to inhalation injury.

Nursing care of a patient with inhalation injury begins with a detailed history of the accident. Inhalation injury is suspected when the accident occurred in a closed space. Close observation of the patient and frequent respiratory assessments are made throughout the initial and acute phase postburn. Initially the patient is observed for hoarseness and stridor, which indicate narrowed airways. Emergency equipment is placed at the bedside to facilitate intubation if necessary. Observing an increased frequency of cough, carbonaceous sputum, and increased inability to handle secretions may indicate possible inhalation injury and the potential for impaired gas exchange. Other important observations include respiratory rate, breath sounds, the use of accessory muscles to aid in respiratory effort, nasal flaring, sternal retractions, increased anxiety, and complaint of shortness of breath. Disorientation, obtundation, and coma may be due to significant exposure to smoke toxins such as carbon monoxide or cyanide. These conditions are managed emergently with 100% oxygen.

Bronchoscopy may be done early to diagnose inhalation injury as well as to facilitate airway clearance. Humidified oxygen should be readily available and applied to patients who have evidence of impaired gas exchange (especially

pediatric patients). Aggressive nasotracheal suction may be indicated if the patient has difficulty managing secretions either because of the increased amount of secretions and/or the decreased effectiveness of the cough. In addition, aggressive pulmonary toilet, including turning, coughing, deep breathing, and up and out-of-bed rocking in mother's arms may be done regularly and frequently. Elevation of the head of the bed, unless contraindicated, will also support and possibly improve ventilation. Trends and changes should be correlated with laboratory results and shared with the team.

Intubation and mechanical ventilation may be required to improve gas exchange. Tube placement should be checked and documented frequently and verified daily by X-ray. Securing the endotracheal tube requires a standard technique for stabilization and prevention of pressure necrosis. Adequate humidity is necessary to prevent secretions from drying and causing mucous plugging. Remember to provide pre-/postsuctioning hyperoxygenation. Sterile technique is used when suctioning to prevent infection. Attention to the details of oral hygiene will provide comfort for the patient and may reduce the occurrence of ventilator-associated pneumonia related to colonization in the oral pharynx.[3]

Criteria for extubation depend on the reasons that the tube was inserted initially, but, overall, stable vital signs and hemodynamic parameters will support the plan for extubation. The patient should be awake and alert in order to protect the airway; therefore pain medications may be reduced before extubation. Ventilatory measurements and blood gas analysis should be within normal limits.

Immediately following extubation, the nurse must be alert for signs and symptoms of respiratory distress, administer suction as needed, monitor blood gas measurements, and provide optimal positioning for ventilation, as well as provide reassurance and support to decrease anxiety.

Age, burn size, and the presence of inhalation injury and pneumonia have been identified as major contributors to mortality.[4] Thus vigilant nursing care (frequent nursing assessments, aggressive pulmonary toilet, etc.) combined with anticipating potential problems and being prepared to deal with those problems will add to the team effort and possibly improve patient outcome.

Acute Care of the Burn Wound

The primary goal for burn wound management is to close the wound as soon as possible. Prompt surgical excisions of the eschar and skin grafting have contributed to reduced morbidity and mortality in severely burned patients.[5–7]

Wound care in the burn unit has become a specialized art of burn nursing practice. It can be extremely challenging and complicated, and, for a new nurse, it can be the most difficult and misunderstood part of burn nursing. The complexity exists because of the variety of wound types, each of which requires different interventions in relation to time postburn or time postoperative. Wound assessment and care is a learned skill that develops over time. These skills must be taught by experienced nurses to new burn nurses. Assessment of the burn wound takes place in the hydrotherapy area, the operating room, and at the bedside.

Wounds may consist of eschar, pseudo eschar, skin buds, autografts, donor sites, hypermature granulating tissue, blisters, and exposed bone and tendons. In addition to the many kinds of possible wounds, there are many topical antibacterial agents available for managing wounds. These choices raise many decisions for the team to address. Topical antimicrobial creams and ointments include mafenide acetate, silver nitrate, silver sulfadiazine, petroleum and mineral oil-based antibacterial products, and Mycostatin powder. Wounds may be treated in the open fashion (topicals without dressings) or closed fashion (topicals with dressings or soaks). There are several techniques for applying dressings to different areas of the body that need to be able to withstand exercise, ambulation, and moving around in bed. Biological dressings, such as homografts or heterografts, may be used as temporary wound coverage. Dressings may also be synthetic or biosynthetic or silver-impregnated. Selection is based on the present condition of the wound and the expected outcome.

Secondary goals of wound care are to promote healing and to maintain function of the affected body part. These goals are accomplished by preventing wound infection, treating wound infection, preventing graft loss and tissue necrosis, providing personal hygiene, and maintaining correct positioning and splinting throughout hospitalization. To prevent burn wound infection, the burn nurse must cleanse the wound with soap and water; débride the wound of loose necrotic tissue, crusts, dried blood, and exudate; apply topicals or dressings; and ensure that dressing changes are ordered and done. The nurse must inspect the wound for evidence of infection: cellulitis, odor, increased wound exudate, and/or changes in exudate; changes in wound appearance; and increased pain in the wound. The physician should be notified so that changes in wound care can be made. Cultures and biopsies may be ordered to identify the type and count of organisms, and infected wounds are treated with a specific systemic antibiotic, topical dressing, soak, or a combination of all treatments. The wound is often the source of bloodstream sepsis. The five cardinal signs of sepsis are hyperventilation, thrombocytopenia, hyperglycemia, disorientation, and hypothermia.[8]

Preventing graft loss is another wound care challenge for nursing. Usually the patient returns from the operating room in a position that is maintained for 3 or 4 days. Any interaction with the patient during this time of graft immobilization requires creativity and care in order to prevent shearing of the graft. Postoperative dressings on the thighs and back are protected with Polysporin/polymyxin and a fine-mesh gauze to prevent soiling by feces and to minimize cleanup. The dressings are continuously monitored for increased drainage and odor, which would indicate possible wound infection. If infection is suspected, then the postoperative dressings may be removed early for a closer inspection of the wound.

Donor sites will also require additional care to prevent infection. Of course, the postoperative care depends on the coverage of the donor site. If the donor site is covered with fine-mesh gauze, initial care is to ensure homeostasis and adherence of the gauze to the wound. Therefore the postop pressure dressing remains intact for 6–12 hours and is then removed. The focus of managing the donor site is to keep

the wound dry. If grafts/donor sites are on the back or backs of the legs, the patient is placed in a Clinitron bed for 4–5 days to promote drying. If the donor site remains wet, additional drying techniques (hair dryers, external heaters) may be used periodically during the day.[9]

If the donor site is covered with a synthetic or biological dressing, the same principles apply. Basically, a pressure dressing is applied to ensure adherence to the wound for a short period of time postoperatively and then the wound is exposed to the air to support drying. A bed cradle is used to keep bed linen from contacting wounds. The location of the graft, donor site, and eschar may all be on the same extremity, which again requires creativity to accomplish all three interventions of care.

Nurses must always be vigilant when it comes to skin assessment; early detection and prevention is the key ingredient in preventing pressure ulcers in major burn patients. Pressure ulcers are no longer treated as a burn wound. There is evidence to support nursing practices in the prevention of pressure ulcers in burn patients. Burn patients have many risk factors that predispose them to developing pressure ulcers. Initially hypovolemic shock with blood flow shunted away from the skin to preserve vital organ function is a factor. Additional injuries may increase the risk for pressure ulcers, such as inhalation injury, which may require intubation and use of paralytic agents to manage the airway. Fluid resuscitation may contribute to massive edema in both burned and unburned areas. The edema is maximized at about 2–3 days postburn, which also decreases the blood flow to the skin and adds weight to all parts of the body.

Maintaining systemic hydration can continue to be a problem long after the patient has received adequate resuscitation for burn shock. Continued fluid therapy to replace fluid loss through the burn wound is essential. If systemic hydration is not maintained, even normal skin may be at risk. To complicate this situation, the quantity of fluid lost through the burn wound may increase the moisture on normal skin adjacent to the burn wound. This moisture may cause the normal skin to break down and predisposes the skin to further compromise.

All patients, except those with skin grafts postoperatively, will benefit from a bath or shower. Large acute burns are placed on a shower cart and the wounds are gently showered with warm water. The overhead heater is turned on, and the room temperature is maintained at 85°F (29°C) or higher. Large acute burns are not immersed in a tub of water to prevent autocontamination and electrolyte imbalance.[10] Hydrotherapy can be used for careful assessment of wounds, as well as for personal hygiene such as shampooing, mouth care, face care, and perineal care.

Hydrotherapy is an excellent opportunity for the nurse to teach the patient and family about wound care and dressing application. As the patient gets closer to discharge, families are required to do more of the care. The trend for earlier release from the hospital poses additional challenges for nursing since it reduces the time available to prepare the patient for discharge. The better the patient and family are educated, the better the outcome. Early involvement with patient and family helps identify potential obstacles at discharge and facilitates care coordination in the discharge process.

Surgical Care

The perioperative setting combines a number of professionals with different levels of experience and expertise, all directed toward patient care. Each team member has a specialized role: the surgeon provides surgical intervention, the surgical technician supports the surgeon, the anesthesiologist or certified registered nurse anesthetist (CRNA) provides life support functions, and the circulating nurse's role is to provide safe patient care by ensuring that all team members adhere to professional standards and guidelines. The perioperative nurse is a professional registered nurse who provides nursing care to patients in the preoperative, intraoperative, and postoperative phases of surgery. Perioperative burn nursing care can be described as hot, intense, and demanding. Burn nursing, in fact, represents one of the profession's most challenging specialties.

Once surgery is completed, perioperative nurses provide postoperative care and assessment. This phase of nursing care can also be challenging for the nurse caring for the patient during the immediate postoperative period. Nursing care and plan for care depend on many factors: amount of blood loss, surgical time, and the site(s) and extent of excision and grafting. The postanesthesia nurse caring for the burn patient must be knowledgeable about the medications and procedures used during surgery to provide appropriate safe nursing care.

Many burn-injured patients will make repeated trips to the operating room for surgical excision of the burn wound and grafting, with grafts taken from unburned areas. These procedures may require the patient to be anesthetized for long periods of time. Patients are at risk for pressure ulcers in the operating room; thus proper positioning and the use of pressure-reducing devices is essential to reduce the risk of pressure ulcer formation. During these operative procedures the patient may lose large quantities of blood, resulting in decreased tissue perfusion, and the patient may develop shock. Vasopressors and fluid resuscitation are the usual treatments for shock. Low-flow states and the use of vasopressors may also result in decreased tissue perfusion and increased risk of pressure ulcer formation.

Postsurgery, the patient or surgical area is often immobilized with large bulky dressings and splints to protect the grafts. These dressings need to be applied with enough pressure to stop bleeding from the grafted wound and the donor site. But if the dressings are applied too tightly, or if edema develops after dressing application, this may cause increased pressure on the skin.

To prevent wound bed desiccation, antimicrobial ointments or soaks are used to maintain moisture in the grafted wound and to aid in decreasing wound colonization with bacteria. This moisture, when in contact with adjacent normal skin, may increase the risk of tissue breakdown.

Inadequate nutrition prior to or after the burn injury is potentially a significant problem. The hypermetabolic response in the burn-injured patient leads to protein malnutrition if caloric intake is compromised. To reduce the risks of systemic infection and to promote wound healing, enteral hyperalimentation is most frequently used and the patient is fed by nasogastric or nasojejunal tubes.

In summary, burn patients are among the high-risk populations for pressure ulcer development. The physiology of the burn injury combined with many of the therapies and treatments used during hospitalization impacts the burn patient's risk for pressure ulcers.

Nutrition and Metabolic Changes

Hypermetabolism, or metabolic stress, is the direct response to a burn injury. The amount of stress increases proportionally to the extent of the injury and strongly influences a patient's nutritional requirements. This response can magnify the normal metabolic rate by 200%. Malnutrition, starvation, and delayed wound healing will result if calories are not provided consistently to meet nutritional requirements. Children require more calorie and protein replacement than do adults because they have additional nutritional demands to support growth and development.

Managing nutritional intake and monitoring output are among nursing's primary responsibilities. An accurate record of intake and output is critical to patient care because potential problems can be detected early and alternate options of care can be individualized to help the patient achieve his or her goals. Accurate weights, daily or as ordered, are also important. Remember to record whether dressings, splints, or linens are included in the weight. Obviously, including additional elements does not reflect an accurate weight, but trends in weight either up or down may be identified and may be helpful in the overall management of the patient.

Typically when patients cannot consume enough calories by mouth, then enteral feedings are begun. Sometimes enteral feedings are started before the patient is given the option of eating because the amount of calories is so great and/or the condition of the patient is unstable. Parenteral nutrition is used when enteral nutrition fails to deliver adequate nutrition. The goal is to provide adequate nutrients, calories, and protein. A nasogastric tube is inserted initially and used to decompress the stomach until bowel sounds return. Then tube feedings are started at a very low volume per hour to act as a buffer against ulcer formation. The nasogastric tube allows for checking hourly gastric residuals, gastric pH, and guaiac. If the gastric pH falls below 5, or if the guaiac is positive, Maalox and Amphojel are given every 2 hours, alternately every hour.

Aspiration of stomach contents is a potential complication and always a concern. Gastric residuals are checked before suctioning to prevent the patient from vomiting and possibly causing aspiration. Another precaution is to keep the head of the bed elevated. A Dobbhoff tube is also inserted initially, and feedings are begun as soon as 6 hours postburn. The rate starts slowly and is advanced as tolerated to meet the calculated amount of nutritional replacement. Tube feedings continue until the patient can take the required amount of calories by mouth.

Another potential problem with both tubes is dislocation; therefore it is important to check placement periodically throughout the day. When gastric residuals start climbing, it may be because the Dobbhoff tube has slipped into the stomach or the patient is septic. Tube feedings may become contaminated and become a source of infection for the patient, leading to significant morbidity. Routine procedures should be established to prevent this occurrence, and care should include sterilization of the blender and limiting to 4 hours the amount of time that tube feedings can be hung at the bedside. The tubing and container should be changed every 4 hours.

Sometimes when patients are encouraged to begin taking food by mouth, tube feedings may be discontinued during the day and be used only at night. Not scheduling painful activities around meal times and providing frequent mouth care will also contribute to improved oral intake.

Regular bowel patterns are expected in the postburn period. Patients are given many medications during hospitalization that may contribute to either diarrhea or constipation. Patients are expected to have at least one bowel movement per day. If not, then a bowel evacuation regimen should be considered. If diarrhea is the problem and the volume exceeds 1500 mL/day, then bulking agents and/or antidiarrhea medication may be useful to promote routine bowel elimination.

The importance of monitoring and documenting the many parameters of intake and output cannot be overemphasized. Established clinical protocols and guidelines facilitate the implementation and evaluation of the nutritional program.

Other strategies to support the hypermetabolic phenomenon of the burn patient are to keep the room temperature higher than 85°F (29°C) and to keep the room door closed to prevent drafts. Also frequent rest periods must be provided during the day. Nursing generally makes the schedule of activities for the day, so including frequent rest periods is just as important as anything else that needs to be done during the day. Adequate sleep during the night is also very important: often this makes the difference between a good day and a bad day. A quiet comfortable environment without sensory overload (lights and noise) is essential for the patient to sleep.

Nurses are the grand communicators of progress and/or problems. Nurses work closely with dietitians, physicians, patients, and families to ensure that optimal metabolic and nutritional support is achieved during the postburn period.

Pain and Anxiety Assessment and Management

Throughout the acute phase of care the burn patient is predisposed to pain and anxiety. Pain in the burn wound and fear of pain cause patients to try not to move. Careful titration of anxiolytics and narcotics can result in an alert patient who is relatively pain-free, but this requires intense attention to detail from the nursing staff. The expected outcome for pain and anxiety management is for the patient to achieve a balance between successful participation in activities of daily living and therapies and being comfortable enough to rest and sleep as needed. The ultimate goal is for the patient to be satisfied with the pain management plan as it is implemented. Assessment of pain and anxiety provides a baseline for evaluation of pain and anxiety relief measures. Pain and anxiety scales are essential to quantify painful episodes and to evaluate effectiveness of medication. Knowing when and how much to intervene is guided

by knowing the baseline pain and anxiety rating for the individual. Patients and families should be given information upon admission on how to use the assessment scales and to identify an acceptable level of pain and anxiety.

Intravenous administration of opioids and anxiolytic agents is essential to manage pain and anxiety during the initial stage of injury due to the altered absorption and circulation volume following a major burn injury. A patient-controlled analgesia (PCA) pump is useful for children older than 5 years and adults. It is important to manage background pain as well as procedural pain, for which medication should be given 15–30 minutes prior to a painful procedure. Nursing-driven protocols for sedation and analgesia have been developed for the burn ICU and were reported to be effective in controlling pain. Nurses positively supported the introduction of the protocol but junior nurses seemed to be more uncomfortable with its use than more senior nurses.[11]

Constipation is frequently a complication of pain management; thus a bowel management program should be instituted at the same time.

Relaxation, guided imagery, music therapy, hypnosis, and therapeutic touch are adjunct techniques to complement analgesia and reduce anxiety.[12] Virtual reality is a relatively new technique used for pain control and has been quite successful.[13] It involves a computer software program with which the patient actively interacts, thereby transferring the patient's attention away from the painful event. Emotional support and patient and family education decrease fear and anxiety, thereby enhancing the pain management plan.[14]

Patient and Family Education

In order for nurses to be competent teachers, they must be competent practitioners with solid theoretical foundations. Continuing education to maintain competency is key for clinical staff because of their role as educators of patients and families. Reinforcement of the educational process (assess, plan, implement, evaluate, and document), characteristics of patient populations, updates on educational strategies, age-appropriate interventions, and ways to evaluate learning are topics that will sharpen educator competency.

Discharge planning and education begins upon admission. It begins with a thorough assessment of the patient's life prior to the injury. Identifying knowledge deficits and barriers to education, prioritizing strategies for education, and providing supplemental educational handouts and/or classes, as well as developing a plan for evaluating the effectiveness of the teaching opportunity are integral parts of the educational process.

Assessment provides essential information for planning an educational program to meet the specific individual needs of each patient and family. It is also done periodically during different stages of the educational process to determine if the plan remains valid or changes need to be made.

The assessment findings become part of the educational plan in that the plan is tailored to meet the needs and concerns of the patient and family. The plan includes the learning objectives, strategies for education, and learning materials. All of these parts of the educational goal are agreed upon by the patient, family, and educator.

Implementation of the plan is the next step, followed by a thorough evaluation of the effectiveness of learning and/or determination of whether the educational goal is being accomplished. Alterations in the original plan may be needed at any time during the educational process depending on unforeseen situations or unanticipated changes in conditions.

The benefits are many. This process ensures communication of educational topics among the team members, provides a historical account of education, and documents progress and/or changes in the plan. It benefits the patient and family by making them competent in their role as care provider when discharged from the hospital. Knowledge allays anxiety about the unknown and aids in compliance with recommended care after discharge, thus improving the long-term outcomes.[15] Patients and families can be empowered to become active participants in the burn care team early in the postburn course through a well-structured educational plan.

Rehabilitation of the Burn Patient

A major burn is one of the most devastating injuries, both physically and emotionally, known to man. After weeks of being an invalid, undergoing repeated surgeries, fighting infection, having the body ravaged by the metabolic consequences of injury, and enduring pain and anxiety, the patient now faces months of continued physical therapy to regain the level of function that he or she had known before the injury. Most patients who have sustained a major burn will continue to have a higher than normal metabolic rate for more than a year and thus find that they do not have the stamina to easily regain their lifestyle.[16] In addition to the catabolic effects of burn injury, being hospitalized and in bed with minimal activity for many weeks or months causes loss of muscle and bone weakening. Children are more prone to fractures.[17] During the rehabilitation phase these patients must continue to exercise to prevent contractures, but they may not have the physical strength or endurance necessary to actively participate in such programs. In addition, these patients frequently become depressed as they face an altered self-image and a forced physical dependence on others. They fear that they will never look normal and that they will not be able to return to a normal life. For adults, the concerns of whether they will be able to return to work or have to change occupation is also a factor. What is the role of the nurse at this phase of treatment? Although nurses have been very involved in the care of the patient in the early phases of care, the role of the nurse changes at this stage. The transition from the hospital to home care is often difficult for both the patient and family. It is important prior to discharge that the patient and family be educated in the care of open wounds, healed skin, itching, pain, and anxiety before they leave the hospital. They also need information about the normal depression that occurs posthospitalization and resources in their home community to which they have access. This is where the nurse case manager becomes an integral part of the patient care team. Hospital-based nurse case managers can begin to work with the

patient and family soon after admission to assess the patient's future needs and coordinate these with outside agencies to ensure that the transition goes smoothly. Often case managers from workmen's compensation carriers or health maintenance organizations (HMOs) are involved during the early phase as well. Coordination of activities between case managers is important to provide seamless care. With children, it is important for the nurse case manager to begin working with the school nurse or community health nurses to provide for this seamless transition in care.

Although the rehabilitation therapist plays an important role in providing referrals to community therapists and psychologists, and social workers frequently make referrals to community mental health providers, the nurse case manager should be involved in the overall coordination of these and other services to foster a unified approach. The free flow of communication among all providers is necessary for optimal rehabilitation of the patient.

WORK-HARDENING PROGRAMS FOR ADULTS

For adult patients, work-hardening programs have been shown to more rapidly return the patient to his or her optimum level of functioning.[18] These programs may be available through community rehabilitation facilities, vocational rehabilitation agencies, HMOs, hospitals, or health centers with cardiac rehabilitation programs or through workmen's compensation carriers. The major concern for the nurse case manager and the burn team is early identification of which patients need these programs and at what point the patient will benefit most from such intensive programs.

Assessment

Burn patients, like those recovering from coronary heart disease and surgery, find themselves deconditioned. Even 3 weeks of bedrest in a healthy subject can result in a 25% decrease in maximal oxygen consumption. Thus burn patients who are hospitalized for 2 or more weeks may need to be considered for such programs. Burn patients should be first assessed for risk factors associated with coronary heart disease. Such risk factors include:

- age and sex
- elevated blood lipids
- hypertension
- cigarette smoking
- physical inactivity
- obesity
- diabetes mellitus
- diet
- heredity
- personality and behavior patterns
- high uric acid levels
- pulmonary function abnormalities
- ethnic race
- electrocardiographic abnormalities during rest and exercise
- tension and stress

Cardiac stress testing is usually recommended prior to beginning an exercise program. If the patient has several risk factors, the exercise program can be tailored to fit the patient's needs.[19]

Planning

What is available? Often the major issue is what is available and who will pay for this care. When an adult is injured on the job, this is often arranged and paid for by the compensation carrier since they have a vested interest in returning the patient to work as soon as possible.

Implementation

Once the details are worked out, the next hurdle is to get buy-in from the patient and family. Some programs require the patient to be in a facility some distance from the home; this may present issues for both the patient and family. Similarly if the program is in the local community, daily visits to the rehabilitation facility may pose transportation issues, especially if the patient is unable to transport him- or herself. These details can usually be worked out with cooperation of all caregivers and the family involved. Motivation and determination are often the most difficult factors to overcome. This is especially true if the patient is suffering from depression. The nurse case manager can be very instrumental in rallying the burn team and caregivers in the community to help the patient and family to see this as a way to return the patient to more normal function.

Evaluation

Success in such programs requires that all involved have the same goals and that these goals result in measurable outcomes. The goal of such programs is not only to increase the patient's tolerance to exercise but also to improve his or her psychological and social functioning and to return the patient to work or to the same level of functioning as before the injury.

EXTENSIVE EXERCISE IN CHILDREN

Children may suffer from the same deconditioning as adults, especially if they have suffered total body surface area (TBSA) burns of 40% or greater. Cucuzzo et al. have shown that children with greater than 40% TBSA burns have bone demineralization.[20] This deconditioning can lead to low energy, decreased motivation, and depression. This can make it difficult for the child to return to school, where he or she must be alert and attentive for 6–8 hours a day. Younger children learn much about their environment and world through play and various activities. Limitations in movement from burn scars or low energy may decrease their rate of learning. Also, children learn much about socialization through their participation in sports activities. Physical limitations in sports may provide a type of isolation from their normal group of peers. Treatment of these patients with long-term anabolic agents and intensive exercise programs to improve strength and endurance can return the patient's metabolic status to normal and help with the patient's reintegration back into his or her normal preburn activities more quickly.

Assessment

Children and their family situation should be evaluated to determine what exercise program is best for their burn

injury and their family situation. Generally, children 7 years of age and older can participate in an intensive exercise program. This is an estimated age based on the child's size (ability to use exercise equipment that is manufactured for adults) and maturity (ability to follow direction so that a safe environment can be provided). For larger burns (60% TBSA and greater), a 12-week exercise program is prescribed. For smaller burns, a shorter period of time of about 6 weeks may be sufficient. The best time to start such a program depends on the patient's family situation. The program can start immediately after discharge or can be delayed for a few months to allow the family to return home and prepare for the next phase of intensive exercise rehabilitation care. As with adults, individualized programs that consider the pediatric patient's current general state of health are necessary. Because the child is under the care of and dependent on the parent, it is important for the parent or a responsible adult member of the family to be involved. This may be a significant factor in when the patient is able to start such a program. For children younger than 7 years of age, more creative interactive play and exercise programs have been developed utilizing music therapy as a stimulus for children to participate in the exercise program. These activities can include riding tricycles, playing sports games, obstacle courses, racing, dancing, stretching, and any activity that can be made into a game that promotes strength and endurance. The use of activities set to music can increase stamina, actively stretch scar tissue, and increase joint mobility.

Planning

Although cardiac rehabilitation programs and the like may be readily available in most major towns and cities in this country, often they do not admit children. Children's hospitals often have rehabilitation units or outpatient programs for children that can offer programs similar to those in adult cardiac programs. Children's hospitals are usually found in major cities; thus these programs may not be as accessible as programs for adults. In some communities, school-aged children may be able to obtain help within the school sport programs, especially if they have qualified athletic trainers. Children aged 4–6 may have more difficulty finding programs outside of children's hospitals. Some early childhood intervention and pre-kindergarten programs may be available for younger children.

Another issue is to determine who pays for this care. Unlike the adult with insurance or workman's compensation insurance, children are often without funding for this rehabilitative care. State programs for children with special needs (e.g., Title V programs) are one avenue to explore. Other sources of funding may come from private or public charities, school-mandated programs, or vocational rehabilitation programs for the older teenager.

Implementation

Motivating the child and parent can be a major task. Often the parent and child have spent weeks or months away from home during the acute phase of care. If there are other children in the home or if the parent normally works outside the home, the parent may not feel that he or she can be away from home an additional 2–3 months. The child may also not want to leave the safety of the home environment. Thus motivating the child and parent is often difficult. Helping the parent see this as a valuable program will require the whole burn team to work together with the patient and family. Alternatives may be available for older children within the community by utilizing local gyms or fitness centers. Communicating a prescription for exercise to the local facility and maintaining regular follow-up of progress can be as effective as having the patient remain within the larger hospital system.

Evaluation

The outcome of these programs for the child can be measured in increased exercise tolerance and improved psychological and social adjustment. A major function of these programs is to convince the child and parent that the patient is a normal child and can succeed mentally and physically. If the child returns home and can keep up with his or her peers, this alone improves the child's self-esteem.

Reconstructive Care

ASSESSMENT

The role of the nurse in the reconstructive care phase may include clinic visit assessments, physical care associated with surgical procedures, education related to reconstructive care and expectations, and care coordination, including social and financial support. The nursing role of patient advocate may be the most important for the patient and family. Due to a lack of knowledge or understanding, patients and families may have unrealistic expectations for reconstructive surgery. They may have the hope that plastic surgery can "fix" the burn scars and make the patient look the same as before the burn. The nurse's role in the outpatient clinic or physician's office is to listen to the patient and family and to understand their hopes and expectations. The nurse can take this opportunity to provide education about the expected course of burn care and realistic expectations for scars left from the burn injury. Often when the surgeon discusses what should or could be done to improve the patient's appearance or function, the patient and family member are reticent to ask questions or to describe what they want. Patients' priorities are often different from the surgeons, and this leads to dissatisfaction. This is when the nurse should help the patient ask questions or voice concerns.

PLANNING

The timing of reconstructive surgeries often varies between surgeons. Many surgeons prefer to wait until the scar has matured to begin reconstructive surgery, but occasionally surgery will be attempted if the scar tissue is interfering with function. This is especially true where scar tissue may cause bone deformity if left until it has matured. In children, some reconstructive procedures are best postponed until the child has matured. Surgery is often better accepted by the child at the beginning of high school or just prior to starting further education. The nurse case manager can be instrumental in helping the family find the funding and resources to provide reconstructive surgery for the patient.

If the patient is working or in school, planning the procedures should accommodate the patient's school or work schedule as much as possible. For children, funding through Services for Children with Special Needs may be available. Working with insurance companies and HMOs can be complicated if the surgery is presented as cosmetic rather than corrective surgery.

IMPLEMENTATION

Preparing the patient for surgery is the responsibility of the nurse and physician. Providing the patient with realistic expectations is often difficult, but educating the patient about the surgical procedure and expected timelines for healing and utilizing photographs of similar burn wounds improves understanding. Many times, immediately after the surgery, the area will look worse and the patient may feel dissatisfied and depressed. Preoperative preparation of the patient and family may allay some of these issues. Surgery itself is frightening enough for the patient and family. In children as well as adults, this can be especially frightening because it may bring up memories of their original burn injury, hospitalization, and the pain associated with it. Postoperatively the nurse's role is to teach the patient and family how to care for the wound to prevent infection, promote healing, and prevent further scarring. Throughout the reconstructive and rehabilitation phase the nurse is supportive of the patient and family as the scar matures. The nurse's role during this time is one of education, support, and encouraging the patient to continue with exercise, splints, and pressure garments, as ordered.

EVALUATION

Whose body is it anyway! A line from a famous play actually sums up the evaluative process for reconstructive surgery. As professionals, we may see great improvement in the patient's condition after surgery. But if the patient is not satisfied with his or her appearance, little has been gained by the surgery. This is the reason that the patient and family must have realistic expectations prior to surgery. On the other hand, the patient may be perfectly happy with his or her scars and how they look and not desire any surgery. And although a surgeon may have a great deal to offer with reconstructive surgery, the patient's decision must be respected.

Recovery and Social Reintegration

Nursing covers the spectrum of providing care from health to illness and hopefully back to wellness, including the physical, psychosocial, and spiritual realms, and the same concept applies to burn nursing. Nursing care must continue past the physical healing of the burn wound. Complete healing must also include the psychosocial and spiritual domains of the patient. Helping the patient to accept his or her "new me" is paramount to recovery. After any traumatic event in an individual's life, the person often claims to be different or changed, whether physically or psychologically. Often burn scars cause patients to avoid public situations where people may gaze at them for looking different. Support should be provided, and the patient should be encouraged to realize that he should not be defined by his physical body. Who they are is defined by what is in their minds, hearts, and souls. Through family support, professional counseling, and/or peer support the burn survivor can be taught to accept him- or herself and set a path for life. Some choose to cover their scars, some accept them as they are, and some wear their scars as badges of honor for the personal war they have triumphed over. Training is available for those who are uncomfortable with being out in public settings. Continued support from the burn team, the family, and support groups can help with the reintegration process.

Conclusion

Burn nursing is a unique field of practice. In the United States, there are currently only 127 burn centers, and only 67 of those are verified burn centers. Hospital burn units are often much different from other care units in a hospital because they frequently house a wide range of patients, young to old, with minor burns to critically ill patients with major burns, to patients receiving rehabilitation or reconstructive care. It can be difficult for the nurse to change patient assignments from one day to the next considering the wide range of care needed and to maintain skills in all areas. Nursing shortages can be common among burn units due to the general shortage of nurses and the challenging area in which they work.[21] It is important that nurses are made an active part of the burn care team to utilize the special insights that they have concerning the patient's physical condition and the psychosocial needs of the patient and family. Utilizing a nursing workload measurement for burn care may help provide information on staffing needs to ensure adequate staffing is made available for the burn unit. Assessing patients' daily wound care needs and medication/IV fluid needs can be utilized to assess nonintensive or intensive needs and then rank patients into categories by the levels of care demanded.[22] Finally it is important to give patient care nurses the opportunity to become involved in other areas of burn care. A great way for nursing to become involved with the burn team is for a nurse to become involved in better understanding an issue or in improving burn care. This can be done through research activities or through quality improvement activities. Nurses can often identify areas for improvement but may not have the resources to encourage change. Providing education opportunities to nurses can create a culture for change and improvement. Education can include in-services, publications,[23] and mentoring to support the nurse who is interested in this area. Research and quality improvement initiatives can make changes and improvements in care, including improving nutritional intake, decreasing pressure sores, decreasing infections, decreasing pain, and improving patient satisfaction. The burn nurse is an invaluable member of the burn care team. Her unique insights offer important information to the successful outcome of the burn patient. Active participation in the

physical care of the burn patient, attending to the psychosocial needs of the patient and family, and continually observing for ways to improve care are paramount to the ultimate success of the burn team.

Complete references available online at www.expertconsult.inkling.com

Further Reading

Carrougher G. *Burn Care and Therapy*. St. Louis, MO: Mosby; 1998.

ISBI Practice Guidelines Committee. ISBI practice guidelines for burn care. *Burns*. 2016;42:953-1021.

Gordon MD, Gottschlich M, Helvig EL, et al. Review of evidence-based practice for the prevention of pressure sores in burn patients. *J Burn Care Rehabil*. 2004;25:388-410.

References

1. Artz C, Moncrief J. Nursing care and psychological considerations. In: *The Treatment of Burns*. Philadelphia: W.B. Saunders; 1969:271-287.
2. ISBI Practice Guidelines Committee. ISBI practice guidelines for burn care. *Burns*. 2016;42:953-1021.
3. Hixon S, Sole M, Kir T. Nursing strategies to prevent ventilator associated pneumonia. *AACN Clin Issues*. 1998;9(1):1-15.
4. Shirani KZ, Pruitt BA Jr, Mason AD. The influence of inhalation injury and pneumonia on burn mortality. *Ann Surg*. 1987;205:82-87.
5. Tompkins RG, Burke JF, Schoenfield DA, et al. Prompt eschar excision: a treatment system contributing to reduced burn mortality. *Ann Surg*. 1986;204:272-281.
6. Herndon DN, Gore D, Cole M, et al. Determinants of mortality in pediatric patients with greater than 70% full thickness total body surface areas of thermal injury treated by early total excision and grafting. *J Trauma*. 1987;27:208-212.
7. Tompkins RG, Remensnyder JP, Burke JF, et al. Significant reductions in mortality for children with burn injuries through the use of prompt eschar excision. *Ann Surg*. 1988;208:577-585.
8. Ramzy PI. Infections in burns. In: Wolf SE, Herndon DN, eds. *Burn Care*. Austin, TX: Landes Bioscience; 1999:73-80.
9. Dziewulski P, Barret J. Assessment, operative planning and surgery for burn wound closure. In: Wolf SE, Herndon DN, eds. *Burn Care*. Austin, TX: Landes Bioscience; 1999:19-51.
10. Carrougher G, Gretchen G. Burn wound assessment and topical treatment. In: Carrougher G, ed. *Burn Care and Therapy*. St. Louis: Mosby; 1998:133-165.
11. Fry C, Edelman L, Phil M, Cochran A. Response to a nursing driven protocol for sedation and analgia in a burn-trauma ICU. *J Burn Care Res*. 2009;3(1):112-118.
12. Patterson DR. Non-opioid based approaches to burn pain. *J Burn Care Rehabil*. 1995;16:372-376.
13. Gonzalez M, Hoffman H, Pena R, et al. Virtual reality distraction for children with large severe burns during repeated burn wound debridement in the ICU. *J Burn Care Res Supp*. 2017;38(2):223.
14. Marvin JN. Pain assessment versus measurement. *J Burn Care Rehabil*. 1995;16:348-357.
15. Falvo DR, Donna R. *Effective Patient Education*. Gaithersburg, MD: Aspen; 1994.
16. Hart DW, Herndon DN, Klein G, et al. Attenuation of posttraumatic muscle catabolism and osteopenia by long-term growth hormone. *Ann Surg*. 2001;233:827-834.
17. Klein GL Bone loss in children following severe burns: increase risk for fractures in osteoporosis. Osteoporosis Update 1999. Xian, PR, China. *Proceedings of the Third International Congress on Osteoporosis*. 1999:63–68.
18. Zeller J, Strum G, Cruse C. Patients with burns are successful in work hardening programs. *J Burn Care Rehabil*. 1993;14:189-196.
19. Adams RB, Tribble GC, Tafel AC, et al. Cardiovascular rehabilitation of patients with burns. *J Burn Care Rehabil*. 1990;11:246-255.
20. Cucuzzo N, Ferrando A, Herndon D. The effects of exercise programming vs traditional outpatient therapy in the rehabilitation of severely burned children. *J Burn Care Rehabil*. 2001;22:214-220.
21. Yurko L, Coffee T, Yowler C. The burn nursing shortage: a burn center survey. *J Burn Care Res*. 2004;25(2):216-218.
22. De Jong A, Leeman J, Middelkoop E. Development of a nursing workload measurement instrument in burn care. *Burns*. 2009;35:942-948.
23. Olszewski A, Yanes A, Stafford J, et al. Development and implementation of an innovative burn nursing handbook for quality improvement. *J Burn Care Res*. 2015;37(1):20-24.

34 Care of the Burned Pregnant Patient

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Introduction

Approximately 8% of women experience trauma during their pregnancies.[1] Trauma in pregnancy is the most common cause of nonobstetric-related death;[2] more generally, trauma is the leading cause of death in the age group under 40 in the United States.[3–5] Women in their reproductive years are the population at the greatest risk of trauma.[3] While it is rare to see a pregnant woman in the burn ICU in industrialized nations, burn trauma is a great risk to pregnant women in developing countries. Correspondingly, recent literature regarding the care of burned pregnant patients more commonly comes from journals in these developing countries[6] and consists mainly of small studies and case reports. Burn injury during pregnancy tends to happen in the home environment.[7] In developing countries, this may be in part attributable to the large proportion of women who attempt suicide via self-immolation.[8]

Due to the particular paper paucity pertaining to pregnant patients, there is no great consensus on the population of burned pregnant women, size of burn disease burden in the population, or mortality of mother and fetus.[6,9–14] However, what does exist in the literature reveals that the maternal mortality rate exceeds 50% and has been reported at 100% when total body surface area (TBSA) burned exceeds 40–60%.[10,12] This statistic remains unchanged from Rode's study in 1990 showing that when TBSA was greater than 50%, maternal survival "was unlikely."[13] These appalling mortality data contrast a contemporaneous study by Herndon et al. that determined the lethal burn size for 50% (LD50) of pediatric patients reached 98% TBSA burned.[15] Despite progress made in survival rates of other burned populations, pregnant burned victims suffer the same mortality rates as in the 1960s. In a recent study, 60% of burned pregnant burned patients died, with an overall 50% mortality rate of the fetus.[16] As could be predicted, fetal survival greatly depends on maternal survival, although there is a high spontaneous labor rate among burned pregnant patients. While pregnancy does not greatly influence treatment protocols, it might factor into maternal outcome following thermal insult, given the enormously high mortality rate of pregnant women with severe burn injury when compared to the mortality rates of nonpregnant women and men with comparable burn wound sizes. However, more study is obviously necessary.

Mortality Factors

A consensus in literature exists: burn size correlates most significantly with the mortality of both mother and fetus. Large burn size is the single most predictive indicator for mortality.[10,13,17–21] The odds of mortality of the mother rise by 1.08 per percentage of TBSA burned ($P < 0.0001$).[22] Furthermore, there is an association between mortality, TBSA burned, and the incidence of intentional burns. Women who attempt suicide via self-immolation had greater TBSA and resultantly higher mortality rates,[17] especially those with greater than 50% TBSA burned. Rode reported a direct relationship between the size of burn and the frequency rates of spontaneous abortion and premature delivery.[13] Rezavand et al. demonstrated that, in every trimester, maternal TBSA burned positively correlated with fetal death as well as maternal demise.[12] Agarwal found fetal loss occurred at a higher rate than maternal death even at greater maternal TBSA burned.[17]

The second strongest predictor of mortality of both mother and fetus is smoke inhalation,[10] the treatment of which remains controversial. Maternal fatalities and mothers with fetal losses were more common in those with concurrent inhalation injuries.[10] The resultant hypoxia strongly correlates with maternal and fetal death.[23] Closed and structural fires emit smoke potentially imbued with cyanide (CN) and carbon monoxide (CO) gases. Upon inhalation, CO and CN demonstrate synergistic effects; furthermore, they concentrate at higher levels in the fetus than the mother[24] as fetal hemoglobin binds CO and CN more avidly than maternal.[5] As such, providers must treat two patients with awareness of potential effects of CO and CN poisoning on both mother and child.[24] Facial burns, large burns, and self-inflicted, intentional burns all strongly associate with inhalation injury. Significant thermal injury in the pregnant patient population can have not only direct but indirect effects on the pulmonary system. Unique to the pregnant burn patient, vital lung capacity decreases while mucosal edema,[25] oxygen consumption, and minute ventilation increase.[26] As with the severely burned nonpregnant patient, should a pregnant burn victim be suspected of suffering from inhalation injury, emergent intubation ought to be instituted. Given the known physiologic changes of pregnancy, which are compounded by burn edema, early intubation in the severely burned pregnant patient should be strongly considered. Hydroxycobalamin, the cyanide antidote[27] recommended in Chapter 32, is a pregnancy

category C drug and should only be used if the benefits outweigh the risks because cyanide crosses the placenta and will poison the fetus to a greater extent than the mother.[24,28]

Gestational age was also a factor reported in several studies.[16,17] Argawal found fetal survival in the third trimester correlated less to maternal survival but rather strongly to gestational age.[17] Liu determined gestational age-specific risk of birth to be greater among the population of injured mothers than noninjured in each gestational week until week 38, irrespective of medical condition.[29] Gestational age is not the sole criteria for neonatologists and obstetricians in determining viability of a fetus. The fetal weight benchmark of 500 g has been adopted, which is the lower size limit at which intubation is feasible.[30,31] Given the potentiality of obstetric intervention, it is imperative to precisely ascertain the gestational age and weight of the fetus via fetal ultrasound and menstrual and sexual patient history data early in the management of acute burns.

Hypovolemic shock[7] and sepsis[32] have also been found to be complications resulting in maternal and fetal death.[22] Recurrent septicemia is a major challenge in the management of a severely burned obstetric patient. Intraabdominal hypertension and abdominal compartment syndrome develop in most severely burned patients within 48 hours of injury.[33] Intraabdominal hypertension is present when intraabdominal pressure measures in excess of 12 mm Hg, and abdominal compartment syndrome exists when intraabdominal pressure is greater than 20 mm Hg, particularly if additional organs display dysfunction.[34] Pregnancy induces physiologic changes in all major maternal organ systems, mimicking early perturbations seen in multisystem organ dysfunction (MOD).[35] All these complications potentially lead to MOD, compounding the existing state present in the pregnant population and further jeopardizing severely burned obstetric patients.

Fetal Viability

Managing obstetrical complications provides an additional challenge to the burn team. Second to death of the mother, placental abruption is the most common cause of the death of the fetus following trauma.[3] Due to the intense kinetics undergone by a pregnant patient postburn, the fetus often spontaneously delivers.[12] In layman's terms, this is a miscarriage. Consistently studies show that fetal mortality rates were highest during the first trimester in the setting of major burns.[16,17] However, with aggressive fetal monitoring, appropriate obstetrical intervention can preserve the life of the fetus earlier in the course of pregnancy. Studies indicate this approach starts approximately in the 22nd week of gestation.[36] Determining the gestational age[6] and weight[37,38] of the fetus enables the healthcare team to most effectively guide this care. In a large study, Linder et al. demonstrated that early preterm, low-risk deliveries increased the risk of fetal complications with higher rates of neonatal ICU (NICU) admission, sepsis, and antibiotic treatment as compared to late-term neonates or the gestational control population.[39] While the study only began evaluation at gestational week 37 of low-risk singleton deliveries, it did show that neonatal morbidity risk corresponds with early term deliveries. The burn, obstetric, and neonatal teams must collectively weigh the risks of preterm delivery against the risks of the fetus remaining in utero and besieged by the expected effects of severe burn trauma.

Table 34.1 Indications for Emergent Caesarian Section in the Setting of Severe Burns when the Fetus is in Distress

FETAL DELIVERY IN THE SETTING OF SEVERE MATERNAL BURN		
Fetal Stage	**Gestational Age**	**Delivery Indicated**
Previable	0–21 weeks	No
Periviable, weight <500 g	22–26 weeks	No
Periviable, weight ≥500 g	26–28 weeks	Yes
Early viability	26–28 weeks	Yes
viability	28–32 weeks	Yes
Preterm	32–37 weeks	Yes
Term	37–40 weeks	Yes

PRACTICAL MANAGEMENT ALGORITHM

Adverse pregnancy outcomes are not associated with incidents of minor trauma during pregnancy.[40] However, severe burns are major trauma. As a practical matter, management of the pregnant burn patient can be divided into five phases: previablity, periviability, early viability, viability, and term (Table 34.1). Obstetrical complications (e.g., uterine rupture and placental abruption) are potential mechanisms of preterm delivery following acute maternal trauma.[29] During the period of previability, defined as the period in the pregnancy from conception to gestation week 22 or 23[31,36,41] and a fetal weight of less than 500 g,[30] the fetus cannot survive independent of the mother.[31] While the previability stage of pregnancy is currently defined at gestational week 24 by the American College of Obstetrics and Gynecology,[42] neonatologists and maternal fetal medicine specialists have extended the gestational age of periviability to 22 weeks.[36] However, this is dependent on a fetus of 500 g.[30,37,38] Most obstetricians will attempt resuscitation at 22 weeks,[36] but 24 weeks and 500 g remains the benchmark for viability because fetal mortality at 22 weeks remains incredibly high. Providing total burn care to the mother will make her womb the optimal incubator, thereby managing fetal care as best as is possible. The data indicate that there is a high spontaneous abortion rate;[12] however, there is no proven advantage to performing a termination of the pregnancy unless maternal death seems likely otherwise.[12] Effort should be exerted to avoid medications known to be hazardous to the fetus but not to the extent that the mother succumbs to shock and/or sepsis, which have very high rates of fetal loss.

The multidisciplinary team must balance burn care among several factors during periviability (22–26 weeks) and early viability (26–28 weeks). Prophylactically, antenatal corticosteroids should be administered upon admission in the setting of a severely burned obstetric patient. Demonstrated to be the optimal interventions to reduce morbidity and mortality in premature neonates, these also promote

organ growth[43,44] and can be administered for fetuses as young as 23 weeks.[45,46] Betamethasone (two 12-mg doses given 24 hours apart) and dexamethasone (6 mg every 12 hours in four doses) are the most commonly used antenatal corticosteroids.[43,47] There is no benefit to shorter dosing intervals, and it is recommended that the first dose be applied even if administration of a second dose is unlikely.[43] However, antenatal corticosteroids remain contraindicated when the risk to mother and child is greater by prolonging the pregnancy than is emergent delivery. Effective to forestall labor for up to 48 hours, tocolytic therapy is particularly useful in situations needing to delay labor until after the administration of antenatal corticosteroids or transfer of the patient to an appropriate burn center.[43,48] In the setting of severe burns, tocolytic therapy may be indicated prior to viability to inhibit contractions incited by intra-abdominal surgery.[47,48] Many different drug classes have been employed (e.g., calcium channel blockers, β-mimetics, and magnesium sulfide), but a recent study showed prostaglandin inhibitors to be the optimal first-line tocolytic agents to delay labor with the lowest maternal side-effect profile.[48–50] Calcium channel blockers potentially have the best neonatal outcomes of the tocolytic therapies.[51,52] While traditionally used to inhibit acute preterm contractions,[53] predelivery administration of magnesium sulfate conveys neuroprotection[54,55] and has been shown to be ineffective as a tocolytic agent.[56] Transdermal nitroglycerin for pregnancies of less than 28 weeks is not recommended due to its significant side-effect profile.[57] Because these medications can exacerbate the burn shock besetting a patient, coordination among critical care, obstetrics, neonatologists, and pharmacists is critical to guide therapy and avoid further risk to mother and child.

The dilemma of delivery and resuscitation must be measured against the fetus's odds of survival and chances of leading a normal life. If the perceived risk to the child remaining in utero exceeds the risk in the NICU, the infant should be delivered and cared for ex utero. During in utero critical care, the fetus must be monitored and medications chosen to avoid fetal harm. If toxic medications must be given, the risk should be balanced against the risk of fetal harm. Additionally, if intrauterine fetal death results, irrespective of the reason, the uterus should be evacuated. Retained stillbirth, septic abortion, and missed abortion can lead to disseminated intravascular coagulation (DIC).[58,59] Correlating with high rates of maternal morbidity and mortality, DIC induced by fetal loss is best prevented by prompt evacuation of the dead conceptus.[60,61] It is ethically reprehensible to attempt resuscitation on a child who has or will soon perish regardless of measures taken.

Treatment

It is widely acknowledged that burn patients suffer from altered pharmacokinetics that make them unique among trauma victims. While it could be presumed the treatment protocols would alter significantly given the fetus, they do not (Fig. 34.1). Early wound excision and coverage, aggressive fluid resuscitation, antibiotic administration (though limited in options), and sufficient nutrition are the foundation of managing burned pregnant patients.[17] However, emergency responders and the burn team may be unaware a patient is pregnant. Thus, the first simple and requisite precaution in treating reproductive-age female burn victims is to suspect pregnancy until proven otherwise.[3] Immediately upon determination of pregnancy, high-risk obstetric consultation must be sought, even before excision of the wound. Fetal heart tones must be established and an ultrasound performed to corroborate gestational age obtained from patient menstrual history to determine fetal viability. If the fetus is deemed viable, administer antenatal corticosteroids to mature the lungs for delivery, regardless if the fetus displays signs of distress. This also delays delivery, enlarging the time for stabilization and prep of the mother, and it improves outcomes for the child. After these consults and corticosteroid treatments, initiate antibiotic therapy and coagulopathy support prior to wound excision and/or emergent delivery.

As with nonpregnant burned patients, early wound excision is key in managing severely burned pregnant patients. Surgical interventions include escharotomies, as indicated, and coordination with an obstetrics team if fetal distress is evident. The burn team must proceed with the awareness that two patients require care. Studies have demonstrated that maternal demise strongly correlates to fetal death.[3] We advocate early excision of abdominal eschar to prevent abdominal compartment syndrome and decrease the risk of infection. Should the fetus be viable and in distress, excision of the burn wound can proceed immediately upon delivery. However, early wound excision with fetal survival is rare in the setting of major burns. If early wound excision is indicated and the fetus is not of gestational age or sufficient weight to support emergency caesarean section (e.g., at least 22–24 weeks by either ultrasonographic measurements and/or patient history of last menstrual period[31,36] and measured fetal weight of 500 g by ultrasound[36]), published data and our experience indicate that the mother will not carry the fetus to term. The best chance of both fetal and maternal survival is to deliver the fetus upon signs of distress and manage the maternal burn injuries. If the fetus shows no signs of distress, proceed with early excision and wound coverage and monitor the fetus. In this setting, should the fetus become distressed, perform an emergent caesarean section. If the fetus does not display distress, the mother remains the best incubator, but diligent monitoring is required. Even if the fetus is not viable gestationally, the burn team must proceed with the burn wound excisions because the mother would be subjected to an unacceptable risk of shock and sepsis. The care of the mother must take precedence over that of the child.

The anatomical and physiological changes brought about by pregnancy drastically increase the difficulty in the anesthetic, obstetric, and surgical management of burn patients. "Normal" vital signs and labs in pregnant patients sometimes differ from those of nonpregnant individuals. Current early warning system triggers used to evaluate deteriorating patients are based on nonpregnant values and thus require refinement for the pregnant population.[62] Therefore, awareness of the differences and consultation with appropriate specialists are fundamental to proper care. The changing cardiovascular profile includes increases in cardiac output, uterine blood flow, and blood volume as the fetus matures.[9] Crucially, pelvic blood flow autoregulation

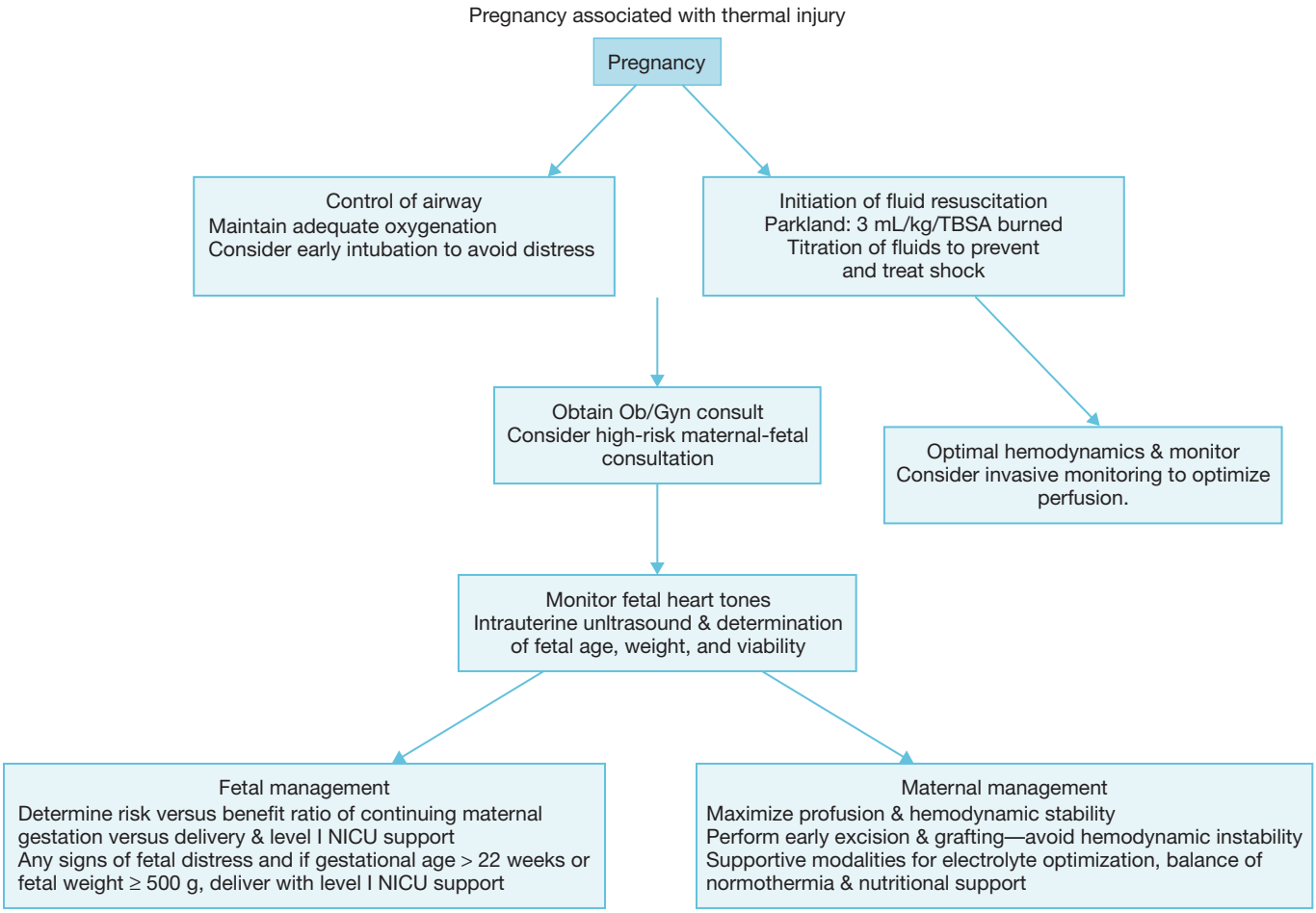

Fig. 34.1 Algorithm of the optimal treatment of the burned pregnant patient.

is absent because pregnancy maximally dilates the uterine vasculature. Resultantly, uterine blood flow depends solely on maternal mean arterial pressure. Furthermore, dilutional anemia of pregnancy may complicate assessments of blood loss and sufficiency of the oxygen-carrying capacity in burn patients.[4] Aggressive fluid resuscitation is vital in the early stages of maternal and fetal salvage. Early interventions during resuscitation include close monitoring of hemodynamics and perfusion indices to evaluate how those respond to initial resuscitation. We further recommend institution of a Foley catheter, central venous catheter, and an arterial line with advanced hemodynamic monitoring upon admitting a severely burned obstetric patient to determine adequate volume status and perfusion. The approach to fluid resuscitation remains the same in the pregnant population as in the nonpregnant group, with the goal to support fluid and plasma loss, early recognition of hypoperfusion, and prompt management of shock while avoiding hypoxia. We use a modified Parkland formula to begin resuscitation at 3 mL/kg per TBSA burned and titrate accordingly, with a targeted urine output of 0.5 mg/kg per hour. Careful monitoring of hemodynamics as well as of blood pressure, hematocrit, and heart rate should tailor resuscitation. Interestingly, one recent case report suggested that it is optimal to decrease the infusion volume of fluid resuscitation, especially following the delivery of the fetus, should that be necessitated,[6] but this has yet to be corroborated. After the 8th week of gestation, pregnant women should present with physiological dilutional anemia,[63] which, if absent, is an early marker of hemoconcentration (Hg > 13 g/dL)[64] and hypovolemia.[65] During the third trimester, instituting an intra-abdominal bladder pressure monitor for resuscitation is a necessary precaution to monitor those patients receiving in excess of 5 mL/kg per TBSA burned. The inability to accurately and timely assess for intra-abdominal hypertension and compartment syndromes in severely burned pregnant patients presents an additional challenge to the burn team. Care must be taken to ensure the pregnant patient does not develop acidemia, hypoperfusion, hypoxia, or thromboembolic complications stemming from high levels of coagulation factors common to pregnant women.[3] Supportive modalities include serial electrolyte and hematologic monitoring to support normalization of electrolyte levels, monitoring of hemoconcentration and fluid balance, and maintaining normothermia. Should such complications arise, the life of the fetus could be jeopardized. When that occurs, a review of the literature reveals that the pregnancy will most often spontaneously abort.[6,9,18] Should obstetrical intervention be indicated, such action must be taken expeditiously to preserve the lives of both mother and child. However, greater study is merited to determine the most efficacious triggers for obstetrical

intervention as well as the optimal amount for fluid resuscitation.

The U.S. Food and Drug Administration (FDA) classified drug recommendations by five grades (A, B, C, D, and X) according to the possible side effects for the fetus when administered to pregnant and/or lactating women[66] (Table 34.2). Animal studies showed no adverse reactions to grade B drugs (e.g., macrolides, cephalosporins, penicillins, lincomycin, and clindamycin), and these are presumed safe to treat pregnant women.[6] In fact, benzylpenicillin remains

Table 34.2 Available Pharmaceuticals for Pregnant and Lactating Women and Their Recommendations

DRUG RECOMMENDATIONS FOR PREGNANCY AND/OR LACTATION IN BURN PATIENTS (*LR = LOW RISK)				
Drug	**Pregnancy Category**	**Pregnancy Recommendations**	**Lactation Recommendations**	**Comments**
A. Topicals				
Bacitracin-like products	C	Compatible	Compatible	Limited fetal exposure would be expected after topical use
Dakin's solution (Na hypochlorite 0.125%, 0.25%, 0.5%)	_	May use during pregnancy; no human data available; risk of fetal harm not expected based on limited systemic absorption	Safety unknown; inadequate literature available to assess risk; caution advised	
Mafenide	C	No human data; should not be withheld because of pregnancy	No human data	
Miconazole	C	Avoid vaginitis treatment in the 1st trimester or application to large areas at any time during pregnancy		
Mupirocin	B	No human data; probably compatible	No human data; probably compatible	
Nystatin	C	Compatible	Compatible	
Silver nitrate	C	None	No human data	
SSD	B	No recommendations		
B. Antibiotics				
Aminoglycosides	D	Human data—LR	Compatible	Streptomycin linked to hearing loss in newborns and should be avoided, unless specific benefit established. Short-term use of others in class acceptable with monitoring, if benefits outweigh the risk
Penicillins	B	Compatible	Compatible	Generally safe to use
Carbapenems (meropenem)	B	Probably compatible	Probably compatible	Use with caution only when penicillins or cephalosporins not an option
Cephalosporins (all generations)	B	Compatible	Compatible	Generally safe to use; use ceftriaxone with caution at term due to risk of kernicterus
Clindamycin	B	Compatible	Compatible	Appears to be safe and effective
Daptomycin	B	Limited human data; animal data—LR	Limited human data; probably compatible	May use if benefits outweigh risks
Vancomycin	B	Compatible	Limited human data; probably compatible	Safe and effective
Metronidazole	B	Human data—LR (see comments)	Hold breastfeeding (single dose); see comments	Contraindicated 1st trimester; lactation is potentially toxic for divided dose; "topical" metronidazole should be avoided
Linezolid	C	Compatible	No human data; potentially toxic	May use if benefits outweigh risks
Sulfamethoxazole, trimethoprim	C	Human data suggest risk in 3rd trimester	Limited human data; potentially toxic	Avoid in 1st trimester due to major congenital malformations. Sulfamethoxazole should be avoided after 32 weeks' gestation due to risk of kernicterus

Table 34.2 Available Pharmaceuticals for Pregnant and Lactating Women and Their Recommendations—cont'd

DRUG RECOMMENDATIONS FOR PREGNANCY AND/OR LACTATION IN BURN PATIENTS (*LR = LOW RISK)				
Drug	**Pregnancy Category**	**Pregnancy Recommendations**	**Lactation Recommendations**	**Comments**
B. Antibiotics				
Tetracyclines	D	Contraindicated in 2nd and 3rd trimesters	Doxycycline; compatible	Should be avoided
Tigecycline	D	Contraindicated in 2nd and 3rd trimesters	Limited human data; probably toxic	Avoid in pregnancy unless benefits outweigh risks
C. Antifungals				
Fluconazole	D/C	Associated with fetal mortality and congenital abnormalities	Compatible	
Posaconazole	C	Animal data suggest risk of skeletal malformations	No human data; potential toxicity	
Voriconazole	D	Animal studies have demonstrated fetal harm	No human data; potential toxicity	
Micafungin	C	Animal data revealed embryotoxic effects but have not been replicated in adults	No human data; probably compatible	
Amphotericin	B	Observational data suggest rate of human birth defects is similar to that of the general population	Not recommended	
D. Pain Medications				
Codeine	C	Human data suggest risk	Limited human data; probably compatible	Although the AAP has classified codeine as compatible with breastfeeding, data suggest that, for some women, codeine can not be considered safe during nursing, especially if therapy is >1–2 weeks
Fentanyl	C	Human data suggest risk in 3rd trimester	Compatible	Neonatal withdrawal, respiratory depression
Hydrocodone/APAP	C	Human data suggest risk in 3rd trimester	Limited data; potential toxicity	
Morphine	C	Human data suggest risk in 3rd trimester	Limited human data; probably compatible	
Oxycodone	C	Human data suggest risk in 3rd trimester	No human data; probably compatible	
Tramadol	C			

the most commonly antibiotic administered to pregnant women.[67] Categories C, D, and X have been demonstrated to generate negative side effects in fetal development. In cases where the benefits of treating a pregnant woman with a grade C drug, such as quinolones and fluconazole, greatly outweigh the risks associated with the drug or no alternative exists, they are warranted for use in pregnant women.[6] Drugs belonging to class D will rarely warrant administration, and only if the risk of harm is strongly outweighed by the benefit. Category X should only be administered in instances where fetal loss is assured or an accepted ramification of using the medication to preserve the life of the mother.[66] Adding to the complexity, recommendations vary depending on trimester or for a lactating burn patient. As part of the multidisciplinary team, the clinical pharmacist plays an integral role in assuring safe and effective pharmacological therapy for each patient in the burn unit. A pharmacist should be knowledgeable and current on the changing recommendations of all drugs safe for administration to pregnant and nursing patients, from antibiotics to renal dosings. As such, the clinical pharmacist is indispensible in advising the team on the optimal therapy for burned pregnant patients.

It comes as no surprise that pregnancy increases the mother's metabolic requirements. Early enteral nutrition remains key to the management of the severely burned pregnant patient. Within 48 hours of admission to our hospital, we initiate dietary consultation and estimate caloric need. Special considerations that can develop with severely burned pregnant patients include postoperative ileus with caesarean delivery and surgical interventions. For those in this patient population who may have undergone an emergent caesarean section, the risk of developing acalculous cholecystitis is elevated. Management of acalculous

cholecystitis complications can be complex given a postpartum surgical abdomen.

Additional Considerations

HEMATOLOGY AND COAGULOPATHY

In the severely burned patient, DIC can develop.[68] DIC is defined as an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization originating from and causing damage to the microvasculature, potentially leading to MOD by the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis.[69,70] In the early, acute phase of burn, DIC presents as the fibrinolytic phenotype; later in the course of burn pathophysiology, DIC is often sepsis induced.[68,71–73] The syndrome is characterized by excessive thrombosis, unchecked inflammation and MOD, insufficient anticoagulation mechanisms, and increased fibrinolysis.[72] Massive transfusions are common in patients with DIC.[74] Management of coagulopathy in the severely burned pregnant patient includes transfusions of fresh frozen plasma, packed red blood cells, cryoprecipitate, and platelets while in the operative theater and for patients at risk of significant bleeding. This is covered in greater depth in Chapter 22 on hematology, hemostasis, thromboprophylaxis, and transfusion medicine.

Pregnancy normally induces a hypercoagulable state that is compounded by thermal insult. This presents an additional challenge for supportive and screening therapies throughout the course of care. Prophylaxis administration of heparin, specifically low-molecular-weight heparins, is recommended. Routine weekly Doppler exams are suggested, given the high suspicion of thrombosis in the pregnant population. Extensive findings of deep vein thrombosis (DVT) in conjunction with the inability to fully anticoagulate a severely burned pregnant patient require the burn team to weigh the risks versus the benefits of placing an inferior vena cava filter device, as thrombosis is likely to further propagate.

PSYCHOLOGICAL ISSUES

Pregnant burn prevalence is greater in developing countries. Furthermore, the etiology of traumatic injury differs between industrialized and developing countries: a far greater numbers of women are likely to deliberately set themselves on fire in mostly futile suicide attempts in developing countries.[12,75] However, a noted rise in self-inflicted burns in industrialized countries exists.[76] This bespeaks a lack of psychiatric and social support for expectant mothers that, were it better addressed, might help prevent such incidences.[23] Underreporting of suicide is perennially problematic because no standard method exists to evaluate pregnancy at time of death.[77] The high incidence of thermal insult found in the uneducated or illiterate populations of obstetric patients illustrates the benefit that education imparts in reducing burn injuries.[23,75] Greater education and access to psychological support is needed.

Perinatal loss resultant from burn injury compounds the already traumatic psychological effects of burn patients. Women are adversely impacted by the image-altering effects common to burn survivors, especially from severe burns.[78] Shepherd showed a positive correlation between trauma symptoms and appearance concerns.[79] Cumulatively complicating recovery, mothers may also experience depression,[80–82] posttraumatic stress,[83] and anxiety[84] following fetal loss. These may also be experienced by any potential partner[82] in addition to the psychological distress experienced by spouses and close relatives of burn and trauma survivors,[85] resulting in notable adverse sequelae for the couple.[86] All these may profoundly and detrimentally impact any potential recovery of the mother. The inclusion of psychiatric consultations should be a standard part of burn care protocols, especially given the profound psychological upheaval following traumatic and unexpected fetal loss for both the maternal survivor and any spouse or partner. In developing countries, greater psychiatric and social work support for expectant mothers should be made readily accessible to better prevent suicides and suicide attempts by self-immolation.[23]

In the case where the fetus survived despite maternal complications, we observed a disassociation bond between mother and child. Supportive modalities in keeping with the multidisciplinary approach included recognition of maternal signs of depression and anxiety by consequently referring the patient to psychiatry for pharmacologic and other therapies to address her posttraumatic and adjustment stress disorders. In our experience, early family interaction has been instrumental for a patient's recovery from traumatic injury, along with early initiation of infant bonding.

Also to consider are support modalities for the multidisciplinary team. Managing the care of pregnant patients, especially those who have suffered traumatic injuries, and fetal demise can create stressors within the critical care medical and nursing staff that must be managed to avoid provider burnout.[87]

NONSEVERE BURNS

The text of this chapter has dealt with the care of the severely burned obstetric patient. The approach to the nonseverely burned pregnant victim is much the same (Fig. 34.1). Obtain a high-risk obstetric consult upon admission of the pregnant burn patient. Establish and monitor fetal heart tones. Perform an ultrasound to determine fetal viability and gestational age, as well as acquire patient history regarding last menstrual cycle. Optimize fluid resuscitation and perfusion, beginning with the Parkland formula. Utilize the multidisciplinary team to maximize management of the burned pregnant patient. In contrast with the treatment of the severely burned pregnant population, early wound excision can be balanced between the risk and benefit to both patients of surgical intervention versus topical treatments. Protocols must be established regarding critical care, perinatal support, lactation consultation, and nursing monitoring should the fetus be viable and delivered; anesthetic consultation and support should surgical intervention be indicated; nutrition optimization; clinical pharmacist consultation regarding recommendations for optimal medications; DVT prophylaxis initiated and aggressive screening established to monitor the hypercoagulable

state native to pregnant women; and physical therapy regimens.

Conclusion

Given the dearth of data, the burn surgeon must respond to the challenge presented by a pregnant burn victim by coordinating the best practices of burn, surgical, and critical care in a team approach with a high-risk obstetrician, neonatologist, and clinical pharmacist. What exists in literature points to the positive association between maternal death and TBSA burned, that, fetal survival depends on maternal survival, and that, despite the massive physiological and anatomical changes induced by pregnancy, the care of a burned pregnant patient is similar to that of a nonpregnant burned victim. Indeed, the standard of care remains as follows: aggressive fluid resuscitation, early wound excision and coverage, empiric but class-restricted antibiotic administration, and adequate nutrition. Patients should be carefully resuscitated based on standard resuscitation algorithms, titrating infusion to urine output and hemodynamics. Burn wounds should be excised early and wounds grafted as quickly as practical. Severely burned pregnant women are ideally treated in burn centers specialized to handle severe burns and concurrently manage neonatal deliveries.[1] The fetus must be monitored continuously for signs of distress in order to guide obstetric intervention should it be warranted. Each additional week of gestation gained corresponds to significant decreases in neonatal morbidity and mortality.[88] For burns occurring after gestational week 28, the risk to the child from premature birth is moderate. Ideally, these children can be carried to term with close monitoring. However, a very low threshold for delivery should be maintained to avoid fetal harm from episodes of shock, sepsis, toxins, or infections. For a fetus younger than gestational week 22, care must focus on maintaining the mother in the hope the fetus can survive in her womb. Between 22 and 26 weeks, the gray period of neonatal survival, the womb is the preferred environment, but, should the fetus begin showing signs of distress, collaboration with a high-risk obstetrician and a neonatologist is imperative to attempt to preserve the lives of both mother and child. The coordinated efforts of a multidisciplinary team whose members include burn, trauma, critical care, obstetric, neonatal, and psychiatric specialists are requisite to provide the best management of the physiological and psychological challenges presented by severely burned obstetric patients. Further systemic research into the care of mother and fetus following thermal insult is necessary to better refine treatment algorithms.

Complete references available online at
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Further Readings

American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 171: Management of Preterm Labor. *Obstet Gynecol*. 2016;128(4):e155-e164.

Montagnana M, Franchi M, Danese E, et al. Disseminated intravascular coagulation in obstetric and gynecologic disorders. *Semin Thromb Hemost*. 2010;36(4):404-418.

Parikh P, Sunesara I, Lutz E, et al. *Burns*. During pregnancy: implications for maternal-perinatal providers and guidelines for practice. *Obstet Gynecol Surv*. 2015;70(10):633-643.

Sawyer T, Umoren RA, Gray MM. Neonatal resuscitation: advances in training and practice. *Adv Med Educ Pract*. 2017;8:11-19.

References

1. Distelhorst JT, Krishnamoorthy V, Schiff MA. Association between hospital trauma designation and maternal and neonatal outcomes after injury among pregnant women in Washington state. *J Am Coll Surg*. 2016;222(3):296-302.
2. Tweddale CJ. Trauma during pregnancy. *Crit Care Nurs Q*. 2006;29(1): 53-67, quiz 68-69.
3. Kuczkowski KM. Trauma in the pregnant patient. *Curr Opin Anaesthesiol*. 2004;17(2):145-150.
4. Kuczkowski KM. Trauma during pregnancy: a situation pregnant with danger. *Acta Anaesthesiol Belg*. 2005;56(1):13-18.
5. Romero VC, Pearlman M. Maternal mortality due to trauma. *Semin Perinatol*. 2012;36(1):60-67.
6. Shi Y, Zhang X, Huang BG, et al. Severe burn injury in late pregnancy: a case report and literature review. *Burns Trauma*. 2015;3:2.
7. Rayburn W, Smith B, Feller I, et al. Major burns during pregnancy: effects on fetal well-being. *Obstet Gynecol*. 1984;63(3):392-395.
8. Mehrpour O, Javadinia SA, Malic C, et al. A survey of characteristics of self-immolation in the east of Iran. *Acta Med Iran*. 2012;50(5):328-334.
9. Amy BW, McManus WF, Goodwin CW, et al. Thermal injury in the pregnant patient. *Surg Gynecol Obstet*. 1985;161(3):209-212.
10. Maghsoudi H, Samnia R, Garadaghi A, Kianvar H. Burns in pregnancy. *Burns*. 2006;32(2):246-250.
11. Polko LE, McMahon MJ. Burns in pregnancy. *Obstet Gynecol Surv*. 1998;53(1):50-56.
12. Rezavand N, Seyedzadeh A, Soleymani A. Evaluation of maternal and foetal outcomes in pregnant women hospitalized in Kermanshah Hospitals, Iran, owing to burn injury, 2003–2008. *Ann Burns Fire Disasters*. 2012;25(4):196-199.
13. Rode H, Millar AJ, Cywes S, et al. Thermal injury in pregnancy–the neglected tragedy. *S Afr Med J*. 1990;77(7):346-348.
14. Taylor JW, Plunkett GD, McManus WF, et al. Thermal injury during pregnancy. *Obstet Gynecol*. 1976;47(4):434-438.
15. Herndon DN, Rutan RL. Comparison of cultured epidermal autograft and massive excision with serial autografting plus homograft overlay. *J Burn Care Rehabil*. 1992;13(1):154-157.
16. Vaghardoost R, Kazemzadeh J, Rabieepoor S. Epidemiology of burns during pregnancy in Tehran, Iran. *Burns*. 2016;42(3):663-667.
17. Agarwal P. Thermal injury in pregnancy: predicting maternal and fetal outcome. *Indian J Plast Surg*. 2005;38(2):95-99.
18. Chama CM, Na'Aya HU. Severe burn injury in pregnancy in Northern Nigeria. *J Obstet Gynaecol*. 2002;22(1):20-22.
19. Gang RK, Bajec J, Krishna J, et al. Unusual development of granulomas on the healing surface of burn wounds associated with MRSA infections. *Burns*. 1996;22(1):57-61.
20. Mago V. Burn wound septicaemia: analysis of burn infection in burn ward at Dr. S.T.M. Forest Hospital, Haldwani. *J Burn Care Res*. 2009;30(3):540.
21. Unsur V, Oztopcu C, Atalay C, et al. A retrospective study of 11 pregnant women with thermal injuries. *Eur J Obstet Gynecol Reprod Biol*. 1996;64(1):55-58.
22. Parikh P, Sunesara I, Lutz E, et al. Burns during pregnancy: implications for maternal-perinatal providers and guidelines for practice. *Obstet Gynecol Surv*. 2015;70(10):633-643.
23. Karimi H, Momeni M, Momeni M, et al. Burn injuries during pregnancy in Iran. *Int J Gynaecol Obstet*. 2009;104(2):132-134.
24. Roderique EJ, Gebre-Giorgis AA, Stewart DH, et al. Smoke inhalation injury in a pregnant patient: a literature review of the evidence and current best practices in the setting of a classic case. *J Burn Care Res*. 2012;33(5):624-633.
25. Ramos ESM, Martins NR, Kroumpouzos G. Oral and vulvovaginal changes in pregnancy. *Clin Dermatol*. 2016;34(3):353-358.
26. Practice Bulletin No. 170 Summary: Critical Care in Pregnancy. *Obstet Gynecol*. 2016;128(4):929-930.
27. MacLennan L, Moiemen N. Management of cyanide toxicity in patients with burns. *Burns*. 2015;41(1):18-24.
28. Foresti R, Clark JE, Green CJ, et al. Thiol compounds interact with nitric oxide in regulating heme oxygenase-1 induction in endothelial cells. Involvement of superoxide and peroxynitrite anions. *J Biol Chem*. 1997;272(29):18411-18417.
29. Liu S, Basso O, Kramer MS. Association between unintentional injury during pregnancy and excess risk of preterm birth and its neonatal sequelae. *Am J Epidemiol*. 2015;182(9):750-758.
30. Hack M, Fanaroff AA. Outcomes of extremely-low-birth-weight infants between 1982 and 1988. *N Engl J Med*. 1989;321(24):1642-1647.
31. Salihu HM, Salinas-Miranda AA, Hill L, et al. Survival of pre-viable preterm infants in the United States: a systematic review and meta-analysis. *Semin Perinatol*. 2013;37(6):389-400.
32. Acosta CD, Harrison DA, Rowan K, et al. Maternal morbidity and mortality from severe sepsis: a national cohort study. *BMJ Open*. 2016;6(8):e012323.
33. Azzopardi EA, McWilliams B, Iyer S, et al. Fluid resuscitation in adults with severe burns at risk of secondary abdominal compartment syndrome–an evidence based systematic review. *Burns*. 2009;35(7):911-920.
34. Malbrain ML, De Keulenaer BL, Oda J, et al. Intra-abdominal hypertension and abdominal compartment syndrome in burns, obesity, pregnancy, and general medicine. *Anaesthesiol Intensive Ther*. 2015; 47(3):228-240.
35. Poole JH. Multiorgan dysfunction in the perinatal patient. *Crit Care Nurs Clin North Am*. 2004;16(2):193-204.
36. Sawyer T, Umoren RA, Gray MM. Neonatal resuscitation: advances in training and practice. *Adv Med Educ Pract*. 2017;8:11-19.
37. Phillips B, Zideman D, Wyllie J, et al. European resuscitation council guidelines 2000 for newly born life support. A statement from the Paediatric Life Support Working Group and approved by the Executive Committee of the European Resuscitation Council. *Resuscitation*. 2001;48(3):235-239.
38. Jevon P. Resuscitation Council (UK) newborn life support course. *Pract Midwife*. 2001;4(11):22-23.
39. Linder N, Hiersch L, Fridman E, et al. The effect of gestational age on neonatal outcome in low-risk singleton term deliveries. *J Matern Fetal Neonatal Med*. 2015;28(3):297-302.
40. Weiner E, Gluck O, Levy M, et al. Obstetric and neonatal outcome following minor trauma in pregnancy. Is hospitalization warranted? *Eur J Obstet Gynecol Reprod Biol*. 2016;203:78-81.
41. Margato MF, Martins GL, Passini Junior R, et al. Previable preterm rupture of membranes: gestational and neonatal outcomes. *Arch Gynecol Obstet*. 2012;285(6):1529-1534.
42. Obstetric Care Consensus No. 4: Periviable birth. *Obstet Gynecol*. 2016;127(6):e157-e169.
43. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 171: Management of preterm labor. *Obstet Gynecol*. 2016;128(4):e155-e164.
44. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev*. 2006;(3):CD004454.
45. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Committee Opinion No. 677: Antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol*. 2016;128(4): e187-e194.
46. American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine. ACOG Obstetric Care Consensus No. 3: Periviable birth. *Obstet Gynecol*. 2015;126(5):e82-e94.
47. ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 475: Antenatal corticosteroid therapy for fetal maturation. *Obstet Gynecol*. 2011;117(2 Pt 1):422-424.
48. Haas DM, Caldwell DM, Kirkpatrick P, et al. Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. *BMJ*. 2012;345:e6226.
49. Refuerzo JS, Alexander JF, Leonard F, et al. Liposomes: a nanoscale drug carrying system to prevent indomethacin passage to the fetus in a pregnant mouse model. *Am J Obstet Gynecol*. 2015;212(4):508 e1-508 e7.
50. Petousis S, Margioula-Siarkou C, Kalogiannidis I. Effectiveness of tocolytic agents on prevention of preterm delivery, neonatal morbidity, and mortality: is there a consensus? A review of the literature. *Obstet Gynecol Surv*. 2016;71(4):243-252.
51. King JF, Flenady V, Papatsonis D, et al. Calcium channel blockers for inhibiting preterm labour: a systematic review of the evidence and a protocol for administration of nifedipine. *Aust N Z J Obstet Gynaecol*. 2003;43(3):192-198.
52. Delorme P, Le Ray C. [Efficiency and tolerance of calcium channel blockers as first-line tocolysis]. *J Gynecol Obstet Biol Reprod (Paris)*. 2015;44(4):324-340.
53. Crowther CA, Hiller JE, Doyle LW. Magnesium sulphate for preventing preterm birth in threatened preterm labour. *Cochrane Database Syst Rev*. 2002;(4):CD001060.

54. Marret S, Ancel PY. [Neuroprotection for preterm infants with antenatal magnesium sulphate]. *J Gynecol Obstet Biol Reprod (Paris)*. 2016;45(10):1418-1433.
55. Horton AL, Lai Y, Rouse DJ, et al. Effect of magnesium sulfate administration for neuroprotection on latency in women with preterm premature rupture of membranes. *Am J Perinatol*. 2015;32(4):387-392.
56. Crowther CA, Brown J, McKinlay CJ, et al. Magnesium sulphate for preventing preterm birth in threatened preterm labour. *Cochrane Database Syst Rev*. 2014;(8):CD001060.
57. Conde-Agudelo A, Romero R. Transdermal nitroglycerin for the treatment of preterm labor: a systematic review and metaanalysis. *Am J Obstet Gynecol*. 2013;209(6):551 e1-e18.
58. Erez O, Mastrolia SA, Thachil J. Disseminated intravascular coagulation in pregnancy: insights in pathophysiology, diagnosis and management. *Am J Obstet Gynecol*. 2015;213(4):452-463.
59. Honda M, Matsunaga S, Era S, et al. Intrapartum anti-disseminated intravascular coagulation therapy leading to successful vaginal delivery following intrauterine fetal death caused by placental abruption: a case report. *J Med Case Rep*. 2014;8:461.
60. Montagnana M, Franchi M, Danese E, et al. Disseminated intravascular coagulation in obstetric and gynecologic disorders. *Semin Thromb Hemost*. 2010;36(4):404-418.
61. Letsky EA. Disseminated intravascular coagulation. *Best Pract Res Clin Obstet Gynaecol*. 2001;15(4):623-644.
62. Dennis A, Hardy L. Defining a reference range for vital signs in healthy term pregnant women undergoing caesarean section. *Anaesth Intensive Care*. 2016;44(6):752-757.
63. Means RT. Anemias during pregnancy and the postpartum period. In: Greer JP, ed. *Wintrobe's Clinical Hematology*. Vol. 1. 12th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009:1239-1246.
64. Kacmar RM, Traynor AJ. Physiologic changes of pregnancy. In: Bucklin BA, Baysinger CL, Gambling D, eds. *A Practical Approach to Obstetric Anesthesia*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2016:3-16.
65. Campbell T, Galwankar S. Emergency medical resuscitation in pregnancy with trauma. In: Singal RK, ed. *Medical Update 2008*. 18: Association of Physicians of India; 2008.
66. Food, Drug Administration HHS. Content and format of labeling for human prescription drug and biological products: requirements for pregnancy and lactation labeling. Final rule. *Fed Regist*. 2014;79(233):72063-72103.
67. Heikkila A, Erkkola R. Review of beta-lactam antibiotics in pregnancy. The need for adjustment of dosage schedules. *Clin Pharmacokinet*. 1994;27(1):49-62.
68. Dobson GP, Letson HL, Sharma R, et al. Mechanisms of early trauma-induced coagulopathy: the clot thickens or not? *J Trauma Acute Care Surg*. 2015;79(2):301-309.
69. Gonzalez E, Moore EE, Moore HB, et al. Trauma-induced coagulopathy: an institution's 35 year perspective on practice and research. *Scand J Surg*. 2014;103(2):89-103.
70. Taylor FB Jr, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost*. 2001;86(5):1327-1330.
71. Gando S, Sawamura A, Hayakawa M. Trauma, shock, and disseminated intravascular coagulation: lessons from the classical literature. *Ann Surg*. 2011;254(1):10-19.
72. Gando S, Wada H, Thachil J, et al. Differentiating disseminated intravascular coagulation (DIC) with the fibrinolytic phenotype from coagulopathy of trauma and acute coagulopathy of trauma-shock (COT/ACOTS). *J Thromb Haemost*. 2013;11(5):826-835.
73. Hayakawa M, Kushimoto S, Watanabe E, et al. Pharmacokinetics of recombinant human soluble thrombomodulin in disseminated intravascular coagulation patients with acute renal dysfunction. *Thromb Haemost*. 2017.
74. Hayakawa M, Gando S, Ono Y, et al. Fibrinogen level deteriorates before other routine coagulation parameters and massive transfusion in the early phase of severe trauma: a retrospective observational study. *Semin Thromb Hemost*. 2015;41(1):35-42.
75. Khadzhiiski S. [Burns during pregnancy]. *Khirurgiia (Sofiia)*. 1991;44(3):26-29.
76. Caine PL, Tan A, Barnes D, et al. Self-inflicted burns: 10 year review and comparison to national guidelines. *Burns*. 2016;42(1):215-221.
77. Dannenberg AL, Carter DM, Lawson HW, et al. Homicide and other injuries as causes of maternal death in New York City, 1987 through 1991. *Am J Obstet Gynecol*. 1995;172(5):1557-1564.
78. Macleod R, Shepherd L, Thompson AR. Posttraumatic stress symptomatology and appearance distress following burn injury: an interpretative phenomenological analysis. *Health Psychol*. 2016;35(11):1197-1204.
79. Shepherd L. A pilot study exploring the relationship between trauma symptoms and appearance concerns following burns. *Burns*. 2015;41(2):345-351.
80. Gaudet C, Sejourne N, Allard MA, et al. [Women and the painful experience of therapeutic abortion]. *Gynecol Obstet Fertil*. 2008;36(5):536-542.
81. Gausia K, Moran AC, Ali M, et al. Psychological and social consequences among mothers suffering from perinatal loss: perspective from a low income country. *BMC Public Health*. 2011;11:451.
82. Hutti MH, Armstrong DS, Myers JA, et al. Grief intensity, psychological well-being, and the intimate partner relationship in the subsequent pregnancy after a perinatal loss. *J Obstet Gynecol Neonatal Nurs*. 2015;44(1):42-50.
83. Bennett SA, Bagot CN, Arya R. Pregnancy loss and thrombophilia: the elusive link. *Br J Haematol*. 2012;157(5):529-542.
84. Woods-Giscombe CL, Lobel M, Crandell JL. The impact of miscarriage and parity on patterns of maternal distress in pregnancy. *Res Nurs Health*. 2010;33(4):316-328.
85. Bond S, Gourlay C, Desjardins A, et al. Anxiety, depression and PTSD-related symptoms in spouses and close relatives of burn survivors: when the supporter needs to be supported. *Burns*. 2016.
86. Gold KJ, Sen A, Hayward RA. Marriage and cohabitation outcomes after pregnancy loss. *Pediatrics*. 2010;125(5):e1202-e1207.
87. Sahraian A, Fazelzadeh A, Mehdizadeh AR, et al. Burnout in hospital nurses: a comparison of internal, surgery, psychiatry and burns wards. *Int Nurs Rev*. 2008;55(1):62-67.
88. Manuck TA, Rice MM, Bailit JL, et al. Preterm neonatal morbidity and mortality by gestational age: a contemporary cohort. *Am J Obstet Gynecol*. 2016;215(1):103 e1-e14.

35 Special Considerations of Age
THE PEDIATRIC BURNED PATIENT

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Introduction

According to the National Burn Repository, burn injuries are responsible for 40,000 annual hospital admissions, of which one third are pediatric patients.[1] Despite the steady decrease of burn injuries over the past three decades, children continue to represent a disproportionately high proportion of this population. The pattern of burn injuries affecting children differs from the pattern observed in adult burns.

House fires are among the leading causes of burn injuries and burn-related deaths in the United States, with approximately 2,600 deaths and 13,000 injuries reported per year.[2] Children under 5 years of age are at a greater risk. Deaths due to house fire among preschool children are at a rate of more than twice the national average for all ages (29.6 deaths/million children, or an average of 20% of all home fire deaths).[2,3] In addition, scald burns constitute the most common mechanism of injury in the pediatric population, representing approximately 71% of all burn injuries nationwide.[3] Scald burns are more frequently observed in children 6 years or younger. Scald injuries may be due to household accidents or can be deliberate abuse. More than half of these burns are attributable to hot liquids related to cooking, including spilling hot coffee or water, or to children reaching up to countertops, pulling pot handles or cords attached to cooking appliances, and spilling the contents onto themselves. Other causes include unknowingly putting body parts under a hot water faucet or climbing into a bathtub with hot water and intentionally or unintentionally being placed into or brought in contact with a hot substance by another individual. According to epidemiologic studies, minorities and children living in areas with lower incomes are disproportionately more affected by burn injuries.[4,5] Notably, flame burns are the dominant cause in adolescents and are associated with increased severity and increased need for hospitalization when compared to other burns.[4,6]

Drastic changes in burn care over the past decades, which include aggressive and early fluid resuscitation, prompt excision and grafting of burn wounds, improved infection control, modulation of the hypermetabolic response, and management of inhalation injury, have promoted a substantial decline in in-hospital mortality after burn injury.[7] This overall improvement in mortality is most perceptible in children. For example, in 1949, a pediatric patient (aged 0–14) with a burn covering 50% of total body surface area (TBSA) had an expected mortality rate of 50%; today, a similar mortality rate is expected in a pediatric patient (same age group) with a 98% TBSA burn.[8,9]

A retrospective study involving 103 children with burns covering more than 80% of TBSA over a 15-year period reported an overall mortality of 33%. Mortality was significantly higher in children under 2 years of age and in those with more than 95% TBSA burn (Figs. 35.1 and 35.2).[10] Delay in obtaining intravenous (IV) access was an additional predictor of mortality (Fig. 35.3). Aggressive fluid resuscitation during the first hour after burn increased survival. The mortality rate also increased significantly with inhalation injury, sepsis, and multiorgan failure.[10]

In addition to biological derangements, a severe burn produces tremendous psychological challenges to a child. Anatomical differences specific to the pediatric population make procedures and interventions more challenging.

Initial Evaluation

First, the burn patient needs to be removed from the source of thermal injury expeditiously and clothing and jewelry removed immediately. Pouring cold water onto the burn can cause hypothermia in large burns and should be avoided. After the burning process is stopped, the patient should be kept warm by covering with a sterile (if available) or clean sheet or blanket. If the burn is chemical, the patient should be removed from the chemical immediately, and the burn should be irrigated with copious amounts of water for at least 30 min. If the chemical is powder, it should be brushed off first prior to irrigation.[11,12]

Burn patients should be assumed to be trauma patients, and any potential life-threatening injuries should be identified and treated. The airway should be assessed first. One-hundred percent oxygen should be administered if inhalation injury is suspected. In addition, arterial blood gas and carboxyhemoglobin levels should be measured: pulse oximetry readings will be falsely normal in patients with elevated carboxyhemoglobin levels because carboxyhemoglobin is read as oxyhemoglobin by the pulse oximeter.[13]

Tachypnea, stridor, and hoarseness indicate an impending airway narrowing due to inhalation injury or edema, and immediate intubation should be considered. A full-thickness circumferential chest burn can interfere with ventilation. Chest expansion should be observed to ensure adequate air movement. If the patient is on a ventilator, airway pressure and P_{CO_2} should be monitored. If ventilation is compromised, escharotomy of the chest should be performed to improve ventilation.

Blood pressure measurement may be difficult in patients with burned extremities. These patients may require an arterial line to monitor their blood pressure. A radial

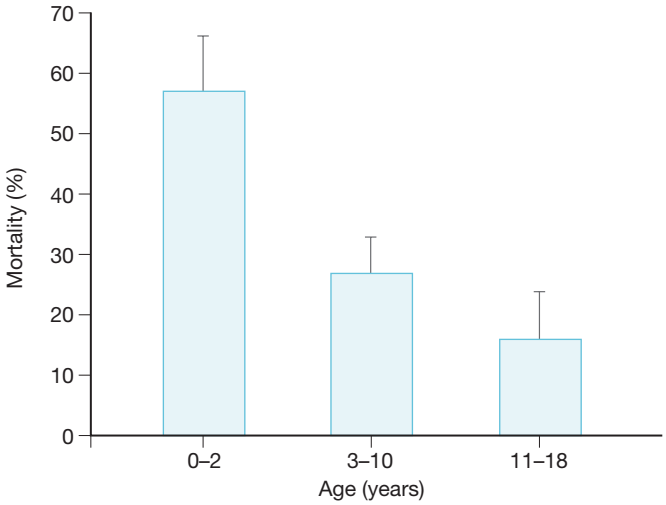

Fig. 35.1 Mortality in burns of more than 80% total body surface area for various ages.

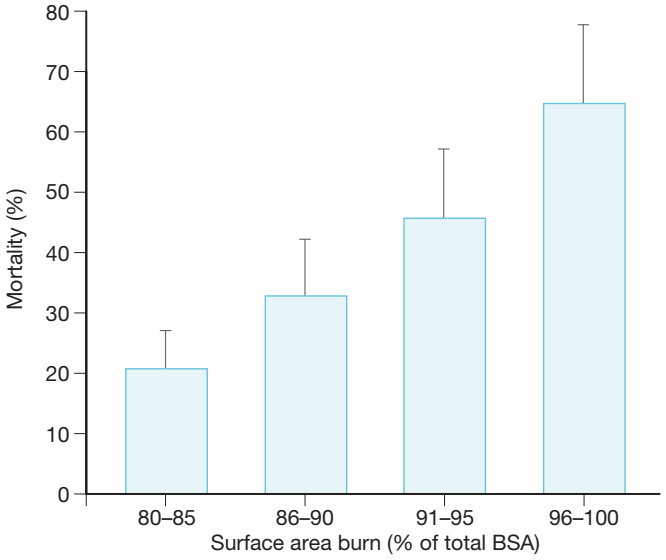

Fig. 35.2 Mortality for increasing burn size.

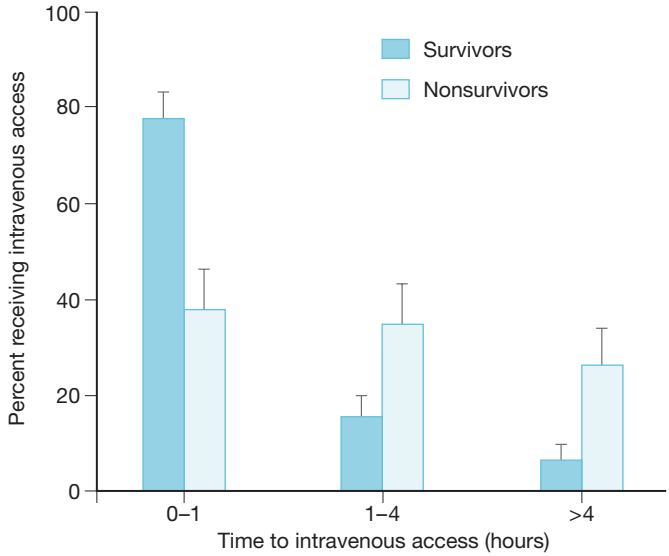

Fig. 35.3 Time to intravenous access in survivors and nonsurvivors. Mortality increases with delays in starting an intravenous line and instituting volume resuscitation.

arterial line may not be reliable in pediatric patients with extremity burns and may be difficult to obtain. A femoral arterial line may be more reliable and easier to secure.

An urinary catheter is placed to monitor urine output as a measure of successful resuscitation. Placement of a nasogastric tube is recommended in patients with severe burns because they can develop gastric ileus. Persistent tachycardia should alert a clinician to a missed injury or underresuscitation. Accurate and prompt determination of burn size is fundamental for the proper management of burn injury.

Resuscitation

There is a systemic capillary leak after a major burn, which increases with burn size. Intravenous access should be established immediately for the administration of fluids. Delays in commencement of resuscitation of burned patients result in worse outcome.[14] Therefore it is vital that IV access be obtained as early as possible. Due to the small circulating volume in children, resuscitation should be started immediately; even short delays increase the risk of shock. Peripheral IV access is preferred, and it must go through burned skin if necessary. IV access should be well secured. When peripheral IV access is not available because of severe extremity burns, a central venous line must be placed. Children with large burns should have two large-bore IV lines for fluid administration. The presence of two IV lines provides a safety margin if one stops functioning.

When vascular access is unobtainable, the intraosseous route is a viable option. Fluid volumes in excess of 100 mL/h can be administered directly into the bone marrow.[15] Intramedullary access can be utilized in the proximal tibia until IV access is accomplished. A 16–18-gauge bone marrow aspiration needle, spinal needle, or commercially available intraosseous needle can be used to cannulate the bone marrow compartment. Although previously advocated only for children younger than 3 years of age, intraosseous fluid administration can be safely performed in all pediatric age groups.[16,17] The proximal anterior tibia, medial malleolus, anterior iliac crest, and distal femur are preferred sites for intraosseous infusion. The needle should be introduced into the bone, avoiding the epiphysis, either perpendicular to the bone or at a 60-degree angle, with the bevel facing the greater length of bone (Fig. 35.4). The needle has been properly inserted when bone marrow can be freely aspirated. Fluid should be allowed to infuse by gravity drip. The use of pumps should be discouraged in case the needle becomes dislodged from the marrow compartment.

Fluid losses are proportionally greater in children owing to their small body weight-to-body surface area ratio. Normal blood volume in children is approximately 80 mL/kg body weight and in neonates 85–90 mL/kg, compared to an adult whose normal blood volume is 70 mL/kg. The

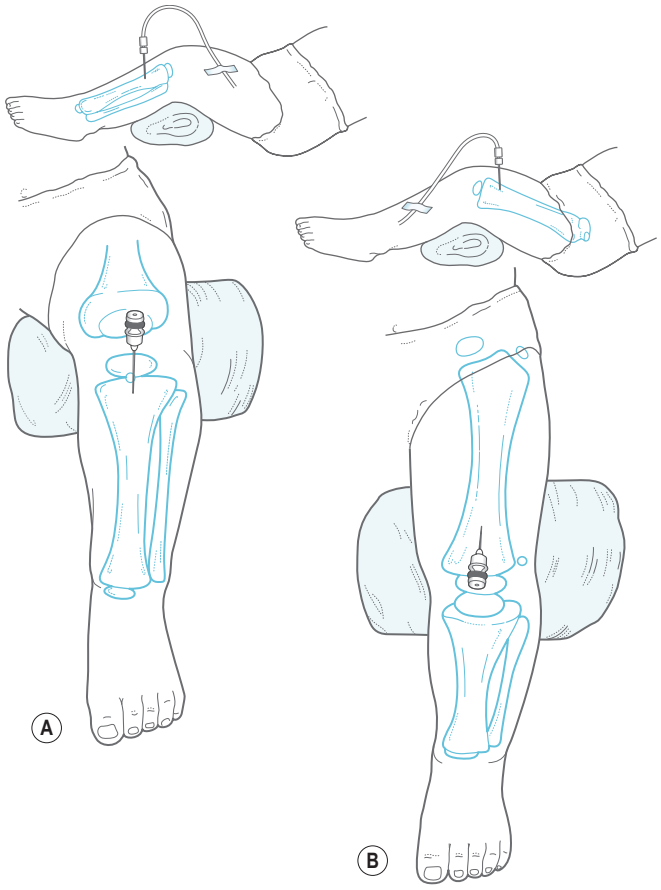

Fig. 35.4 Intraosseous line placement in the proximal tibia (A) and distal femur (B). (From Fleisher G, Ludwig S, eds. *Textbook of Pediatric Emergency Medicine*, 2nd ed. Baltimore: Williams & Wilkins; 1988: 268.)

commonly used "rule of nines," useful in adults and adequate in adolescents, does not accurately reflect the burned body surface area of children under 15 years of age (Fig. 35.5). The standard relationships between body surface area and weight in adults do not apply to children because infants possess a larger cranial surface area and a smaller area in the extremities than adults. The use in children of the most popular resuscitation formulas (initially designed for the adult population) can easily result in suboptimal resuscitation (Table 35.1).

Pediatric burned patients should therefore be resuscitated using formulas based on body surface area, which can be calculated from height and weight using a standard nomogram (Fig. 35.6) or formulas (Table 35.2). The commonly used resuscitation formula in pediatric patients calls for the administration of 5000 mL/m^2 TBSA burned plus 2000 mL/m^2 TBSA for maintenance fluid given over the first 24 hours after burn, with half the volume administered during the initial 8 hours and the second half volume given over the following 16 hours.[18] The subsequent 24 hours, and for the rest of the time their burn wound is open, the requirement is 3750 mL/m^2 TBSA burned or remaining open area plus 1500 mL/m^2 TBSA for maintenance. The fluid requirement decreases as a patient achieves more wound coverage and healing. As in the adult patient, resuscitation formulas offer a guidance for the amount of fluid necessary for replacing lost volume, and the amount of fluid should be titrated according to the patient's response. Resuscitation formulas have been incorporated into manual calculators, electronic devices, and smartphone applications in order to decrease the risk of error and increase the speed of calculation.[19] Hyponatremia is a frequently observed complication in pediatric patients after the first

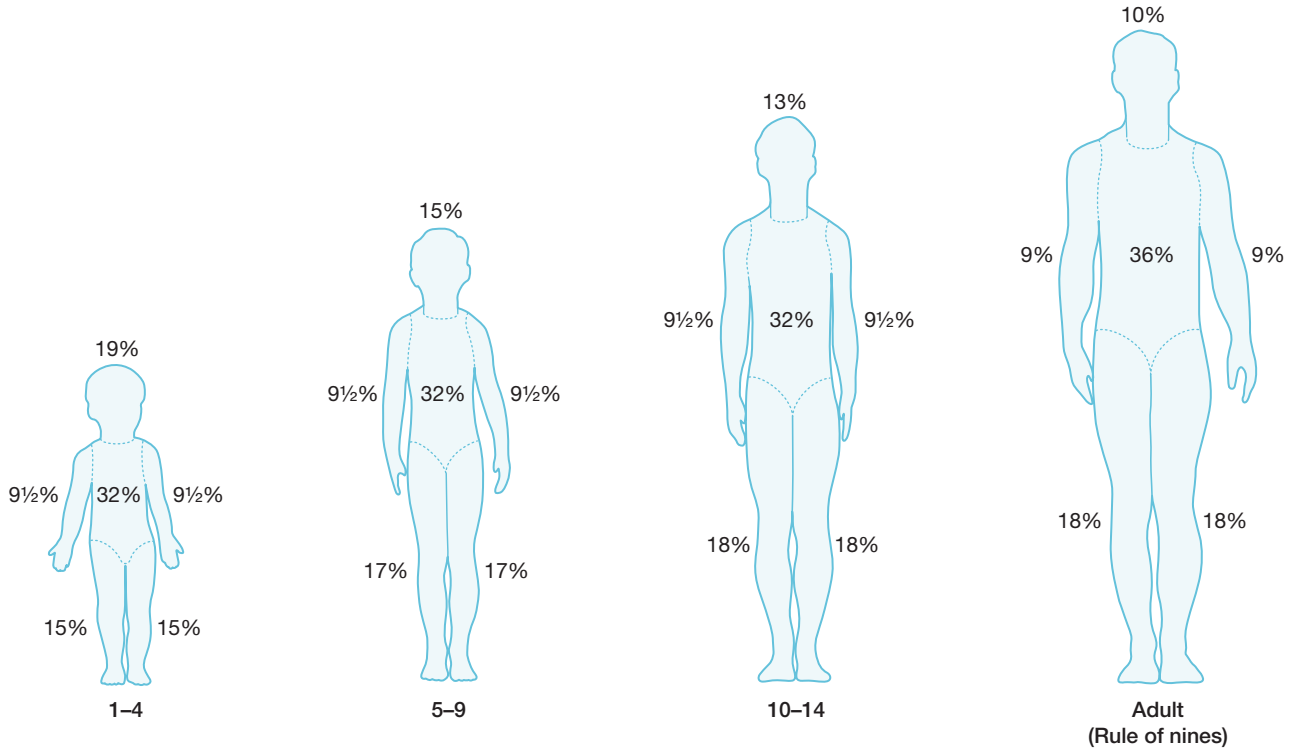

Fig. 35.5 The "rule of nines" altered for the anthropomorphic differences of infancy and childhood.

Table 35.1 Resuscitation by the Parkland Formula Only Compared to Maintenance Fluid Requirements Alone

	CALCULATED NEEDS		REPLACEMENT BURN LOSS		
Example	**% Burn**	**Resuscitation***	**Maintenance†**	**mL**	**mL/kg/%**
1 year old	15	600	800	−200	−1.33
10 kg	30	1200	800	400	1.33
0.48 m^2 BSA	60	2400	800	1 600	2.67
	90	3600	800	2 800	3.11
4 years old	15	990	1200	−210	−0.85
16.5 kg	30	1980	1200	780	1.58
0.68 m^2 BSA	60	3900	1200	2 760	2.79
	90	5940	1200	4 940	3.33
12 years old	15	2400	2250	1 150	1.92
40 kg	30	4800	2550	2 550	2.12
1.13 m^2 BSA	60	9600	2250	7 350	3.06
	90	14,400	2250	12 150	3.38

*4 mL/kg/% burn.
†2000 mL/m^2 BSA.

Table 35.2 Formulas for Calculating Body Surface Area (BSA)

Dubois formula	BSA (m^2) = ht (cm)$^{0.725}$ × wt (kg)$^{0.425}$ × 0.007184
Jacobson formula	BSA (m^2) = [ht (cm) + wt (kg) − 60]/100

48 hours post burn. Frequent monitoring of serum sodium is necessary to guide appropriate electrolyte and fluid management. Children under 1 year of age may require more sodium supplementation because of higher urinary sodium losses. Hypernatremia can also develop, and it has been identified as an independent predictor of mortality in adult burn patients.[20] Potassium losses are usually replaced with oral potassium phosphate rather than potassium chloride, as hypophosphatemia is frequent in this population.[21] Calcium and magnesium losses also must be supplemented.

Intravenous resuscitation fluid should be isotonic and replace lost electrolytes. Lactated Ringer's solution is the most commonly used resuscitation solution for the first 24 hours post burn. Children less than 1 year of age should also receive a separate maintenance fluid solution containing dextrose to prevent hypoglycemia because their glycogen stores are limited.

Assessment of Resuscitation

The routine clinical signs of hypovolemia in adult burn patients, such as low blood pressure and decreased urine output, are late manifestations of shock in the pediatric patient, and tachycardia is ubiquitous. Due to their cardiopulmonary physiologic reserve, pediatric patients do not show overt signs of hypovolemia until a decrease of at least 25% of the total blood volume occurs; at this point, hemodynamic decompensation occurs abruptly. Changes in distal extremity color, capillary refill, pulse pressure, and mental status reflect volume status. Capillary refill is a good indicator of volume status in pediatric patients. Decreased capillary refill should warn a clinician of imminent cardiovascular collapse. Measurements of arterial pH, base deficit, and lactic acid are of particular importance in this age group, reflecting decreased tissue perfusion. Improvements in base deficit or lactic acid show successful resuscitation.[22]

Normal blood pressure range varies according to age, with a systolic blood pressure of 100 mm Hg or less considered normal in patients younger than 9 years (Table 35.3). Renal compensatory mechanisms for hypovolemia (e.g., tubular concentration) are not well-developed in young children, contributing to hypovolemia with sustained urine production despite reduced intravascular volume.

An indwelling urinary drainage catheter is essential for burns of greater than 20% during resuscitation. During the early phase of resuscitation, urine output should be assessed hourly and the resuscitation fluid adjusted appropriately. Fluid administration should be titrated to achieve a urine output of 1 mL/kg/h in children and 2 mL/kg/h in infants. Initial fluid boluses should be administered in amounts appropriate to the size of the child and should be less than 25% of the total blood volume (20 mL/kg).

Overresuscitation must be avoided because it can lead to congestive heart failure, pulmonary edema, abdominal and extremity compartment syndromes, and cerebral edema in burn patients. In children, cardiac output depends mainly on the heart rate due to the low compliance of the heart, which limits increase in stroke volume. In addition, the heart is more susceptible to volume overload. Cardiac output can be measured using transpulmonary thermodilution devices, which are less invasive than a pulmonary artery catheter and only require an arterial catheter and a central venous line.[23] Transthoracic or transesophageal echocardiograms should be used early to assess cardiac function in patients who are not responding to conventional therapy. Children are particularly prone to the

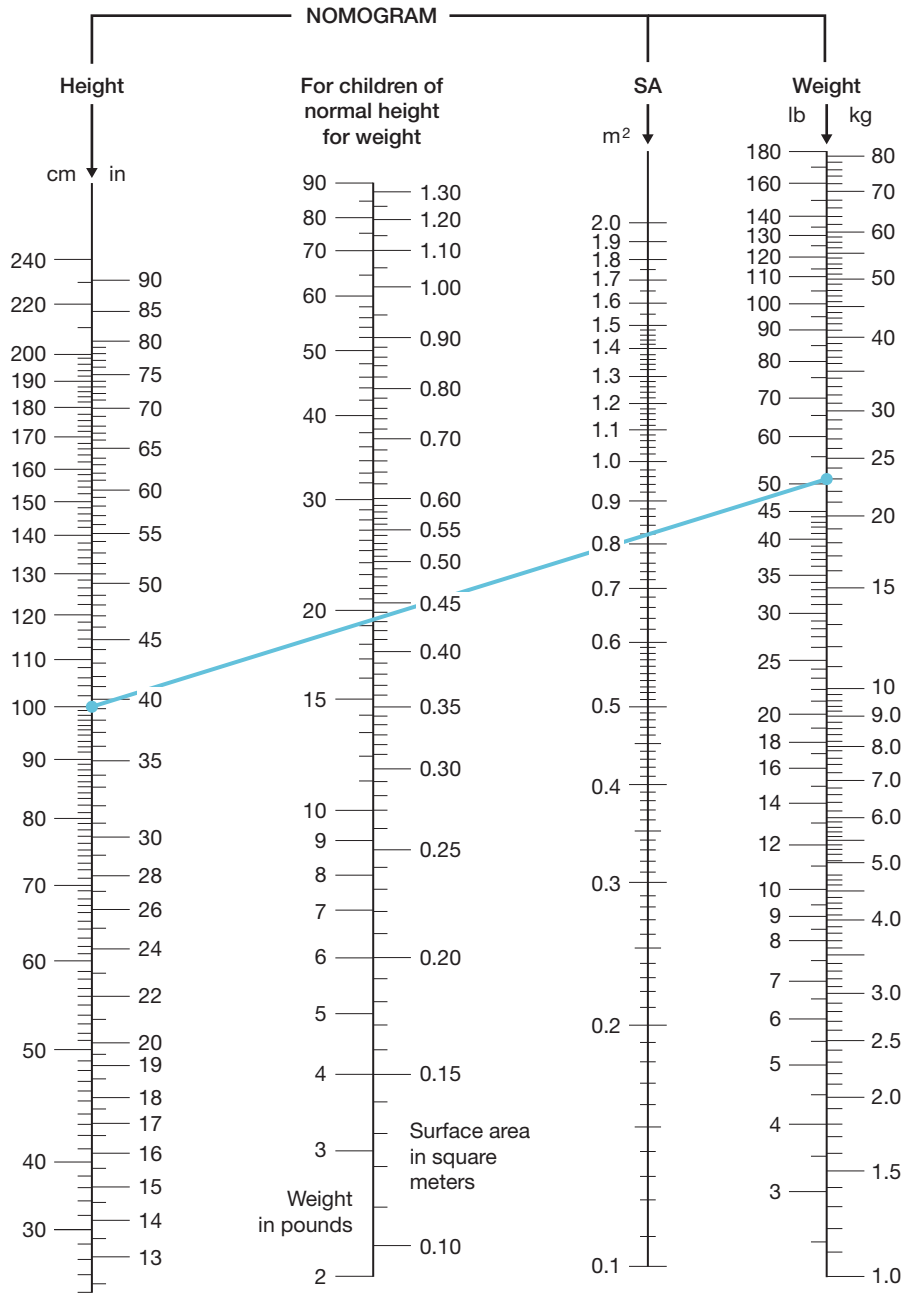

Fig. 35.6 Standard nomogram for the determination of body surface area based on height and weight. The example depicted is for a child of 100 cm in height and 23 kg in weight. (From Eichelberger MR, ed. *Pediatric Trauma: Prevention, Acute Care and Rehabilitation*. St Louis: Mosby Year Book; 1993: 572.)

Table 35.3 Normal Pediatric Vital Signs

Age	Minimum Heart Rate (beats/min)	Systolic Blood Pressure (mmHg)	Respirations (breaths/min)	Minimal Hemoglobin (g/dL)	Minimal Hematocrit (%)
<2 years of age	100–160	86–106	30–40	11.0	33.0
2–5 years of age	80–140	89–112	20–30	11.0	33.0
6–9 years of age	70–120	97–115	18–25	11.5	34–5
9–12 years of age	70–115	102–120	18–25	11.5	34–5
>12 years of age	60–110	90	12–20	12.0	36.0

development of edema from both vasogenic and hydrostatic sources. Vasogenic edema occurs in the early post-burn period when vascular integrity is impaired. The maintenance of intravascular osmotic pressures reduces the likelihood of edema development. In difficult resuscitation, colloids such as albumin can be used. Albumin can be expected to remain in the intravascular space if administered more than 8 hours after burn.

Evaluation and Management of Airways

Airway evaluation and management must be given priority. Children are more prone to obstruction due to the smaller aperture of their trachea. Airway edema causes disproportionate increments in resistance with concomitant reduction of the cross-sectional area.[24] Inhalation injury can lead to delayed airway edema after administration of massive resuscitation fluids.

Potential hemorrhage and edema make emergency intubation difficult. Hence, early intubation should be considered when a long transfer is anticipated, severe inhalation injury is present, or a patient has a large burn that likely will develop airway edema secondary to the large amount of fluid resuscitation. Concurrent placement of an endotracheal tube (ETT) over the bronchoscope should be considered at the time of bronchoscopy. A readily available estimate of airway diameter is the width of the patient's little finger, an age-based formula (age + 16)/4, or the use of a Broselow tape.[25]

The ETT must be well secured. In a child, exudative wounds and moist dressings can make this task difficult. One successful approach is to attach the ETT with tape around the back of the head, both above and below the ears. An additional piece of tape over the top of the head, secured to the tape behind the head, will prevent accidental extubation in most children.[26] In addition, commercially available endotracheal tube holders exist; however securing the tubes with tape strips of sufficient length and width has proved superior to two different commercial tube holders.[27]

Inhalation Injury

Inhalation injury is one of the main contributors to burn mortality.[28,29] The mortality rate of children with isolated thermal burns is 1–2%, but increases to approximately 40% in the presence of inhalation injury.[30,31] Expectedly, inhalation injury is associated with longer hospital stay and increased risk of pneumonia.[32] Carbon monoxide poisoning coupled with hypoxia is the most frequent cause of death due to inhalation injury. Any patient with a flame-related injury, particularly if confined in a closed space, should be evaluated for inhalation injury. If inhalation injury is suspected, arterial blood gas and carboxyhemoglobin levels should be obtained, and the patient should be placed on 100% oxygen. Signs of potential inhalation injury include facial burns, singed nasal vibrissae, carbonaceous sputum, abnormal mental status (agitation or stupor), respiratory distress (dyspnea, stridor, hoarseness, wheezing), or an elevated carboxyhemoglobin level of greater than 10%, especially in a closed-space fire.[33,34] The initial carboxyhemoglobin level should be calculated from the time the admission level is drawn, back to the time of the burn injury. A carboxyhemoglobin level of greater than 60% has a greater than 50% chance of mortality. Diagnosis is made by visualization of the airway with fiberoptic bronchoscopy (Table 35.4).

Table 35.4 Carbon Monoxide Poisoning

Carboxyhemoglobin (%)	Symptoms
0–10	Normal
10–20	Headache, confusion
20–40	Disorientation, fatigue, nausea, visual changes
40–60	Hallucination, combativeness, convulsion, coma, shock state
60–70	Coma, convulsions, weak respiration and pulse
70–80	Decreasing respiration and stopping
80–90	Death in less than 1 hour
90–100	Death within a few minutes

Table 35.5 Airway Maintenance, Clearance, and Pharmacological Management

Turn side to side	q2h
Sitting or rocked in chair	As soon as physiologically stable
Ambulation	Early
Chest physiotherapy	q2h
Suctioning and lavage (nasal/oral tracheal)	q2h
Bronchodilators	q2h
Aerosolized heparin/acetylcysteine	q2h alternating
Heparin 5000–10,000 units with 3 mL NS	q4h
Alternated with acetylcysteine 20% 3 mL	q4h

Treatment modalities for inhalation injury include airway maintenance, secretion clearance, and pharmacological management (Table 35.5). Further care is mainly supportive and includes ventilator support as needed, vigorous pulmonary toilet, humidification of inspired air, and antibiotics for documented infection. A combination of nebulized heparin and N-acetylcysteine has been shown to decrease the duration of mechanical ventilation after inhalation injury.[35–37]

Hypermetabolism

Profound hypermetabolism is a classic feature of children with large burn injury. No other pathological state produces

as dramatic an effect on the metabolic rate as burn injury.[38,39] Hypermetabolism slows wound healing, prolongs generalized weakness, and can lead to loss of lean body mass.

The hypermetabolic response increases with increasing burn size. There is an upregulation of catabolic agents, such as catecholamine, cortisol, and glucagon, which induces a hyperdynamic cardiovascular response; elevated oxygen consumption; increased energy expenditure; proteolysis, lipolysis, and glycogenolysis; loss of lean body mass; delayed wound healing; and immune suppression.[40–43]

Pharmacological agents have been used to attenuate hypermetabolism in burn injury. In order to minimize lean body mass loss, several therapeutic agents have been used in pediatric burned patients: anabolic hormones such as recombinant human growth hormone, insulin, and insulin-like growth factor-1 (IGF-1); anabolic steroids such as testosterone and synthetic analogue oxandrolone; and adrenergic antagonists such as propranolol.[44–50]

THERMOREGULATION

Hypothalamic dysregulation induced by various inflammatory cytokines and pain causes elevation of core body temperature after a major burn even in the absence of infection. Burn patients strive for temperatures of around 38°C. Low temperature is more likely indicative of overwhelming sepsis or exhausted physiological capabilities. The augmented heat loss secondary to epidermal loss after a major burn makes conventional methods of heat conservation inappropriate in burn patients.[51,52] In addition, low muscle mass in young children and their limited shivering capacity are factors that increase the risk of hypothermia in this population.[53]

Every effort should be made to reduce heat loss. Environmental temperature should be maintained at 30–33°C in order to reduce energy demands and evaporative water losses. Bathing should be performed expeditiously, with avoidance of unnecessary environmental exposure.[54]

Hypothermia produces numerous consequences. The heart is particularly sensitive to temperature, and ventricular arrhythmias are not uncommon. Hypothermia also increases the susceptibility of the myocardium to changes in electrolyte concentrations. The oxyhemoglobin dissociation curve is shifted to the left by decreased body temperature, impairing peripheral oxygenation. In extreme cases, hypothermia produces central nervous system and respiratory depression, coagulopathy, and loss of peripheral vasomotor tone.[41]

NUTRITIONAL SUPPORT

Nutritional support becomes an essential part of treatment of acute burn patients. Early enteral nutrition is used to accomplish nutritional support of the hypermetabolic response in severely burned patients. Early enteral nutrition preserves gut mucosal integrity, improves intestinal blood flow and motility, and can abate the hypermetabolic response to burn.[55,56] Patients with smaller burns should receive a high-protein, high-calorie diet to support their metabolic response. Those with burns covering more than 30% of the TBSA benefit from enteral feedings to supplement their diet.

Table 35.6 Nutritional Requirements for Children

	Galveston	Modified Curreri
Infant burn	2100 kcal/m^2 + 1000 kcal/m^2 burn	BMR + 15 kcal/%
Toddler burn		BMR + 25 kcal/%
Child burn	1800 kcal/m^2 + 1300 kcal/m^2 burn	BMR + 40 kcal/%
Adolescent burn	1500 kcal/m^2 + 1500 kcal/m^2 burn	

Feeding tubes can be placed beyond the pylorus and enteral nutrition initiated within a few hours of admission. Most children will tolerate enteral feedings as early as 1–2 hours post burn. Several studies have demonstrated the efficacy of early alimentation and its additional salutary effects.[57,58] Enteral feedings can be given through a flexible nasoduodenal or nasojejunal feeding tube, bypassing the stomach.

Several formulas are available to estimate caloric requirements in burn patients. Since caloric demands are related to burn size, caloric support should be given in amounts calculated based on total and burned body surface areas in burned children. A series of different formulas based on body surface areas have been developed to meet the differing requirements of the various age groups.[59–61] The Curreri formula has likewise been amended to reflect the differing demands of the pediatric group (Table 35.6).

Growth Delay

Increased protein degradation has been reported up to 9 months after major burns. Growth delay and osteopenia can persist up to 2 years in children.[44,62,63] Despite adequate nutritional support, children with greater than 40% TBSA burn have a linear growth delay of height and weight and a decrease in maximal exercise capacity during the first year after burn, which slowly resolves to near normal distribution by post-burn year 3.[64] Administration of propranolol and oxandrolone has been shown to ameliorate growth delay secondary to burn injury in children.[50]

Management of Burn Wound

One of the most important advances in the care of burn patients is the early surgical excision and grafting of the burn wound. Improvements in the treatment of burn wounds with the practice of early excision and grafting, along with improvements in fluid resuscitation and the general care of burn patients, have reduced the incidence of sepsis in burn patients.[65] Prior to early excision and grafting, third-degree burns were treated by removing small amounts of eschar at a time followed by grafting. Commonly, eschar was allowed to separate through lysis by bacterial enzymes, which led to a high incidence of invasive

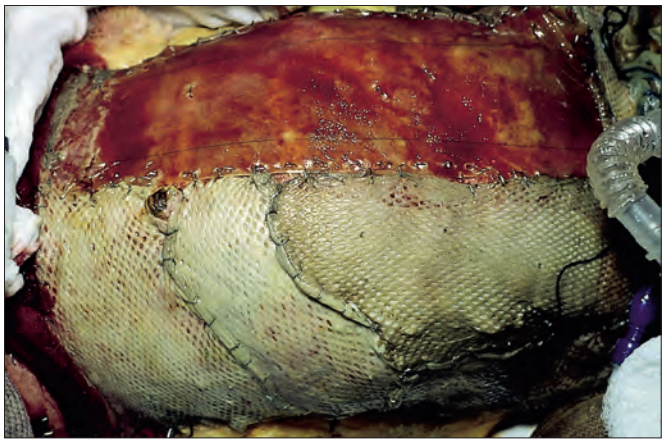

Fig. 35.7 Dermal and skin substitutes can be used as temporary cover for severe burns. Integra, a bilaminar skin substitute, can replace homografts as temporary cover. The Silastic superficial layer can be removed after 3 weeks and a super-thin autograft then placed on top. The entire wound can be covered with Integra, which is subsequently autografted when donor sites are available. (From Barret J, Herndon DN, eds. *Color Atlas of Burn Care*. London: WB Saunders; 2001: 107,„late 6.95.)

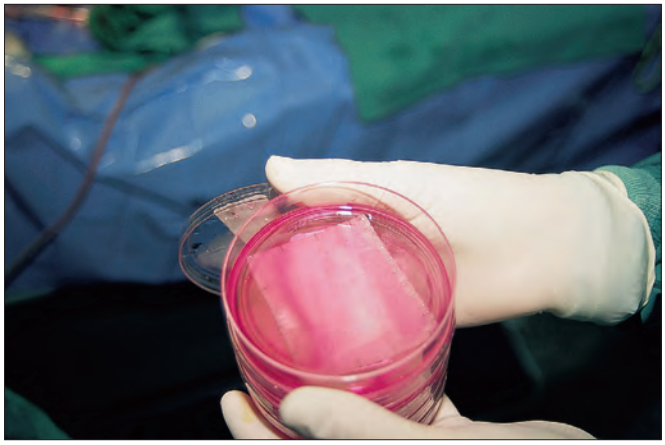

Fig. 35.8 The cultured epidermal autografts are ready to use 18–21 days later. Extreme care with handling is needed because of the fragility of the cultured cells. (From Barret J, Herndon DN, eds. *Color Atlas of Burn Care*. London: WB Saunders; 2001: 106, plate 6.89.)

infection, wound sepsis, increased length of hospital stay, and increased mortality. Currently, massive excision can be easily managed in children and contributes to shortened length of hospital stay and reduced mortality.[66,67] Early excision of massive burns in the first 24 hours is safe and effective.[68]

By using skin substitutes such as allograft, xenograft, and Integra (Fig. 35.7), the burn wound can be covered and protected until donor sites are available for procurement. Cultured epidermal autografts (CEA) are available for massive burn injuries (Fig. 35.8). Although it is an effective way to cover large burns where donor sites are limited, it may not be the most cost-effective approach. A group of patients treated with CEA had greater hospital costs, a longer hospital stay, and required more reconstructive surgical admissions when compared to patients who received conventional treatment with meshed autograft skin.[66]

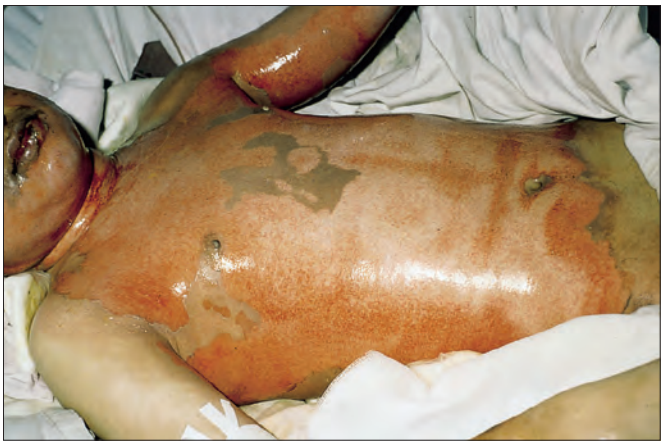

Fig. 35.9 Superficial and small areas of deep second-degree scald burns before topical treatment: 25% total body surface area. (From Barret J, Herndon DN, eds. *Color Atlas of Burn Care*. London: WB Saunders; 2001: 79, plate 5.39.)

Traditionally, topical antimicrobials were the most commonly used treatment in partial-thickness burns. One of the drawbacks of using topical antimicrobials in burn wounds is the pain associated with dressing changes, especially in children. Immediate application of Biobrane is one of the treatment options for partial-thickness burns, primarily scald burns covering less than 30% of the TBSA. Biobrane can be safely used in children, including infants. When applied within 48 h of burn, there is no difference in infection rates between Biobrane and topical antimicrobials. Furthermore, Biobrane application leads to less pain, shorter hospitalizations, and shorter healing times compared to topical antimicrobials.[69–71] Other silver-based dressings such as Acticoat, Aquacel, Silverlon, and Mepilex Ag are available for partial-thickness burns that can be left on for several days, thus decreasing the number of dressing changes and the associated pain.[72–74]

It may be difficult clinically to determine the precise depth of scald burns during the early post-burn period because the wounds may be indeterminate and contain a mixture of superficial and deep partial-thickness burns and sometimes even full-thickness burns. Indeterminate-depth scald burns covering less than 20% of the TBSA in young children are best managed with delayed surgical intervention instead of early excision. Unless the wound is clearly full thickness, the scald burn should be conservatively managed for approximately 2 weeks to allow the wound to heal or demarcate (Figs. 35.9 and 35.10). This delayed surgery results in a smaller area of wound being excised and less blood loss.[75]

Large scald burns can be treated with allograft or xenograft, which significantly reduces the pain involved with dressing change and wound care. Scald burns covering more than 20% of the TBSA and of indeterminate depth were randomized to treatment with allograft skin versus topical antimicrobial therapy. Treatment with allograft skin led to faster healing and less pain.[76] In another study, patients with greater than 40% TBSA burn were randomized to treatment with allograft skin or topical antimicrobials. Patients who received allograft skin had a significantly shorter length of hospital stay.[77]

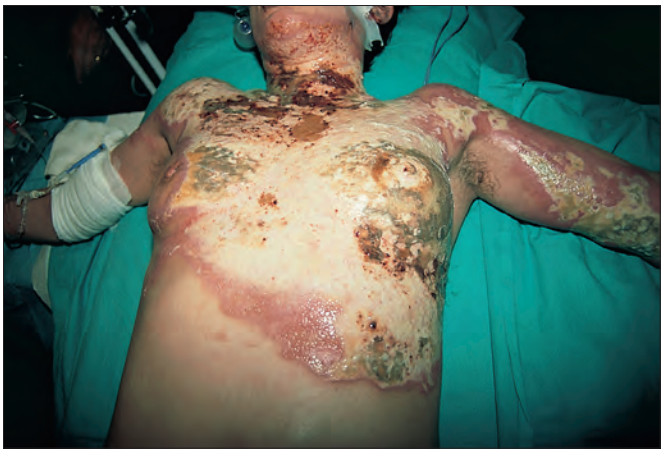

Fig. 35.10 Deep second-degree burns treated for 10 days with silver sulfadiazine. Note that the edges are regenerating. Pseudo-eschar challenges the evaluation of the wounds. Foul smell, discoloration, surrounding cellulitis, and eschar separation are signs of infection. (From Barret J, Herndon DN, eds. *Color Atlas of Burn Care.* London: WB Saunders; 2001: 77, plate 5.31.)

Pain Management

Therapeutic interventions such as wound care, surgical interventions, and physical therapy cause significant pain.[78,79] Despite advances in burn care, procedural pain continues to be severe and undertreated.[80] Well-controlled pain in the post-burn period has been associated with improved clinical outcomes (i.e., wound healing, re-epithelialization rates).[80–82] Conversely, poorly managed pain is associated with dysesthesias, chronic pain, and debilitating psychological conditions.[83]

Pain assessment in pediatric patients must be individualized to the patients' age, clinical conditions, and preferences. Verbal pain scales that assess pain severity are the most commonly used assessment tools.[84] Published studies report that burn patients preferred face and color scales over visual analogs and adjective scales.[85] When factors related to the injury or the treatment limit the capacity of the patient to communicate, the evaluation of the patient's behavior is a valid alternative. However it is recognized that these patients are at increased risk for inadequate treatment of their pain.[86]

The intravenous route is the preferred mode of analgesic administration in the acute phase post-burn. Significant changes in the metabolism of nonopioid medications (altered volume distribution due to carrier protein changes, alterations in receptor sensitivity) have been reported after burn injury.[87–89] Morphine sulfate and lorazepam pharmacokinetics seem to remain unaltered after burn injury; however it has been reported that their clearance rates increase after massive burns (>80% TBSA burn).[90–92] Morphine sulfate is one of the most commonly used analgesic in pediatric burn patients.[93] Fentanyl is another safe and efficacious alternative. Despite enthusiasm and increased interest, the routine use of intravenous local anesthetics is not advocated.[94]

Fentanyl Oralet (10 μg/kg) has been used successfully in the outpatient setting for dressing changes and wound care. Most outpatients are treated with hydrocodone/acetaminophen, and some require longer-acting narcotics such as methadone.

Nonpharmacological methods, including hypnosis, distraction techniques, and the use of virtual reality can be used in combination with pharmacological options for the treatment of pain and anxiety.[78,95–98]

Rehabilitation

One of the integral parts of successful treatment of burn injury is rehabilitation. During the acute phase of burn care, splints and proper positioning are used to minimize joint deformities and contractures. Splints are fabricated and adapted to meet individual needs and used preferably from the first day of hospitalization. Bedside therapy, including passive and active range of motion, is started early. Patients with leg grafts are kept on bed rest after the operation, but on postoperative day 3 they are allowed and encouraged to ambulate. Early physical therapy and ambulation are the keys to success in the long-term rehabilitation of burned children. When patients are discharged from their acute-care hospitalization, they follow rigorous outpatient treatment plans that include stretching, range of motion, and strengthening exercises.

Prevention

Prevention remains the single best way to reduce pediatric burn injuries. National prevention and education efforts have significantly decreased the number of pediatric burns each year. Lowering the temperature set point on water heaters and educating families to check the bath water temperature before placing a child in the bath have reduced scald burns. Prevention groups have worked with water heater companies and the Consumer Product Safety Commission (CPSC) to provide education to raise gas water heaters 12 inches above the ground, which significantly reduces the risk of accidental explosions and fires.

Three-quarters of "child fire play" involves matches or lighters. All matches and other ignition sources must be placed out of reach of children. A positive step toward prevention occurred in 1994 when the CPSC put into effect a child-resistant lighter to protect children. The importance of placing smoke detectors in multiple areas of the house cannot be overstated. Current prevention education focuses on children and especially infants who are not able to remove themselves from a fire. Educating children as early as possible that fire is dangerous is imperative. Providing safe environments for children and providing appropriate education is the responsibility of healthcare providers, the adults who care for them, and the community.

Complete references available online at
www.expertconsult.inkling.com

Further Reading

Williams FN, Herndon DN, Jeschke MG. The hypermetabolic response to burn injury and interventions to modify this response. *Clin Plast Surg.* 2009;36(4):583-596.

References

1. National Burn Repository. American Burn Association. 2015.
2. Istre GR, McCoy MA, Moore BJ, et al. Preventing deaths and injuries from house fires: an outcome evaluation of a community-based smoke alarm installation programme. *Inj Prev*. 2014;20(2):97-102.
3. Istre GR, McCoy MA, Osborn L, Barnard JJ, Bolton A. Deaths and injuries from house fires. *N Engl J Med*. 2001;344(25):1911-1916.
4. Lee CJ, Mahendraraj K, Houng A, et al. Pediatric burns: a single institution retrospective review of incidence, etiology, and outcomes in 2273 burn patients (1995–2013). *J Burn Care Res*. 2016;37(6):e579-e585.
5. Delgado J, Ramirez-Cardich ME, Gilman RH, et al. Risk factors for burns in children: crowding, poverty, and poor maternal education. *Inj Prev*. *England* 2002;8(1):38-41.
6. Stockton KA, Harvey J, Kimble RM. A prospective observational study investigating all children presenting to a specialty paediatric burns centre. *Burns*. 2015;41(3):476-483.
7. Brigham PA, McLoughlin E. Burn incidence and medical care use in the United States: estimates, trends, and data sources. *J Burn Care Rehabil*. 1996;17(2):95-107. PMID: 8675512.
8. Bull JP, Squire JR. A study of mortality in a burns unit: standards for the evaluation of alternative methods of treatment. *Ann Surg*. 1949;130(2):160-173.
9. Herndon DN, Gore D, Cole M, et al. Determinants of mortality in pediatric patients with greater than 70% full-thickness total body surface area thermal injury treated by early total excision and grafting. *J Trauma*. 1987;27(2):208-212.
10. Wolf SE, Rose JK, Desai MH, et al. Mortality determinants in massive pediatric burns. An analysis of 103 children with > 80% TBSA burns (> 70% full-thickness). *Ann Surg*. 1997;225(5):554-565, discussion 565.
11. Baartmans MGA, de Jong AEE, van Baar ME, et al. Early management in children with burns: cooling, wound care and pain management. *Burns*. 2016;42(4):777-782.
12. Walker A, Baumber R, Robson B. Pre-hospital management of burns by the UK fire service. *Emerg Med J*. 2005;22(3):205-208.
13. Allison K, Porter K. Consensus on the prehospital approach to burns patient management. *Emerg Med J*. 2004;21(1):112-114.
14. Wolf SE, Rose JK, Desai MH, et al. Mortality determinants in massive pediatric burns. An analysis of 103 children with > or = 80% TBSA burns (> or = 70% full-thickness). *Ann Surg*. 1997;225(5):554-565, discussion 565-569.
15. Tocantins LM, O'Neill JF. Infusions of blood and other fluids into the general circulation via the bone marrow. *Surg Gynecol Obs*. 1941;73 SRC:281-287.
16. Fiser DH. Intraosseous infusion. *N Engl J Med*. 1990;322(22): 1579-1581.
17. Engle WA. Intraosseous access for administration of medications in neonates. *Clin Perinatol*. 2006;33(1):161-168, ix.
18. Carvajal HF. A physiologic approach to fluid therapy in severely burned children. *Surg Gynecol Obstet*. 1980;150(3):379-384.
19. Dingley J, Cromey C, Bodger O, Williams D. Evaluation of 2 novel devices for calculation of fluid requirements in pediatric burns. *Ann Plast Surg*. 2015;74(6):658-664.
20. Stewart IJ, Morrow BD, Tilley MA, et al. Dysnatremias and survival in adult burn patients: a retrospective analysis. *Am J Nephrol*. 2013;37(1):59-64.
21. Kreusser W, Ritz E. The phosphate-depletion syndrome. *Contrib Nephrol*. 1978;14:162-174.
22. Ranjit S, Aram G, Kissoon N, et al. Multimodal monitoring for hemodynamic categorization and management of pediatric septic shock: a pilot observational study. *Pediatr Crit Care Med*. 2014;15(1):e17-e26.
23. Wurzer P, Branski LK, Jeschke MG, et al. Transpulmonary thermodilution versus transthoracic echocardiography for cardiac output measurements in severely burned children. *Shock*. 2016;46(3):249-253.
24. Wheeler M, Cote CJ, Todres ID. The pediatric airway. In: Cote CJ, Lerman J, Todres ID, eds. *A Practice of Anesthesia for Infants and Children*. 4th ed. Philadelphia: Saunders; 2009:237-278.
25. Phipps LM, Thomas NJ, Gilmore RK, et al. Prospective assessment of guidelines for determining appropriate depth of endotracheal tube placement in children. *Pediatr Crit Care Med*. 2005;6(5):519-522.
26. Mlcak R, Cortiella J, Desai MH, Herndon DN. Emergency management of pediatric burn victims. *Pediatr Emerg Care*. 1998;14(1):51-54.
27. Shimizu T, Mizutani T, Yamashita S, Hagiya K, Tanaka M. Endotracheal tube extubation force: adhesive tape versus endotracheal tube holder. *Respir Care*. 2011;56(11):1825-1829.
28. Barrow RE, Spies M, Barrow LN, Herndon DN. Influence of demographics and inhalation injury on burn mortality in children. *Burns*. 2004;30(1):72-77.
29. Tan A, Smailes S, Friebel T, et al. Smoke inhalation increases intensive care requirements and morbidity in paediatric burns. *Burns*. 2016;42(5):1111-1115.
30. Herndon DN, Thompson PB, Traber DL. Pulmonary injury in burned patients. *Crit Care Clin*. 1985;1(1):79-96.
31. Thompson PB, Herndon DN, Traber DL, Abston S. Effect on mortality of inhalation injury. *J Trauma*. 1986;26(2):163-165.
32. Liodaki E, Kalousis K, Mauss KL, et al. Epidemiology of pneumonia in a burn care unit: the influence of inhalation trauma on pneumonia and of pneumonia on burn mortality. *Ann Burns Fire Disasters*. 2015;28(2):128-133.
33. McCall JE, Cahill TJ. Respiratory care of the burn patient. *J Burn Care Rehabil*. 2005;26(3):200-206.
34. Mlcak RP, Suman OE, Herndon DN. Respiratory management of inhalation injury. *Burns*. 2007;33(1):2-13.
35. Elsharnouby NM, Eid HEA, Abou Elezz NF, Aboelatta YA. Heparin/N-acetylcysteine: an adjuvant in the management of burn inhalation injury: a study of different doses. *J Crit Care*. 2014;29(1):182.e1-182.e4.
36. Glas GJ, Serpa Neto A, Horn J, et al. Nebulized heparin for patients under mechanical ventilation: an individual patient data meta-analysis. *Ann Intensive Care*. 2016;6(1):33.
37. Miller AC, Rivero A, Ziad S, Smith DJ, Elamin EM. Influence of nebulized unfractionated heparin and N-acetylcysteine in acute lung injury after smoke inhalation injury. *J Burn Care Res*. 2009;30(2):249-256.
38. Lee JO, Benjamin D, Herndon DN. Nutrition support strategies for severely burned patients. *Nutr Clin Pract*. 2005;20(3):325-330.
39. Wilmore DW. Nutrition and metabolism following thermal injury. *Clin Plast Surg*. 1974;1(4):603-619.
40. Pereira CT, Herndon DN. The pharmacologic modulation of the hypermetabolic response to burns. *Adv Surg*. 2005;39:245-261.
41. Williams FN, Jeschke MG, Chinkes DL, et al. Modulation of the hypermetabolic response to trauma: temperature, nutrition, and drugs. *J Am Coll Surg*. 2009;208(4):489-502.
42. Reference removed while revising.
43. Barrow RE, Hawkins HK, Aarsland A, et al. Identification of factors contributing to hepatomegaly in severely burned children. *Shock*. 2005;24(6):523-528.
44. Branski LK, Herndon DN, Barrow RE, et al. Randomized controlled trial to determine the efficacy of long-term growth hormone treatment in severely burned children. *Ann Surg*. 2009;250(4):514-523.
45. Jeschke MG, Kulp GA, Kraft R, et al. Intensive insulin therapy in severely burned pediatric patients: a prospective randomized trial. *Am J Respir Crit Care Med*. 2010;182(3):351-359.
46. Spies M, Wolf SE, Barrow RE, Jeschke MG, Herndon DN. Modulation of types I and II acute phase reactants with insulin-like growth factor-1/binding protein-3 complex in severely burned children. *Crit Care Med*. 2002;30(1):83-88.
47. Jeschke MG, Finnerty CC, Suman OE, et al. The effect of oxandrolone on the endocrinologic, inflammatory, and hypermetabolic responses during the acute phase postburn. *Ann Surg*. 2007;246(3):351-360, discussion 360.
48. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR. Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med*. 2001;345(17):1223-1229.
49. Diaz EC, Herndon DN, Porter C, et al. Effects of pharmacological interventions on muscle protein synthesis and breakdown in recovery from burns. *Burns*. 2015;41(4):649-657.
50. Herndon DN, Voigt CD, Capek KD, et al. Reversal of growth arrest with the combined administration of oxandrolone and propranolol in severely burned children. *Ann Surg*. 2016;264(3):421-428.
51. Ganio MS, Schlader ZJ, Pearson J, et al. Nongrafted skin area best predicts exercise core temperature responses in burned humans. *Med Sci Sports Exerc*. 2015;47(10):2224-2232.
52. Shapiro Y, Epstein Y, Ben-Simchon C, Tsur H. Thermoregulatory responses of patients with extensive healed burns. *J Appl Physiol*. 1982;53(4):1019-1022.
53. Mlcak RP, Desai MH, Robinson E, et al. Temperature changes during exercise stress testing in children with burns. *J Burn Care Rehabil*. 1993;14(4):427-430.
54. McCormack RA, La Hei ER, Martin HCO. First-aid management of minor burns in children: a prospective study of children

presenting to the Children's Hospital at Westmead, Sydney. *Med J Aust*. 2003;178(1):31-33.
55. Mochizuki H, Trocki O, Dominioni L, et al. Mechanism of prevention of postburn hypermetabolism and catabolism by early enteral feeding. *Ann Surg*. 1984;200(3):297-310.
56. Dominioni L, Trocki O, Fang CH, et al. Enteral feeding in burn hypermetabolism: nutritional and metabolic effects of different levels of calorie and protein intake. *JPEN J Parenter Enteral Nutr*. 1985;9(3):269-279.
57. Enzi G, Casadei A, Sergi G, et al. Metabolic and hormonal effects of early nutritional supplementation after surgery in burn patients. *Crit Care Med*. 1990;18(7):719-721.
58. McDonald WS, Sharp CW, Deitch EA. Immediate enteral feeding in burn patients is safe and effective. *Ann Surg*. 1991;213(2):177-183.
59. Hildreth MA, Herndon DN, Desai MH, Broemeling LD. Caloric requirements of patients with burns under one year of age. *J Burn Care Rehabil*. 1993;14(1):108-112.
60. Hildreth MA, Herndon DN, Desai MH, Duke MA. Caloric needs of adolescent patients with burns. *J Burn Care Rehabil*. 1989;10(6):523-526.
61. Hildreth MA, Herndon DN, Desai MH, Broemeling LD. Current treatment reduces calories required to maintain weight in pediatric patients with burns. *J Burn Care Rehabil*. 1990;11(5):405-409.
62. Klein GL, Herndon DN, Langman CB, et al. Long-term reduction in bone mass after severe burn injury in children. *J Pediatr*. 1995;126(2):252-256.
63. Klein GL, Wolf SE, Goodman WG, Phillips WA, Herndon DN. The management of acute bone loss in severe catabolism due to burn injury. *Horm Res*. 1997;48(suppl 5):83-87.
64. Rutan RL, Herndon DN. Growth delay in postburn pediatric patients. *Arch Surg*. 1990;125(3):392-395.
65. Merrell SW, Saffle JR, Larson CM, Sullivan JJ. The declining incidence of fatal sepsis following thermal injury. *J Trauma*. 1989;29(10):1362-1366.
66. Herndon DN, Parks DH. Comparison of serial debridement and autografting and early massive excision with cadaver skin overlay in the treatment of large burns in children. *J Trauma*. 1986;26(2):149-152.
67. Thompson P, Herndon DN, Abston S, Rutan T. Effect of early excision on patients with major thermal injury. *J Trauma*. 1987;27(2):205-207.
68. Barret JP, Wolf SE, Desai M. Total burn wound excision of massive paediatric burns in the first 24 hours post-injury. *Ann Burns Fire Disasters*. 1999;12(1):25-27.
69. Barret JP, Dziewulski P, Ramzy PI, et al. Biobrane versus 1% silver sulfadiazine in second-degree pediatric burns. *Plast Reconstr Surg*. 2000;105(1):62-65.
70. Lal S, Barrow RE, Wolf SE, et al. Biobrane improves wound healing in burned children without increased risk of infection. *Shock*. 2000;14(3):314-318, discussion 318.
71. Lang EM, Eiberg CA, Brandis M, Stark GB. Biobrane in the treatment of burn and scald injuries in children. *Ann Plast Surg*. 2005;55(5):485-489.
72. Varas RP, O'Keeffe T, Namias N, et al. A prospective, randomized trial of Acticoat versus silver sulfadiazine in the treatment of partial-thickness burns: which method is less painful? *J Burn Care Rehabil*. 2005;26(4):344-347.
73. Caruso DM, Foster KN, Blome-Eberwein SA, et al. Randomized clinical study of Hydrofiber dressing with silver or silver sulfadiazine in the management of partial-thickness burns. *J Burn Care Res*. 2006;27(3):298-309.
74. Schiefer JL, Rahmanian-Schwarz A, Schaller H-E, Manoli T. A novel hand-shaped suprathel simplifies the treatment of partial-thickness burns. *Adv Skin Wound Care*. 2014;27(11):513-516.
75. Desai MH, Rutan RL, Herndon DN. Conservative treatment of scald burns is superior to early excision. *J Burn Care Rehabil*. 1991;12(5):482-484.
76. Rose JK, Desai MH, Mlakar JM, Herndon DN. Allograft is superior to topical antimicrobial therapy in the treatment of partial-thickness scald burns in children. *J Burn Care Rehabil*. 1997;18(4):338-341.
77. Naoum JJ, Roehl KR, Wolf SE, Herndon DN. The use of homograft compared to topical antimicrobial therapy in the treatment of second-degree burns of more than 40% total body surface area. *Burns*. 2004;30(6):548-551.
78. Chester SJ, Stockton K, De Young A, et al. Effectiveness of medical hypnosis for pain reduction and faster wound healing in pediatric acute burn injury: study protocol for a randomized controlled trial. *Trials*. 2016;17(1):223.
79. Lipman AG. Pain as a human right: the 2004 Global Day Against Pain. *J Pain Palliat Care Pharacother*. 2005;85-100.
80. Brown NJ, Kimble RM, Rodger S, Ware RS, Cuttle L. Play and heal: randomized controlled trial of Ditto intervention efficacy on improving re-epithelialization in pediatric burns. *Burns*. 2014;40(2):204-213.
81. Brown NJ, Kimble RM, Gramotnev G, Rodger S, Cuttle L. Predictors of re-epithelialization in pediatric burn. *Burns*. 2014;40(4):751-758.
82. Miller K, Rodger S, Kipping B, Kimble RM. A novel technology approach to pain management in children with burns: a prospective randomized controlled trial. *Burns*. 2011;37(3):395-405.
83. Summer GJ, Puntillo KA, Miaskowski C, Green PG, Levine JD. Burn injury pain: the continuing challenge. *J Pain*. 2007;8(7):533-548.
84. Whaley LF, Wong DL. Effective communication strategies for pediatric practice. *Pediatr Nurs*. 1985;11(6):429-432.
85. Gordon M, Greenfield E, Marvin J, Hester C, Lauterbach S. Use of pain assessment tools: is there a preference? *J Burn Care Rehabil*. 1998;19(5):451-454.
86. Herr K, Coyne PJ, Key T, et al. Pain assessment in the nonverbal patient: position statement with clinical practice recommendations. *Pain Manag Nurs*. 2006;7(2):44-52.
87. Martyn JAJ, Chang Y, Goudsouzian NG, Patel SS. Pharmacodynamics of mivacurium chloride in 13- to 18-yr-old adolescents with thermal injury. *Br J Anaesth*. 2002;89(4):580-585.
88. Martyn JA, Bishop AL, Oliveri MF. Pharmacokinetics and pharmacodynamics of ranitidine after burn injury. *Clin Pharmacol Ther*. 1992;51(4):408-414.
89. Martyn JA, Greenblatt DJ, Hagen J, Hoaglin DC. Alteration by burn injury of the pharmacokinetics and pharmacodynamics of cimetidine in children. *Eur J Clin Pharmacol*. 1989;36(4):361-367.
90. Herman RA, Veng-Pedersen P, Miotto J, Komorowski J, Kealey GP. Pharmacokinetics of morphine sulfate in patients with burns. *J Burn Care Rehabil*. 1994;15(2):95-103.
91. Perreault S, Choiniere M, du Souich PB, Bellavance F, Beauregard G. Pharmacokinetics of morphine and its glucuronidated metabolites in burn injuries. *Ann Pharmacother*. 2001;35(12):1588-1592.
92. Martyn J, Greenblatt DJ. Lorazepam conjugation is unimpaired in burn trauma. *Clin Pharmacol Ther*. 1988;43(3):250-255.
93. Ratcliff SL, Brown A, Rosenberg L, et al. The effectiveness of a pain and anxiety protocol to treat the acute pediatric burn patient. *Burns*. 2006;32(5):554-562.
94. Jonsson A, Cassuto J, Hanson B. Inhibition of burn pain by intravenous lignocaine infusion. *Lancet*. 1991;338(8760):151-152.
95. Kipping B, Rodger S, Miller K, Kimble RM. Virtual reality for acute pain reduction in adolescents undergoing burn wound care: a prospective randomized controlled trial. *Burns*. 2012;38(5):650-657.
96. Suarez-Mejias C, Gomez-Ciriza G, Valverde I, Parra Calderon C, Gomez-Cia T. New technologies applied to surgical processes: virtual reality and rapid prototyping. *Stud Health Technol Inform*. 2015;210:669-671.
97. Hoffman HG, Meyer WJ 3rd, Ramirez M, et al. Feasibility of articulated arm mounted Oculus Rift Virtual Reality goggles for adjunctive pain control during occupational therapy in pediatric burn patients. *Cyberpsychol Behav Soc Netw*. 2014;17(6):397-401.
98. Jeffs D, Dorman D, Brown S, et al. Effect of virtual reality on adolescent pain during burn wound care. *J Burn Care Res*. 2014;35(5):395-408.

36 Care of Geriatric Patients

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Introduction

The quality of life in developed countries has improved over the past 50 years, increasing the average lifespan by nearly 30 years.[1] Individuals aged 65 years and over account for 13% of the U.S. population. This "elderly" population is projected to double from 40.2 million in 2010 to 88.5 million by 2050. Such population aging is unprecedented.[2] By 2050, the number of older adults persons in the world is expected to exceed the number of young for the first time in history.[3] This trend presents a special challenge because older adults will constitute an ever-growing segment of the average surgeon's practice and will influence clinical decisions, ethical decisions, and healthcare costs.

A multicenter study conducted in Tokyo found that 25% of burned patients were older than 65 years of age.[4] A systematic review of more than 186,500 patients in Europe showed that 10–16% were in this age range.[5] In the United States, geriatric patients constitute about 10% of the major burn population. The anticipated rise in the geriatric population makes understanding age-related physiological and metabolic changes even more important for burn care professionals.[6–8] The elderly and the very young are most likely to die from severe burns.[9–13] Adults older than 65 years old have a mortality rate from burns that is five times the national average.[9,13] Treatment of these patients remains a greater challenge than treatment of middle-aged and younger patients because lower physiological reserves and higher underlying comorbidities reduce the margin for error.

Epidemiology

Contact with flame is the main (54%) cause of burn injury.[13] One third of injuries result from cooking accidents: scalds in 22% of cases and contact with hot objects in about 6% of cases.[6–8,13,14] The latter cause is more prevalent in older adults, reflecting increased psychological and physical disability. This fact is also reflected in the rate of fire-related deaths in individuals older 75 years old, which is four times the national average. The male-to-female ratio decreases progressively as age increases, with women exceeding the number of men in the 75 years and older group (compared with the 5:1 male-to-female ratio for young adult burn patients).[13] Most burns in older adults occur at home; therefore, prevention must be focused in the home environment.[13,15] Prevention should also focus on the fact that 30% of geriatric patients are the victims of self-neglect, and at least 10% are the victims of elder abuse.[14]

Outcome

Mortality rates have diminished among all age groups in recent decades.[5,13,16] Technological progress as well as advances in fluid resuscitation, early burn wound excision, skin grafting, and pharmacotherapy have improved survival.[17] The Baux score is calculated as a sum of age and percent total burn surface area (TBSA) and illustrates both the influence of age on outcome and the improvements in burn care: When compared over time, the score at which the survival rate reaches 0% has steadily increased from 100 in the 1940s to 130–140 in the early 2000s.[18] However, mortality and morbidity rates remain higher in geriatric burn patients.[1,2,10,13,17,19] A large registry study of Jeschke et al. reported the LD50 (50% mortality) for 50-year-old patients at burn sizes of 50% TBSA. This LD50 considerably drops to 30–40% TBSA for patients older than 65 years to only 25% for those older than 70.[17] Pereira et al. have found in a large study of mortality trends and autopsy data that LD50 for older adults has remained steady at 35% for decades, which is disconcerting in the light of the overall improvement of burn care. Lung injury and sepsis were the most common primary causes of death noted in burn patients, and an increase in the weights of heart, lung, spleen, and liver was noted in all age groups postmortem.[16] Pomahac et al. reported that increased levels of creatinine at the time of admission were associated with increased mortality in older adults.[20]

Age, TBSA burned, and inhalation injury are associated with increased mortality rates. The mortality rate is 7.4% for all patients with burn injury aged 60–69 years, 12.9% for patients aged 70–79 years, and 21% for patients older than 80 years of age.[13]

Geriatric patients also experience greater long-term disability after burn injury. Only about 50% of elderly patients with a major burn return home within the first year,[7,16,21] and any loss of function, strength, or independence is more difficult to recover than in the younger patient population.[22] The unique risk factors present in this population explain these statistics.

Risk Factors

A number of well-recognized risk factors are present in older adults. Increased risk of infections, pulmonary diseases, and sepsis as well as the variability of comorbidities present in these patients increase morbidity after a burn. Some of the more prominent factors are shown in Box 36.1.

Box 36.1 Risk Factors in Elderly Patients

- Chronic illness (e.g., diabetes)
- Effects of aging (e.g., presbyphagia)
- Cardiovascular disease (e.g., previous infarct)
- Pulmonary reserve (decreased with age)
- Infections (e.g., pneumonia and urinary tract infection)
- Unintentional weight loss
- Decrease in lean body mass
- Impaired nutrition with presence of deficiency states in energy, protein, and macronutrients
- Decreased endogenous anabolic hormones
- Skin aging (thin, decreased synthesis)

Box 36.2 Aging of Skin

- Decreased epidermal turnover
- Decrease in skin appendages
- Thinning of dermis
- Decreased vascularity
- Decreased collagen and matrix
- Decreased fibroblasts and macrophages

DECREASED CARDIOPULMONARY RESERVE

Aging reduces pulmonary reserve for both gas exchange and lung mechanics.[23] Elderly patients are more prone to pulmonary failure, one major cause of burn-related death. The presence of atherosclerosis, coronary artery disease, and previous myocardial infarction is also common.

INFECTIONS

Pneumonia and urinary tract infections are the most prevalent complications in elderly burn patients.[13] The development of pneumonia seems to correlate with male gender, TBSA burned, and the presence of inhalation injury and contributes to higher mortality rates.[19]

MALNUTRITION AND DECREASED LEAN BODY MASS

Aging leads to progressive decreases in lean body mass, and some degree of protein–energy malnutrition is found in more than 50% of elderly burn patients on admission.[24–27] Any preexisting loss of lean body mass will result in increased morbidity, early onset of immune deficiency, organ dysfunction, weakness, and impaired wound healing.[25,28,29] Losses are caused by multiple factors, including impaired nutrition; swallowing disorders (presbyphagia); reduced mobility; and age-related decreases in endogenous anabolic hormones, human growth hormone, and testosterone.[23,25,30]

Decreased anabolic activity prolongs recovery time and greatly delays restoration of muscle. Importantly, older adults respond to exogenous anabolic stimuli such as testosterone analogs, human growth hormone, and resistance exercise similarly to the younger population. At the same time, daily protein requirements are higher in older adults than in the younger population.[31] Therefore, exercise, high-protein nutrition, and anabolic agents are essential for recovery.[32–34]

AGING SKIN AND WOUND HEALING

Aging produces significant changes in the skin. Because of these changes, burns tend to be deeper in older than in younger patients.[35–37] After the age of 65 years, the turnover rate of the epidermis decreases by 50%. A flattening of the rete pegs and fewer epidermal-lined skin appendages are present. These properties significantly delay healing of partial-thickness burns.[36,37]

Additionally, a progressive thinning of the dermis occurs, along with a decrease in both collagen content and other extracellular matrix proteins, especially glycosaminoglycan, which lower skin turgor. There are also decreases in vascularity, macrophages, and fibroblasts, resulting in deeper burns, an impairment of all phases of wound healing (Box 36.2).[36,37]

IMMUNE RESPONSE

It is hypothesized that aging leads to a state of "chronic inflammation" with increased baseline levels of proinflammatory cytokines that increase the vulnerability of elderly patients to negative outcomes after insults.[38,39] A recent study evaluated the unique characteristics of the inflammatory and immune response in elderly burn patients. Stanojcic et al. were able to show an uncoordinated overactivation of proinflammatory and antiinflammatory cytokines that occurred delayed by 2 weeks postburn.[40] This functionally impaired "cytokine storm" is followed by a phase of depletion and a dampened immune reaction in nonsurviving patients. The study concludes that because of the delay in the characteristic cytokine response, it cannot be used as a predictor for mortality in older adults as opposed to adults and children.[40]

Treatment

The increased complications seen in elderly burn patients may to a certain degree result from more cautious and less aggressive treatments. This is due to existing beliefs that elderly burn patients cannot tolerate eschar excision as well as their younger counterparts, resulting in a greater delay in the excision of burn wounds.[41] However, despite these risk factors, elderly patients have repeatedly been shown to tolerate multiple, early surgical procedures, and early wound closure corresponds to a better outcome in these patients.[41–43] In general, elderly patients are treated identically to younger patients, and most differences in burn management between patient groups are related to comorbid conditions and adversities that may arise. One unique exception to this is that massive burns are more commonly managed expectantly in older adults, and palliative care may be indicated.

Box 36.3 Parkland Formula:

Predicted volume (mL) = Weight in kg × TBSA 2nd and 3rd × **4 mL**

Modified Brooke Formula:

Predicted volume (mL) = Weight in kg × TBSA 2nd and 3rd × **2 mL**

Benicke's Formula:

Predicted volume (mL) = (50 × Weight in kg)
+ (300 × TBSA 2nd and 3rd)
+ (3500 × IHI) + (4000 × BAL)
− (3500 × Age ≥ 65 years) *

*First 24 hours; IHI (inhalation injury) present: yes = 1, no = 0; BAL (blood alcohol level), <0.1% = 0, ≥0.1 = 1.
TBSA, Total body surface area.

INITIAL RESUSCITATION

Improved fluid resuscitation over time is one of the factors associated with decreased mortality. Compared with younger patients, more fluid is required to resuscitate elderly patients with the same burn size to avoid hypovolemia.[44] This is likely attributable to decreased skin turgor, which reduces resistance to fluid accumulation or edema production. Burn depth, inhalation injury, and delayed resuscitation can influence fluid requirements.[45] In addition to the Parkland and modified Brooke formulas, Benicke et al. developed a multifactorial resuscitation formula with a compensating factor for advanced age (Box 36.3).[46] Early ventilatory support is more commonly required because of decreased lung reserve.

WOUND MANAGEMENT

Early removal of the burn wound and rapid closure with skin grafts are essential for survival.[35,42,43] Because of thinner skin, thermal injuries often create full-thickness wounds, and skin graft procurement may create significant donor site complications.[35] Thinner skin grafts are necessary, and healing time is prolonged.[36]

METABOLIC AND NUTRITIONAL SUPPORT

Although elderly patients do not generate the degree of hypermetabolism seen in younger patients, the catabolic response is comparable, necessitating a 1.5- to 2-g/kg/day protein intake.[46,47] In already malnourished patients, the goal of nutritional support must be not only maintenance but also replacement therapy, especially for protein and micronutrients.[25,48] Nutrient supplements are invariably required. Most supplements are protein hydrolysates because the gut is more capable of absorbing peptides and amino acids than whole proteins broken down from food.[21,49]

Anabolic agents are valuable adjuncts to optimal nutrition.[33,34,50,51] The effects of insulin and oxandrolone on postburn hypercatabolism have been studied in the pediatric population, and these anabolic agents may be used in older adults, given that endogenous anabolic hormones are decreased in this group after injury.[51–54]

Fram et al. demonstrated continuous insulin infusions, with tight euglycemic control, to restore insulin sensitivity, improve mitochondrial oxidative capacity, and reduce resting energy expenditure.[50] Lower-dose infusions of 9–10 U/h of insulin promote substantial muscle anabolism without the need for additional large doses of carbohydrate.[55] Intensive insulin therapy during acute care reduces morbidity, mortality, and complications caused by infection.[51,56] Testosterone restoration is effective in both male and female burn patients. However, the synthetic analog oxandrolone is preferable because it possesses only 5% of the virilizing androgenic effects of testosterone and is available in a peroral formulation. Oxandrolone restores lean body mass and improves wound healing in burned adults,[52] especially in emaciated subjects whose treatment has been delayed.[54,57] The effects of oxandrolone are independent of age.[53]

Treatment of acute pediatric burn patients with oral oxandrolone (0.1 mg/kg twice daily) enhances the efficiency of protein synthesis and increases anabolic gene expression in muscle. It also significantly increases lean body mass at 6, 9, and 12 months after burn and bone mineral content at 12 months after injury.[58] Recombinant human growth hormone has been successfully used in pediatric patients;[59,60] however, it has several adverse effects, such as hyperglycemia.[61] Its potential positive effects on the adult and elderly burn patient population are currently under investigation in prospective trials.

β-Adrenergic blockade with propranolol during the acute phase and long term attenuates the effects of the burn-induced hypermetabolic response. In severely burned subjects, titration of propranolol to reduce baseline heart rate by 15–20% improves muscle–protein balance and diminishes obligatory thermogenesis, tachycardia, cardiac work, resting energy expenditure, and fatty infiltration of the liver.[47,62,63] However, no study has directly focused on geriatric patients.

Pain, Sedation, and Comfort Care

Geriatric burn patients are often undertreated for pain because of the misconception that less pain occurs with age.[64] This can be detrimental because both pain and anxiety further increase the levels of catecholamines. Reduced clearance of many therapeutic agents occurs with aging, necessitating lower dosages (Table 36.1).[65] For this reason, pain assessment using reliable tools is essential to create an individualized treatment plan, which should also account for any comorbid conditions that may be present on admission. Untreated pain and incorrect sedation may result in posttraumatic stress disorder, major depression, and delirium.[66] In addition, although the burn injury primarily determines the extent of the metabolic response, metabolic rates are also increased by physical activity, background pain, procedure-related pain, and anxiety. Judicious narcotic support, appropriate sedation, and supportive psychotherapy are mandatory to minimize these effects.[67] Combination drug therapy is often required to achieve adequate analgesia. Different approaches ranging from patient-controlled analgesia to virtual reality have been found to ameliorate pain in burned patients. Intravenous

Table 36.1 Commonly Used Drugs Requiring Decreased Doses in Elderly Patients*

Drug	Comments
Barbiturates	Should be avoided; paradoxical pharmacologic response, often leading to restlessness, agitation, or psychosis caused by a decreased rate of elimination
Benzodiazepines	Increased sensitivity to pharmacologic effect; some benzodiazepines may be metabolized more slowly
Narcotic analgesics	Increased sensitivity to analgesic effects: possibly impaired clearance
Tricyclic antidepressants	Increased incidence of cardiac and hemodynamic adverse effects; urinary retention and other anticholinergic effects; decreased drug clearance

*Decreased dose due, in part, to decreased renal function in the elderly.

drug administration is preferable during the acute phase. A proactive geriatrics consultation team may also be beneficial in managing pain. Use of only comfort care measures needs to be considered for elderly patients with burns likely to be fatal.[68]

Perioperative Optimization

Aging produces many changes in the cardiovascular system that make hemodynamic stability more difficult to achieve and increase adverse outcomes. Coronary artery disease is prevalent, being estimated to exceed 80% in patients older than 80 years of age.[69] Elderly patients are at higher risk for congestive heart failure, and special considerations should be taken during acute and long-term treatments.[70] The revised cardiac risk index stratifies patients into risk groups and helps identify those likely to need additional cardiac evaluation.[71] Patients with minor perfusion abnormalities undergoing low-risk surgery may not require catheterization but should be considered for prophylactic β-blockers and aspirin before operation. High-risk subgroups of patients identified based on clinical risk factors and positive noninvasive tests should undergo cardiac catheterization. Patients with significant cardiac lesions should have definitive coronary revascularization via angioplasty before large TBSA burns are excised. The potential benefits of using β-adrenergic blocking agents during the perioperative period have been studied[72,73] because perioperative ischemic events are related to an exaggerated postoperative sympathetic response that leads to an increased heart rate.[72,74] β-Blockade has an added advantage in burn patients:[75] Severe thermal injury induces hypermetabolism that persists for up to 9–12 months,[63] and the resting metabolic rate in burn patients doubles for those injuries covering greater than 40% TBSA.[62] Catecholamines are key in the initiation of various cascades that stimulate postburn hypermetabolism.[76] Preventing initiation of these cascades by blocking the action of catecholamines at the receptor level using β-blockers such as propranolol attenuates this response and reduces supraphysiological thermogenesis,[62] tachycardia, cardiac work, and resting energy expenditure.[76]

The drawback of β-blockade in older adults is that the aging cardiovascular system is less responsive to β-receptor stimulation. This decrease, together with anesthetic agents, may lead to deleterious intraoperative hypotension in the presence of prophylactic β-blockade. Further investigations are necessary to determine the most appropriate therapeutic regimen for reducing perioperative ischemia, cardiac morbidity, and postburn hypermetabolic responses in older adults.

Pulmonary complications are more strongly linked to coexisting comorbidities than to chronological age.[77] Because of the prevalence of chronic obstructive pulmonary disease and asthma in older adults, physicians should be alert for these conditions during perioperative evaluation. With the appropriate diagnosis, aggressive pulmonary rehabilitation including exercise training, patient education, smoking cessation, and medication optimization is effective in elderly patients.[77] All of these aspects must be integrated into long-term patient management. Aggressive use of antibiotics, judicious use of bronchodilators, adequate hydration and postural drainage, and chest physiotherapy reduce the incidence of pneumonia, atelectasis, and other pulmonary complications.

Rehabilitation

Burn rehabilitation is a long multidisciplinary process that aims to preserve patients' functional ability and restore independence. Physical and occupational therapy should begin immediately after injury. Important components of rehabilitation include wound healing, scar prevention and correction, splinting, casting, traction, pressure therapy, pharmacologic therapy, exercise, and psychological support. Older adults should be aggressively managed during rehabilitation to avoid any further loss of function or strength, which are difficult to recover. Older patients are capable of recovering muscle strength with resistance exercise and should not be managed conservatively.[22] As with children, providing support and guidance for caretakers is essential because these individuals will be responsible for the patient's well-being upon discharge.[78,79]

Intentional Burns in Older Adults

Identifying physical abuse by burning in older adults is difficult because no pathognomonic signs exist. Although such abuse is relatively rare, professionals consistently underestimate the prevalence of elder abuse. The growth in the elderly population makes it necessary to raise awareness among health professionals and reevaluate the clinical approach and assessment for burn injuries inflicted intentionally or negligently.[80] Older adults often live alone, interacting predominantly with the caregivers who enact their abuse. These patients may keep their abuse a secret because of shame, guilt, or fear of reprisals.[81,82] Most forms of intentionally inflicted burns have a higher associated morbidity and mortality than equivalent accidental burns, in part because of comorbidity from other physical abuse, substance abuse, or psychological problems that contributed to or resulted from the inflicted burn. Elder mistreatment can

be associated with confidentiality difficulties because they may not want abuse reported. The priority of the examining physician is to treat life-threatening conditions. They should then promptly record symptoms and signs of abuse or neglect (including photographs). Deliberately inflicted burn injuries are best managed by a multidisciplinary team of health care, social service, and legal professionals.[80]

Conclusion

Despite the remarkable reduction in mortality in burned children over recent decades, we have not yet achieved the same results in elderly patients. This age group still constitutes a major challenge. Surgical decision making in these patients must take into account physiological age, preburn functional status, degree of impairment from comorbid conditions, and clear treatment goals. No patient should be denied an operation based on age alone because age-related declines in organ function are predictable for the population but not necessarily for the individual. More so, the burn surgeon's general mindset should be to treat geriatric patients as aggressively as younger patients. Currently, no "score" can improve decisions based on a thorough evaluation and discussion with the patient and family. Favorable outcomes in elderly burn patients should pertain more to relieving suffering and maintaining independence and quality of life rather than expanding lifespan. Clear, repeated communication between the burn team and patients or their surrogates is critical for guiding therapy and achieving acceptable outcomes.

Complete references available online at
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Further Reading

Demling RH. The incidence and impact of pre-existing protein energy malnutrition on outcome in the elderly burn patient population. *J Burn Care Rehabil*. 2005;26(1):94-100.

Manktelow A, Meyer AA, et al. Analysis of life expectancy and living status of elderly patients surviving a burn injury. *J Trauma*. 1989;29(2):203-207.

McGill V, Kowal-Vern A, Gamelli RL. Outcome for older burn patients. *Arch Surg*. 2000;135(3):320-325.

Pereira CT, Barrow RE, Sterns AM, et al. Age-dependent differences in survival after severe burns: a unicentric review of 1,674 patients and 179 autopsies over 15 years. *J Am Coll Surg*. 2006;202(3):536-548.

Stanojcic M, Chen P, Xiu F, Jeschke MG. Impaired immune response in elderly burn patients: new insights into the immune-senescence phenotype. *Ann Surg*. 2016;264(1):195-202.

References

1. Thompson JC. Gifts from surgical research. Contributions to patients and to surgeons (2). *J Am Coll Surg*. 2000;190(5):509-521.
2. Va V. *The Older Population in the United States: 2010–2050*. US Census Bur; 2010.
3. Division UND of E and SAP. *World Population Ageing 2009*. United Nations Publications; 2010.
4. Kobayashi K, Ikeda H, Higuchi R, et al. Epidemiological and outcome characteristics of major burns in Tokyo. *Burns*. 2005;31(suppl 1): S3-S11.
5. Brusselaers N, Monstrey S, Vogelaers D, Hoste E, Blot S. Severe burn injury in Europe: a systematic review of the incidence, etiology, morbidity, and mortality. *Crit Care*. 2010;14:R188.
6. McGill V, Kowal-Vern A, Gamelli RL. Outcome for older burn patients. *Arch Surg*. 2000;135(3):320-325.
7. O'Neill A, Rabbitts A, Himel H, Yurt R. Burns in the elderly: our burn center's experience with patients >= 75 Years Old: 97. *J Burn Care Res*. 2000;21:S183.
8. Rossignol AM. Consumer products and hospitalized burn injuries among elderly Massachusetts residents. *Plast Reconstr Surg*. 1986;78(4):550.
9. Colebrook L, Colebrook V. The prevention of burns and calds: review of 1000 cases. *Lancet*. 1949;254(6570):181-188.
10. Herndon DN, Gore D, Cole M, et al. Determinants of mortality in pediatric patients with greater than 70% full-thickness total body surface area thermal injury treated by early total excision and grafting. *J Trauma Acute Care Surg*. 1987;27(2):208-212.
11. Jeschke MG, Barrow RE, Herndon DN. Recombinant human growth hormone treatment in pediatric burn patients and its role during the hepatic acute phase response. *Crit Care Med*. 2000;28(5): 1578-1584.
12. Saffle JR, Davis B, Williams P, others. Recent outcomes in the treatment of burn injury in the United States: a report from the American Burn Association Patient Registry. *J Burn Care Res*. 1995;16(3):219-232.
13. American Burn Association. 2016 ABA Annual Burn Repository [Internet]. Available from: http://www.ameriburn.org/NBR.php. cited 2016 Jul 5.
14. Bird PE, Harrington DT, Barillo DJ, et al. Elder abuse: a call to action. *J Burn Care Rehabil*. 1998;19(6):522-527.
15. Vendrusculo TM, Balieiro CRB, Echevarría-Guanilo ME, Farina Junior JA, Rossi LA. Burns in the domestic environment: characteristics and circumstances of accidents. *Rev Lat Am Enfermagem*. 2010;18(3):444-451.
16. Pereira CT, Barrow RE, Sterns AM, et al. Age-dependent differences in survival after severe burns: a unicentric review of 1,674 patients and 179 autopsies over 15 years. *J Am Coll Surg*. 2006;202(3):536-548.
17. Jeschke MG, Pinto R, Costford SR, Amini-Nik S. Threshold age and burn size associated with poor outcomes in the elderly after burn injury. *Burns*. 2016;42(2):276-281.
18. Sturdevant JL, Herndon DN, Sparkes B, et al. Improved survival of adult burn injuries: a multicenter evaluation: 127. *J Burn Care Res*. 2001;22:S110.
19. Pham TN, Kramer CB, Klein MB. Risk factors for the development of pneumonia in older adults with burn injury. *J Burn Care Res*. 2010;31(1):105.
20. Pomahac B, Matros E, Semel M, et al. Predictors of survival and length of stay in burn patients older than 80 years of age: does age really matter? *J Burn Care Res*. 2006;27(3):265-269.
21. Larson CM, Saffle JR, Sullivan J. Lifestyle adjustments in elderly patients after burn injury. *J Burn Care Res*. 1992;13(1):48-52.
22. Frontera WR, Meredith CN, O'Reilly KP, Knuttgen HG, Evans WJ. Strength conditioning in older men: skeletal muscle hypertrophy and improved function. *J Appl Physiol*. 1988;64(3):1038-1044.
23. Koupil J, Brychta P, Říhová H, Kincová S. Special features of burn injuries in elderly patients. *Acta Chir Plast*. 2001;43(2):57-60.
24. Demling RH. The incidence and impact of pre-existing protein energy malnutrition on outcome in the elderly burn patient population. *J Burn Care Rehabil*. 2005;26(1):94-100.
25. Kagansky N, Berner Y, Koren-Morag N, et al. Poor nutritional habits are predictors of poor outcome in very old hospitalized patients. *Am J Clin Nutr*. 2005;82(4):784-791.
26. Rasmussen HH, Holst M, Kondrup J. Measuring nutritional risk in hospitals. *Clin Epidemiol*. 2010;2(1):209-216.
27. Shils ME, Shike M. *Modern Nutrition in Health and Disease*. Lippincott Williams & Wilkins; 2006.
28. Darby E, Anawalt BD. Male hypogonadism. *Treat Endocrinol*. 2012;4(5): 293-309.
29. Kotler DP, Tierney AR, Wang J, Pierson RN. Magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS. *Am J Clin Nutr*. 1989;50(3):444-447.
30. Nimmons D, Michou E, Jones M, et al. A longitudinal study of symptoms of oropharyngeal dysphagia in an elderly community-dwelling population. *Dysphagia*. 2016 Jun 15.
31. Ausman LM, Russell RM. Nutrition in the elderly. *Mod Nutr Health Dis*. 1999;1:770-780.
32. Al-Mousawi AM, Williams FN, Mlcak RP, et al. Effects of exercise training on resting energy expenditure and lean mass during pediatric burn rehabilitation. *J Burn Care Res* [Internet]. 2010;31(3):Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3856323/. cited 2016 Jul 5.
33. Demling R, DeSanti L. The beneficial effects of the anabolic steroid oxandrolone in the geriatric burn population. *Wounds*. 2003;15(2): 54-58.
34. Jeschke MG, Barrow RE, Mlcak RP, Herndon DN. Endogenous anabolic hormones and hypermetabolism: effect of trauma and gender differences. *Ann Surg*. 2005;241(5):759-768.
35. Gore DC. Utility of acellular allograft dermis in the care of elderly burn patients. *J Surg Res*. 2005;125(1):37-41.
36. Gosain A, DiPietro LA. Aging and wound healing. *World J Surg*. 2004;28(3):321-326.
37. Waller JM, Maibach HI. Age and skin structure and function, a quantitative approach (II): protein, glycosaminoglycan, water, and lipid content and structure. *Skin Res Technol*. 2006;12(3):145-154.
38. Franceschi C, Bonafè M, Valensin S, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci*. 2000;908:244-254.
39. Nomellini V, Gomez CR, Gamelli RL, Kovacs EJ. Aging and animal models of systemic insult: trauma, burn, and sepsis. *Shock*. 2009;31(1): 11-20.
40. Stanojcic M, Chen P, Xiu F, Jeschke MG. Impaired immune response in elderly burn patients: new insights into the immune-senescence phenotype. *Ann Surg*. 2016;264(1):195-202.
41. Stern M, Waisbren BA. Comparison of methods of predicting burn mortality. *Burns*. 1979;6(2):119-123.
42. Burdge JJ, Katz B, Edwards R, Ruberg R. Surgical treatment of burns in elderly patients. *J Trauma*. 1988;28(2):214-217.
43. Frye K, Luterman A. Management of the burn wound requiring excision in the geriatric patient: results of a defined protocol for treatment: 132. *J Burn Care Res*. 2000;21:S200.
44. Bowser-Wallace BH, Cone JB, Caldwell FT. Hypertonic lactated saline resuscitation of severely burned patients over 60 years of age. *J Trauma*. 1985;25(1):22-26.
45. Greenhalgh DG. Burn resuscitation. *J Burn Care Res*. 2007;28(4): 555-565.
46. Benicke M, Perbix W, Lefering R, et al. New multifactorial burn resuscitation formula offers superior predictive reliability in comparison to established algorithms. *Burns*. 2009;35(1):30-35.
47. Williams FN, Herndon DN, Jeschke MG. The hypermetabolic response to burn injury and interventions to modify this response. *Clin Plast Surg*. 2009;36(4):583-596.
48. Forbes GB. Influence of Nutrition. In: *Human Body Composition*. New York: Springer; 1987:209-247.
49. Lipschitz DA. Approaches to the nutritional support of the older patient. *Clin Geriatr Med*. 1995;11(4):715-724.
50. Fram RY, Cree MG, Wolfe RR, et al. Intensive insulin therapy improves insulin sensitivity and mitochondrial function in severely burned children. *Crit Care Med*. 2010;38(6):1475-1483.
51. Jeschke MG, Kulp GA, Kraft R, et al. Intensive insulin therapy in severely burned pediatric patients: a prospective randomized trial. *Am J Respir Crit Care Med*. 2010;182(3):351-359.
52. Miller JT, Btaiche IF. Oxandrolone treatment in adults with severe thermal injury. *Pharmacotherapy*. 2009;29(2):213-226.
53. Demling RH, DeSanti L. The rate of restoration of body weight after burn injury, using the anabolic agent oxandrolone, is not age dependent. *Burns*. 2001;27(1):46-51.
54. Wolf SE, Thomas SJ, Dasu MR, et al. Improved net protein balance, lean mass, and gene expression changes with oxandrolone treatment in the severely burned. *Ann Surg*. 2003;237(6):801-811.
55. Ferrando AA, Chinkes DL, Wolf SE, et al. A submaximal dose of insulin promotes net skeletal muscle protein synthesis in patients with severe burns. *Ann Surg*. 1999;229(1):11-18.

56. Hemmila MR, Taddonio MA, Arbabi S, Maggio PM, Wahl WL. Intensive insulin therapy is associated with reduced infectious complications in burn patients. *Surgery*. 2008;144(4):629-637.
57. Demling RH, DeSanti L. Oxandrolone, an anabolic steroid, significantly increases the rate of weight gain in the recovery phase after major burns. *J Trauma Acute Care Surg*. 1997;43(1):47-51.
58. Jeschke MG, Finnerty CC, Suman OE, et al. The effect of oxandrolone on the endocrinologic, inflammatory, and hypermetabolic responses during the acute phase postburn. *Ann Surg*. 2007;246(3):351-362.
59. Branski LK, Herndon DN, Barrow RE, et al. Randomized controlled trial to determine the efficacy of long-term growth hormone treatment in severely burned children. *Ann Surg*. 2009;250(4):514.
60. Jeschke MG, Finnerty CC, Kulp GA, et al. Combination of recombinant human growth hormone and propranolol decreases hypermetabolism and inflammation in severely burned children. *Pediatr Crit Care Med*. 2008;9(2):209-216.
61. Singh KP, Prasad R, Chari PS, Dash RJ. Effect of growth hormone therapy in burn patients on conservative treatment. *Burns*. 1998;24(8):733-738.
62. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR. Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med*. 2001;345(17):1223-1229.
63. Pereira CT, Herndon DN. The pharmacologic modulation of the hypermetabolic response to burns. *Adv Surg*. 2005;39:245-261.
64. Ferrell BA. Assessing pain in the elderly. *Consult Pharm*. 2010;(25 suppl A):5-10.
65. Tsujimoto G, Hashimoto K, Hoffman BB. Pharmacokinetic and pharmacodynamic principles of drug therapy in old age. Part 2. *Int J Clin Pharmacol*. 1989;27(3):102-116.
66. Gregoretti C, Decaroli D, Piacevoli Q, et al. Analgo-sedation of patients with burns outside the operating room. *Drugs*. 2008;68(17):2427-2443.
67. Murphy KD, Lee JO, Herndon DN. Current pharmacotherapy for the treatment of severe burns. *Expert Opin Pharmacother*. 2003;4(3):369-384.
68. Stassen NA, Lukan JK, Mizuguchi NN, Spain DA, others. Thermal injury in the elderly: when is comfort care the right choice? *Am Surg*. 2001;67(7):704.
69. Mangano DT. Perioperative cardiac morbidity. *Anesthesiology*. 1990;72(1):153-184.
70. Lenihan DJ, Uretsky BF. Nonpharmacologic treatment of heart failure in the elderly. *Clin Geriatr Med*. 2000;16(3):477-488.
71. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100(10):1043-1049.
72. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *N Engl J Med*. 1997;336(20):1452.
73. Wallace A, Layug B, Tateo I, et al. Prophylactic atenolol reduces postoperative myocardial ischemia. *Anesthesiology*. 1998;88(1):7-17.
74. Mangano DT, Hollenberg M, Fegert G, et al. Perioperative myocardial ischemia in patients undergoing noncardiac surgery—I: incidence and severity during the 4 day perioperative period. *J Am Coll Cardiol*. 1991;17(4):843-850.
75. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. *N Engl J Med*. 1999;341(24):1789-1794.
76. Norbury WB, Herndon DN, Branski LK, Chinkes DL, Jeschke MG. Urinary cortisol and catecholamine excretion after burn injury in children. *J Clin Endocrinol Metab*. 2008;93(4):1270-1275.
77. Couser JI, Guthmann R, Hamadeh MA, Kane CS. Pulmonary rehabilitation improves exercise capacity in older elderly patients with COPD. *Chest*. 1995;107(3):730-734.
78. Manktelow A, Meyer AA, Herzog SR, Peterson HD. Analysis of life expectancy and living status of elderly patients surviving a burn injury. *J Trauma Acute Care Surg*. 1989;29(2):203-207.
79. Suter-Gut D, Am M, Ma D, Im S. Post-discharge care planning and rehabilitation of the elderly surgical patient. *Clin Geriatr Med*. 1990;6(3):669-683.
80. Greenbaum AR, Horton JB, Williams CJ, Shah M, Dunn KW. Burn injuries inflicted on children or the elderly: a framework for clinical and forensic assessment. *Plast Reconstr Surg*. 2006;118(2):46e-58e.
81. O'Connor F. Granny bashing—abuse of the elderly. In: Huchins N, ed. *The Violent Family: Victimization of Women, Children, and Elders*. New York: Human Sciences Press Inc; 1989:104.
82. Lowenstein A. Elder abuse and neglect—"old phenomenon": new directions for research, legislation, and service developments: (2008 Rosalie S. Wolf Memorial Elder Abuse Prevention Award—International Category Lecture). *J Elder Abuse Negl*. 2009;21(3):278-287.

37 Surgical Management of Complications of Burn Injury

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Introduction

Various surgical complications can occur in burn patients resulting from pathologic progression of the burn injury itself or from iatrogenic etiologies. Multiple organ system injuries can exist that require both a thorough assessment and expeditious management according to advanced trauma life support (ATLS) guidelines. Patients with large (>30% of the total body surface area [TBSA]) burns generally require a prolonged hospital stay with numerous debridement and skin grafting procedures that can be complicated by wound infection and subsequent graft failure.

Burn patients are at risk for potential surgical complications involving multiple organ systems, particularly the gastrointestinal (GI) tract. Such complications include stress gastritis and ulceration, acalculous cholecystitis, superior mesenteric artery (SMA) syndrome, and acute pancreatitis. In this patient population, the cause for occult systemic sepsis is frequently attributed to GI sources. Necrotizing enterocolitis (NEC) is a serious GI tract complication in burn patients, representing a phenomenon of transient ischemia–reperfusion injury to the gut. It can progress to full-thickness necrosis of involved segments, perforation, and rapid clinical decline.

Abdominal compartment syndrome (ACS) can occur during the acute phase of massive fluid resuscitation in severely burned patients. Based on determination of increased intra-abdominal pressures (designated as "compartment syndrome") and additional physiologic parameters, a decompressive laparotomy may be necessary to prevent further end-organ damage. A major burn significantly affects hemodynamics, and invasive monitoring may be necessary. As a consequence, catheter-related complications, such as distal limb ischemia and catheter-associated sepsis, can be seen with both arterial and venous vascular access. Prolonged intravascular manipulation secondary to the need for access predisposes to septic thrombophlebitis, central line-associated bloodstream infections (CLABSI), and poor outcomes.

Because of delays in diagnosis and treatment, there is a high risk of nonthermal complications in burn patients. As such, these secondary and sometimes fatal complications demand immediate recognition and treatment. This chapter reviews the frequently encountered, surgical, nonthermal complications in burn patients with respect to diagnosis and management.

Burns and Trauma

Although the overall incidence of combined burn and traumatic injury is low, the mortality is nearly twice that of burns without associated trauma.[1,2] A retrospective study examined upward of 24,000 patients with burn, trauma, or combined injuries and found the overall incidence of combined burn and trauma rate to be low (3.8%),[3] consistent with the National Trauma Data Bank and National Burn Repository data. There was no difference in length of hospital stay, injury severity scores, or mortality among burn or trauma patients alone. However, inhalational injury, length of stay, and mortality in patients suffering from combined injuries were significantly increased (Table 37.1). This increase in mortality was seen despite similar burn size, demonstrating the additive effects of trauma and burns in these patients.[3] In particular, approximately 24% of military burns are associated with concurrent traumatic injuries, compared to the 2–7% of burn/trauma injuries found in civilians in the same study.[4] In order of frequency, injured organ systems include musculoskeletal, head and neck, abdominal, thoracic, and genitourinary. Industrial accidents, attempts to escape house fires, explosions, and electrical burns with falls account for the majority of other victims. High-voltage electrical burns rarely occur at ground level and are often accompanied by falls resulting in spinal cord injuries, solid organ injury, intracerebral hemorrhage, and multiple fractures, including vertebral, rib, pelvic, and long bone fractures.

PRIMARY ASSESSMENT

The shocking appearance of the burn injury may unduly shift attention away from the other seemingly underwhelming injuries in patients with combined trauma, resulting in potential delays in diagnosis. The initial assessment of a trauma patient, including burn victims, should focus on airway, breathing, and circulation according to the ATLS guidelines. With the exception of respiratory compromise secondary to circumferential chest burns, the burn injury itself is usually not immediately life-threatening. Inhalational injury is common in burn patients. Some of the common signs of inhalational injury include singed nasal and facial hair, erythematous oropharynx, cough, stridor, and carbonaceous sputum. Asphyxia can be seen with carbon monoxide, for which pulse oximetry is an unreliable measure of oxygenation. Intubation or a surgical airway is

Table 37.1 Increased Morbidity and Mortality With Combined Burn and Trauma[3]

	Trauma (n = 22,284)	Burn (n = 1717)	B/T (n = 92)
Age	35.1 (±27.5)	31.0 (±23.2)	40.1 (±25.4)*
TBSA	N/A	17.5% (±19.7)	20.8% (±24.4)
ISS	5.5 (±10.3)	12 (±14)	23 (±16)*
LOS (days)	5.3* (±12.2)	13.7 (±16.5)	18 (±20.8)
INH	N/A	11.0%	44.5%*
Mortality	4.3%	9.8%	28.3%*

B/T, burn/trauma; TBSA, total body surface area; ISS, injury severity score; LOS, length of stay; INH, inhalation injury.
*$P < 0.05$ (Age, B/T vs. Burn; ISS, B/T vs. Burn and Trauma; LOS, B/T vs. Trauma; Mortality, B/T vs. Burn and Trauma)

warranted when significant respiratory distress exists. The inhalational injury can progress rapidly over hours such that an initial chest radiograph and arterial blood gas may be normal. Smoke inhalation induces a multitude of physiologic changes that result in increased vascular permeability and pulmonary edema, infiltration by leukocytes, and bronchorrhea.

Once the airway has been secured, attention should focus on the rest of the primary assessment. Third-degree circumferential chest burns can impair respiratory mechanics and require escharotomy to release the constrictive eschar. This should be performed in a sterile manner with incisions extending from the clavicle to the costal margin in the anterior axillary line bilaterally and may be joined by transverse incisions. The more common thoracic injuries, such as pneumothorax and hemothorax, should be managed as they would be in any other blunt or penetrating thoracic injury. However, because burns carry such a high risk of infection, thoracostomy tubes should be placed away from burned skin whenever possible to reduce the risk of infectious complications such as empyema. Finally, adequate circulation should be assessed. Pericardial tamponade resulting from a heavy impact to the anterior chest wall can be detected by focused assessment with sonography for trauma (FAST) examination and managed with pericardiocentesis or a pericardial window. Myocardial dysfunction may be encountered, especially with electrical injuries, and dysrhythmias should be managed accordingly. If central venous access is necessary, it should similarly be placed away from burned tissue when possible.

ASSOCIATED INJURIES

Burn victims frequently present with concomitant trauma injuries. Bone fractures are the most common associated injuries; in these cases, multidisciplinary management is mandatory. Fractures anatomically distant to the burned area can be treated with reduction and/or casting, as indicated. In addition, open fractures are preferably treated within the first 24 hours; surgical treatment options include irrigation, debridement of nonviable soft tissue, and internal fixation. If the injury occurs in—or the operative incision is made through—a burned area, the wound closure must be performed to the level of the fascia. Additional considerations in the treatment of fractures in burned patients include characteristics of the fracture (stability, displacement, and complexity), need of grafting of the burned area, wound care, and prompt initiation of physical therapy.

A complete physical evaluation is needed in all patients; the cervical spine should be stabilized until spinal injuries have been ruled out. When intracranial pressure (ICP) monitoring is indicated, placement of the ICP monitor is preferably done through a nonburned area of the scalp.

Severe burn injury may mask intra-abdominal injuries that may have devastating complications due to the delay in diagnosis. Furthermore, hemodynamic fluctuations secondary to intra-abdominal injuries may be overshadowed by the massive fluid shifts and inflammatory response following thermal injury. If an intra-abdominal injury is suspected, diagnosis and treatment modalities that are used in nonburned trauma patients should be utilized. Laparoscopy may be a useful approach for the delineation of intra-abdominal injuries but achieving adequate peritoneal insufflation may be difficult with the presence of significant abdominal eschar. If laparotomy is indicated, wound dehiscence is a known complication regardless of burn wound location. Retention sutures or alternative methods of abdominal wall closure should be considered when there is increased tension when closing the abdomen. Frequently, ACS may develop in the massively burned patient that may require emergent laparotomy and temporary wound closure.

Vascular injuries also present with a delay in diagnosis in the presence of large burned areas, anasarca, hypotension, and compartment syndromes. The assessment of vascular injuries includes the routine use of Doppler ultrasound and ankle-brachial index (ABI). Both of these modalities have their limitations in areas of significant burned or edematous skin. Computed tomography (CT) angiography is a highly sensitive and specific method useful to diagnose vascular injuries in burn patients.[5]

Gastrointestinal Tract Complications

Although the superficial effects of burn injuries are often striking, the systemic physiological response to these injuries may result in significant end-organ dysfunction and cannot be overemphasized. Burn injuries of greater than 30% TBSA produce a physiological response leading to systemic shock, hypermetabolism, and widespread immunosuppression.[6] The combination of intravascular fluid loss, vasoactive hormone release, catabolism, and immune dysfunction results in the development of nonthermal complications associated with burn injuries.

Physiological changes in blood flow have a dramatic effect on organ response to injury. This has been particularly well demonstrated in the GI tract, where a combination of diffuse capillary leak, hypovolemia, and the release of vasoconstrictive agents can cause a decrease in splanchnic blood flow.[7,8] Splanchnic hypoperfusion occurs early in the post-burn period despite adequate

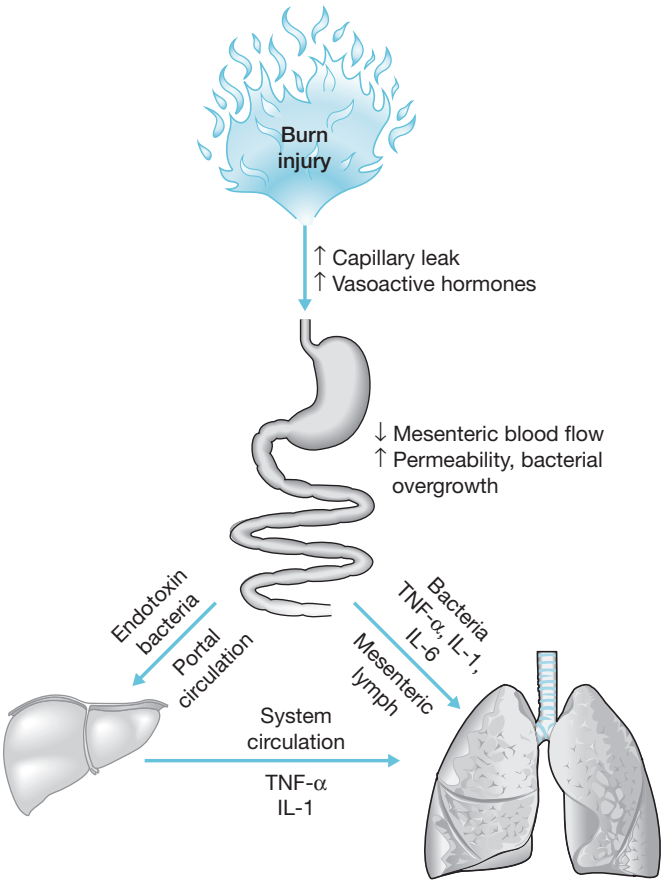

Fig. 37.1 Schematic representation of the role of the gastrointestinal tract in multiorgan sepsis after cutaneous burn injury. (Adapted from Gosain A, Gamelli RL. Role of the gastrointestinal tract in burn sepsis. *J Burn Care Rehabil* 2005;26: 85–91.)

cardiac output and fluid resuscitation, as demonstrated in 40% TBSA pig models that had an early reduction in superior mesenteric blood flow associated with intestinal mucosal hypoxia, acidosis, and increased bacterial translocation.[9–11]

A combination of hypoperfusion and hypermetabolic response can lead to breakdown of the gut mucosal barrier resulting in bacterial translocation from the gut, systemic inflammation, and ultimately, sepsis[12,13] (Fig. 37.1). Several studies have demonstrated the association between massive cutaneous burn injury and bacterial translocation.[10,14,15] Following massive burn injury, the GI tract mucosa sustains immediate atrophy, resulting in significant gut barrier dysfunction. The increase in intestinal apoptosis does not appear to be from mesenteric hypoperfusion alone, but is speculated to be related to proinflammatory mediators.[16] An in vivo study using a 30% TBSA rat burn model confirmed that there was increased bacterial translocation and permeability to macromolecules that peaked at 18 hours post injury, lending credence to the idea that disruption of intestinal barrier integrity in severe burns can lead to sepsis from bacterial translocation.[17] Thus, interventions aimed at preventing splanchnic hypoperfusion and hypermetabolism may circumvent complications associated with severe burns.

PARALYTIC ILEUS

Intestinal ileus is a commonly encountered condition following large burns. Multiple factors contribute to the development of ileus in burn patients, including electrolyte imbalances, narcotic use, prolonged immobilization, abdominal trauma, sepsis, and surgery. In addition, proinflammatory cytokines and proteins that are elevated as part of the postburn systemic response, such as interleukin (IL)-1α, IL-6, tumor necrosis factor (TNF)-α, p38 mitogen-activated protein kinase, and endothelins have been found to be linked to altered intestinal permeability.[15,18–21] Electrolyte disturbances, opioids use, prolonged immobilization, abdominal trauma, sepsis, and surgery are factors that can result in decreased GI motility in burn patients

Cramping abdominal pain, abdominal distension, and intolerance to enteral feedings are the most common symptoms. The cause of ileus should be thoroughly evaluated because it may represent an early indicator of systemic sepsis and can ultimately help direct care.[22] Physical examination must be performed to rule out fecal impaction and to identify signs of peritonitis associated with more serious complications such as acute colonic pseudo-obstruction, also known as Ogilvie's syndrome. The treatment of ileus involves correction of electrolyte derangements and adequate hydration; implementing these basic measures in burn patients can be difficult due to the pathophysiologic changes that occur after severe.[12,15]

OGILVIE'S SYNDROME

Ogilvie's syndrome, first described in 1948, is characterized by massive colonic dilation without a mechanical cause for obstruction.[23,24] This entity has been well described in burns, with a reported incidence of 0.3%.[25] Clinical presentation includes insidious and progressive abdominal distension. Some patients may report a history of diarrhea prior to the onset of distension. Nausea, vomiting, and bowel sounds are not reliable indicators of this condition. Mild abdominal pain can develop as distension increases.[23,26] Diagnosis and management of pseudo-obstruction require that mechanical bowel obstruction be absolutely excluded. Radiologic studies showing colonic air in all colonic segments, including the rectum, are warranted before considering pharmacologic therapy.[27,28]

The goal of the management is to decompress the colon in order to minimize the risk of colonic perforation and ischemia, which are associated with high mortality.[29] Close monitoring including serial physical examinations and plain abdominal radiographs every 12–24 hours to evaluate colonic diameter are recommended. Initial management is conservative in patients without significant abdominal pain, severe colonic distension (>12 cm), or signs of peritonitis. In patients with cecal diameter of greater than 12 cm or who have failed 24–48 hours of supportive management, intravenous neostigmine can be used. In patients who fail or who have contraindications to neostigmine, colonic decompression is indicated.[30] Acute colonic pseudo-obstruction secondary to opiates can benefit from methylnaltrexone prior to decompression.[31] Endoscopic decompression is the preferred method to decompress the colon; surgical decompression (e.g.,

surgical cecostomy) is performed if endoscopic decompression and pharmacologic therapy fail or if there is evidence of perforation or signs of peritonitis. Percutaneous cecostomy should be reserved for patients who are not surgical candidates.[32]

ABDOMINAL COMPARTMENT SYNDROME

ACS refers to the onset of new organ dysfunction caused by increased intra-abdominal pressure.[33,34] Intra-abdominal pressure measurements have allowed grading of ACS; however, for clinical purposes, ACS is defined as new organ dysfunction secondary to increased intra-abdominal pressure without a strict threshold.[35,36] Aggressive fluid resuscitation, severe burns (>30% TBSA), and sepsis increase the risk for ACS.[37–40] Secondary ACS is commonly related to the extent of volume resuscitation. For this reason, the amount of fluid being administered and the development of early signs of ACS should be closely monitored.[41,42] Mortality for patients who have progressed to ACS ranges from 40% to 100%.[36,43]

Nearly all patients have a tense and distended abdomen; however this clinical finding is a poor predictor of ACS.[44,45] Oliguria and increased ventilator requirements are common in patients with ACS. Tachycardia, hypotension, jugular venous distension, and peripheral edema can also be found. Imaging studies are not helpful to diagnose ACS; however expected findings include decreased lung volumes, atelectasis, or elevated hemidiaphragms in chest radiographs. Compression of the inferior vena cava, massive abdominal distension, renal compression or displacement, bowel wall thickening, and bilateral inguinal herniation can be demonstrated in CT of the abdomen.[46]

Management of ACS consists of supportive care and surgical abdominal decompression. However, in patients with abdominal burns, mechanical limitations due to burn eschars can be a significant contributing factor for increased intra-abdominal pressure; thus early escharotomy is advocated.[47,48] Supportive care includes measures that can decrease intra-abdominal pressure, such as evacuation of intraluminal contents (e.g., nasogastric and rectal drainage) and improvement of abdominal wall compliance (supine positioning without head elevation, adequate pain control and sedation, chemical paralysis).[39,49]

Surgical decompression is the definitive management of ACS; however a specific threshold for decompression has not been defined. Several factors can be considered to decide the need for this intervention, including progression of organ dysfunction after supportive measures, intra-abdominal pressure of greater than 25 mm Hg, or abdominal perfusion pressure (difference between the mean arterial pressure and the intra-abdominal pressure) of less than 50 mm Hg.[50,51] Decompression is achieved by making a midline incision through the linea alba to open the abdominal cavity. A temporary abdominal wall closure is often used to maintain an open abdomen.[52]

Complications Associated With Feeding Tubes

Adequate nutrition is one of the major determining factors of success in the treatment of severe burns. Exclusive oral feeding is often a nonviable option due to multiple factors frequently observed in burn patients (e.g., endotracheal intubation, feeding intolerance, compromised mental status, oral burns, concomitant oral and/or facial trauma, etc.). Furthermore, the oral route, in severe burns, is not the preferred route of alimentation because it can represent a limiting factor for the intake of the needed calories to treat severe catabolism.[53]

Nutritional therapy is preferentially delivered via the enteral route.[54] Parenteral nutrition increases the risk of complications such as intestinal atrophy, bacterial overgrowth and translocation, liver malfunction, and catheter-related infections.[53,55]

Nasogastric, nasojejunal, gastric, and jejunal feeding tubes can all deliver enteral nutrition. In the GI tract, malposition, coiling, or kinking of tubes can occur anywhere along the course of the tube, including in the pharynx, pyriform sinus, esophagus, stomach, and duodenum.[56] The presence of a nasogastric or nasoenteric tube impairs the normal function of the lower esophageal sphincter, making the patient more susceptible to reflux of gastric contents. which may lead to esophagitis, esophageal stricture, gastrointestinal bleeding, or pulmonary aspiration.[57] Placing feeding tubes past the pylorus has become standard practice to minimize the risk of aspiration and complications of enteral feeding in patients with impaired gastric emptying. However, a meta-analysis did not find significant differences in the incidence of pneumonia, caloric goal achieved, or mortality between gastric and post-pyloric tube feeding.[58] Nasogastric tubes can cause gastritis or bleeding due to chronic irritation or pressure necrosis due to suctioning of the gastrointestinal mucosa. Patients with bloody gastric drainage require further evaluation, and, whenever possible, the nasogastric tube should be removed.[59] If tubes are left in place for long periods of time, they can be associated with nasal alar necrosis. Frequent retaping of the tube to decrease pressure at any particular point or less traumatic methods of tube fixation can prevent this complication. Patients with prior esophageal or gastric surgery are at risk for gastrointestinal perforation, and infants, children, and patients with facial trauma are at risk for cribriform plate perforation and intracranial intubation.[60,61]

STRESS GASTRITIS

The incidence of acute gastroduodenal ulceration in burn patients, known as Curling's ulcer, has decreased dramatically with the introduction of aggressive fluid resuscitation, early enteral feeding, and the administration of proton pump inhibitors (PPIs). This condition is clinically recognized in most cases only by the onset of upper GI bleeding, and it was once associated with mortality rates of up to 70%. Fortunately, with the institution of the aforementioned interventions, the occurrence of clinically significant ulcers has decreased from 15% to 3%, as has mortality.[62]

Although the exact pathogenesis of Curling's remains unknown, the hypoperfusion, hypermetabolism, and immune dysregulation described earlier are all implicated in ulcer formation. Specifically, intravascular depletion leads to mucosal ischemia and disruption of the protective mucosal barrier. Compounded by the increased acid production, bile reflux, and direct mucosal injury due to the presence of intraluminal tubes, the end result is

gastroduodenal ulceration.[63] Recent studies have proposed an additional mechanism of stress ulcer formation secondary to the systemic production of reactive oxygen species (ROS) in response to stress. Studies have confirmed that the activation of ROS-producing pathways, such as p38 MAPK, results in gastroduodenal ulcer formation.[64]

An effective approach in the prevention of stress gastritis in burn patients is early enteral feeding. It has been proposed that this may be because of dilutional alkalinization or because enteral feeds provide the energy required for mucosal cell resiliency despite ischemia. Studies have shown that intraluminal glucose provides significant protection to ischemic cells of the small intestine and gastric mucosa.[62] Additionally, aggressive fluid resuscitation along with H_2-receptor antagonists or PPIs have proved effective against development of stress gastritis. However, once a stress ulcer is established, many of the same treatments just described are initiated. Aggressive medical therapy, typically involving a high-dose continuous PPI infusion, must be started in patients with massive burns who develop hemorrhage. The PPIs have been demonstrated to reduce instances of rebleeding and the need for subsequent surgery and/or endoscopic treatment.

Endoscopic control of bleeding is indicated as a first approach for patients with gastric bleeding. Specific surgical indications include massive bleeding (>2.5 L in adults, >50% blood volume in children per 24 hours), ongoing uncontrolled blood loss, and evidence of a perforated viscus. Operative repair of ulcers is rarely necessary, the simplest approach consists of a long anterior gastrotomy with oversewing of bleeding sources. In patients who are hemodynamically stable after ligation of actively bleeding ulcers, a vagotomy and pyloroplasty can be added.[65] Although Curling's ulcers are far less common than in the past, they remain a potential risk to all burn-injured patients.

ACALCULOUS CHOLECYSTITIS

Acute acalculous cholecystitis (AAC) is a rare complication of burn injury found in an estimated 0.4–3.5% of burned patients, but it may result in significant morbidity if not quickly recognized and appropriately treated.[66] Patients with extensive burns (>40% TBSA), multiple transfusions, sepsis, dependence on total parenteral nutrition (TPN), and a history of narcotics use are particularly susceptible to the development of AAC. Age, number of packed red blood cell transfusions, and duration of ventilatory support are independent predictive factors for the development of AAC in severely burned patients.[67] Proposed etiologies of AAC include bile stasis, hypoperfusion causing gallbladder ischemia, cystic duct obstruction, and sepsis.[68] Patients with heavy narcotic use for pain control or who are dependent on TPN tend to experience bile stasis. Hypoperfusion affects circulating vasoactive mediators and local tissue perfusion, leading to local ischemia of the gallbladder wall, inflammation, gangrene, and perforation.

AAC commonly presents with fever, right upper quadrant tenderness, leukocytosis, and elevated liver enzymes. AAC is a surgical emergency because patients may rapidly develop complications, including perforation or gangrenous cholecystitis. Mortality following perforation or gangrenous emphysema is reported to be as high as 65%, but early diagnosis and intervention may reduce the likelihood of severe complications significantly, as reflected by the reduction in mortality to 7%.[69]

Ultrasonography is usually the first diagnostic study performed when cholecystitis is suspected; gallbladder wall thickening (>3 mm), pericholecystic fluid, mucosal sloughing, gallbladder distension, emphysematous gallbladder, and frank perforation of the gallbladder with abscess formation are findings suggestive of AAC.[68] When the diagnosis is unclear despite ultrasonography, a hepato-iminodiacetic acid (HIDA) scan can confirm the diagnosis. The specificity of HIDA scan for AAC has been reported as high as 100%, with a sensitivity as low as 67%.[70] CT scanning can also be used to diagnose AAC. Findings suggestive of AAC include absence of gallstones or sludge, gallbladder wall thickening, subserosal halo sign (intramural lucency), pericholecystic fat infiltration, pericholecystic fluid, intramural gas, and gallbladder distension;[68] the accuracies of CT scanning and ultrasonography are similar.[71]

The treatment of AAC consists of initiation of antibiotics with Gram-negative and anaerobes coverage after collecting blood cultures, and either cholecystectomy or placement of a cholecystostomy tube. Prompt treatment is needed or gallbladder gangrene can develop and result in gallbladder perforation. Delayed treatment carries mortality rates as high as 75%.[72] Cholecystectomy is the definitive therapy for AAC, with drainage of associated abscesses often being required. Due to the significant inflammatory process, the laparoscopic approach is challenging, with a higher risk of bile duct and vascular injuries. However, it is appropriate to attempt a laparoscopic approach and convert to open if necessary. For extremely ill patients for whom surgical intervention is not an option, ultrasound-guided percutaneous cholecystostomy should be considered; success rates range from 56% to 100%. Patients treated with a cholecystostomy tube should improve rapidly, usually within 24 hours. Patients with AAC who fail to improve or worsen require cholecystectomy.[73-75]

PANCREATITIS

Acute pancreatitis is an underrecognized complication following thermal injury. Increased serum pancreatic enzymes have frequently been associated with burns, but the nonspecific symptoms, such as epigastric pain radiating to the back, are often overlooked. Reported rates of post-burn pancreatitis range from 0.05% to 40%.[76,77] Despite its rarity, pancreatitis is associated with increased mortality, as survival rates were reported to be only 69% compared to 87% in burn patients unaffected by pancreatitis. Management for acute pancreatitis in the burn patient is similar to the management in nonburn patients. Treatment includes supportive care, bowel rest, fluid resuscitation, and parenteral nutrition. Abdominal ultrasound should be performed to rule out gallstone disease. Occasionally, a more detailed workup with an abdominal CT scan is necessary to identify complications such as pseudocyst formation, pancreatic necrosis, or pancreatic abscess. Operative intervention is rarely indicated.

SUPERIOR MESENTERIC ARTERY SYNDROME

Superior mesenteric artery (SMA) syndrome, or Wilkie's syndrome, occurs when the third part of the duodenum is extrinsically compressed by the superior mesenteric vascular pedicle (Fig. 37.2). SMA syndrome is usually precipitated by rapid and substantial weight loss, leading to a loss of retroperitoneal fat. In burned patients, weight loss resulting from the hypermetabolic response is common. Symptoms include nausea, feeding intolerance, bilious vomiting, and abdominal pain aggravated by feeding and relieved by the knee-to-chest position. The diagnosis is established by an upper GI series demonstrating duodenal dilation, retention of barium within the duodenum, and extrinsic pressure on the third portion of the duodenum with a characteristic sharp cutoff.[78–80]

The management of SMA syndrome consists of nonoperative treatment with nutrition supplementation. Nasojejunal tubes are advocated as the most appropriate mode of feeding because the tube is placed past the obstruction point. In selected cases, TPN may be necessary to optimize the nutritional status of the patient.[79] Surgical procedures are rarely indicated, but, when necessary, the operative goal should be to bypass the point of obstruction caused by the superior mesenteric vascular pedicle. The operation of choice is duodenojejunostomy, in which a lateral duodenotomy is made and the proximal jejunum is then used to create a side-to-side anastomosis. A laparoscopic approach has been used with some success to relieve the duodenal obstruction in patients with SMA syndrome.[81,82] Gastrojejunostomy and the Strong procedure (division of the ligament of Treitz with mobilization of the duodenum) are alternative surgical options, but they have proved inferior to duodenojejunostomy because of failure to adequately relieve the obstruction, peptic ulceration, and blind loop syndrome.[83]

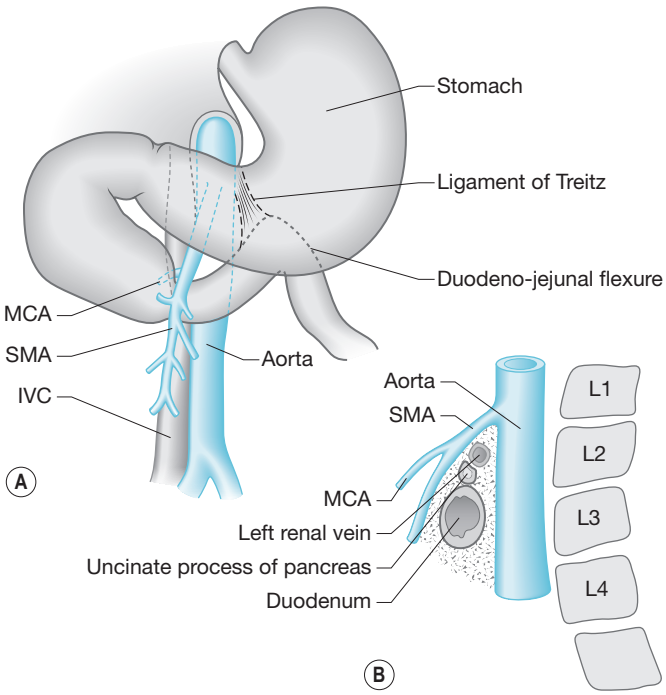

Fig. 37.2 Superior mesenteric artery syndrome. **(A,B)** Schematic illustrations of the mechanism of superior mesenteric artery syndrome, where superior mesenteric vessels extrinsically compress the third portion of the duodenum. SMA, superior mesenteric artery; MCA, middle colic artery; IVC, inferior vena cava. (Adapted from Townsend CM, Jr., Naoum J. Vascular compression of the duodenum, in: Fischer JE (ed.), *Mastery of Surgery*, 5th ed., Philadelphia; Lippincott Williams & Wilkins; 2007: 956.)

NECROTIZING ENTEROCOLITIS

Splanchnic hypoperfusion occurs as a result of hypovolemia and circulating vasoactive mediators. The degree of intestinal insult ranges from mucosal atrophy to full-thickness necrosis and perforation, and is a product of the severity and duration of ischemia combined with reperfusion by resuscitative efforts. Moreover, the presence of virulent bacteria and fungi in the immunocompromised state contributes to intestinal complications and can lead to sepsis. In a study of 2114 patients with burn injury, only 10 (0.5%) patients demonstrated clinically apparent ischemic necrotic bowel disease, and they had more severe burns.[84] Although only 2–5% of patients are clinically diagnosed with this condition, autopsy findings identified pathologic changes consistent with ischemia in 50% of burn patients who died as a result of their injuries.[85] Unfortunately, the mortality rate of patients experiencing ischemic enterocolitis is reported to be extremely high, in the range of 60–69%.[86]

Patients with ischemic bowel demonstrate feeding intolerance, abdominal distension, and abdominal pain. Dilated loops of bowel and pneumatosis intestinalis can be observed in abdominal radiographs (Fig. 37.3A). Because the overall incidence is quite low, early recognition and intervention requires a high index of suspicion. Burn patients with sepsis or an inability to tolerate tube feeds should be started on broad-spectrum antibiotics. Failure to respond to medical treatment mandates surgical intervention, in which frankly necrotic intestinal segments should be resected (Fig. 37.3B). However, questionable areas of necrosis, particularly when they involve extensive lengths, should be re-examined at a second-look operation within 24–48 hours. Thus, the primary goal is to eliminate nonviable bowel while preserving as much intestine as possible to avoid the additional risk of short gut syndrome.

Intestinal ischemia may result in transmural mucosal damage, which predisposes already immunocompromised patients to bacterial translocation and systemic sepsis. Nearly 75% of burn patients with bowel ischemia at autopsy had concomitant sepsis documented at the time of their death, which emphasizes the high incidence of sepsis and mortality associated with intestinal ischemic complications.[87]

CLOSTRIDIUM DIFFICILE INFECTION

Massively burned patients are at high risk for pseudomembranous colitis because they are frequently treated with multiple antibiotics for documented systemic infections and for prophylaxis during burn wound excision and grafting. *Clostridium difficile* overgrowth can result in pseudomembranous colitis, with the potential to progress to fulminant toxic colitis and bowel perforation. In a report of 180

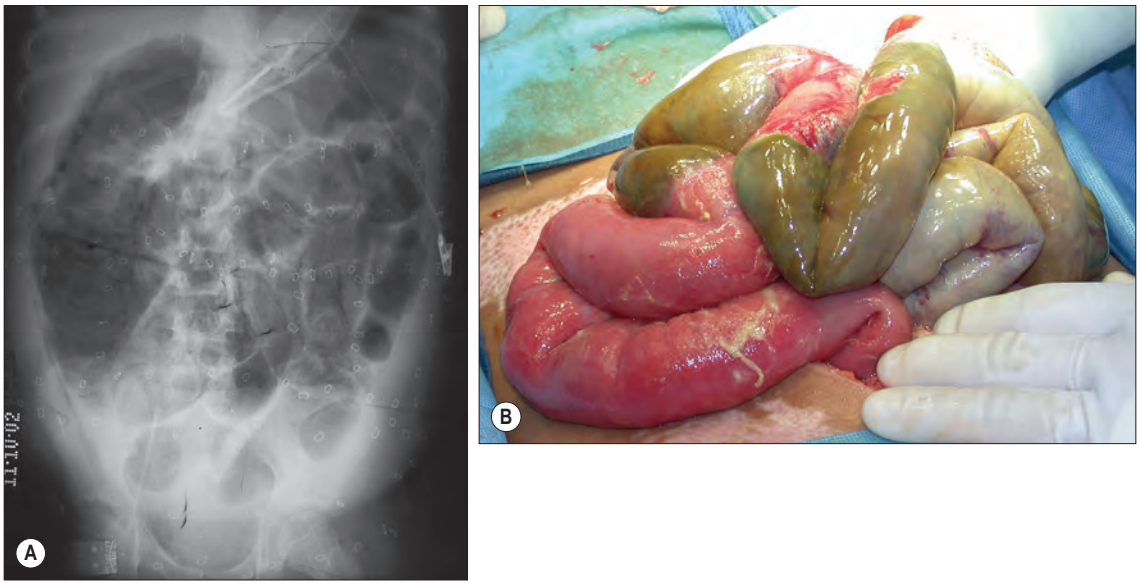

Fig. 37.3 Necrotizing enterocolitis. **(A)** Representative radiograph demonstrating multiple, dilated, persistently "fixed" bowel loops, an ominous sign for full-thickness necrosis of involved segments of bowel. **(B)** At operation, multiple necrotic bowel loops were found.

thermally injured patients, the overall incidence of *C. difficile* infection (CDI) was ~8% with a mean burned TBSA of 42%.[88] Toxic megacolon is a potential complication and places patients at higher risk for colonic perforation.[89] Thus, symptoms of colitis, such as leukocytosis, abdominal pain, distension, and grossly bloody diarrhea, must be promptly recognized. Stool samples are tested for *C. difficile* antigen. All unnecessary systemic antibiotic therapy should be discontinued, and appropriate CDI treatment should be initiated. Guidelines for the treatment of CDI are rapidly evolving. Currently treatment options for the first episode of CDI include oral or IV metronidazole, oral or rectal vancomycin, and fidaxomicin; choice of drug, route of administration, and dosing depend on the severity of the infection, the presence of complications, and other patient-related factors (e.g., drug allergies, pregnancy, prior colonic surgery).[90,91]

Surgical intervention may be required for patients with complicated or fulminant CDI; in addition, surgical intervention must be considered in patients with progressive abdominal distension, peritonitis, shock, signs of sepsis, altered mental status, leukocytosis and lactic acidosis, or failure to improve after 5 days of medical therapy. Subtotal or total abdominal colectomy with end ileostomy has been advocated as the operation of choice.[92,93] An alternative surgical approach is to create a loop ileostomy with intraoperative colonic lavage using warmed polyethylene glycol 3350/balanced electrolyte solution (Go-Lytely) followed by postoperative vancomycin colonic flushes via the ileostomy in an antegrade fashion, with a reported mortality of 19% versus 50% for patients undergoing colectomy. This operation can be performed laparoscopically with a high rate (80%) of reversal of ileostomy for GI tract continuity restoration.[92,94]

Therapeutic options for recurrent infections include fecal microbiota transplant (FMT) and fidaxomicin in addition to the above-mentioned antibiotics; similarly, choice of drug, route, and dosing will depend on the severity and number of recurrences.[90] Novel treatment strategies in development include the use of new antibiotics (ridinilazole, surotomycin, cadazolid), luminal antibodies (oral administration of whey protein concentrate prepared from hyperimmune bovine colostrum against *C. difficile* toxins), intravenous immunoglobulins, vaccines, and nontoxigenic *C. difficile* strains.[95–98]

Vascular Complications

SUPPURATIVE THROMBOPHLEBITIS

Suppurative thrombophlebitis is characterized by venous thrombosis associated with inflammation and bacteremia. Not all of these infections occur in association with venous thrombosis, and specific risk factors for suppurative thrombophlebitis include both burn injury and prolonged intravenous catheterization. The diagnosis may be made based on culture results together with evidence of thrombosis. The classic physical examination findings of edema, erythema, pain, and a palpable cord may not all be present. Burned patients frequently have positive blood cultures and clinical sepsis without an obvious source, and, in the setting of suppurative thrombophlebitis, the most commonly cultured organisms from infected veins reflect those cultured from the burn wound.

The incidence of suppurative thrombophlebitis complications in burn patients has been estimated to be as high as 7%, with significant risk in patients with greater than 20% TBSA burns, and it is associated with significant mortality.[99] The principles of treatment include removing the source of infection, administration of intravenous antibiotics, and/or anticoagulation.[100] Surgical treatment consists of surgical cut-down and evacuation of vein contents. If pus or clot is found, the vein segment should be excised to a normal-appearing vein (usually up to the first uninvolved tributary). If exploration is negative at one site, then

sequential exploration of other sites is necessary until the source of infection is identified. Prompt surgical intervention is necessary to prevent hematogenous dissemination and septic emboli that can result in endocarditis and osteomyelitis. The wound should be loosely packed and allowed to heal either by secondary intention or by delayed closure upon resolution of the infection.[101]

To minimize the incidence of catheter-related complications, the current standard of practice for central venous access at most institutions involves aseptic care at the catheter insertion site along with regularly scheduled catheter site dressing changes.

COMPLICATIONS RELATED TO CENTRAL VENOUS ACCESS

Adequate venous access is imperative in the acute postburn period for aggressive fluid resuscitation. Although large-bore peripheral intravenous catheters are the preferred route for resuscitating trauma patients, placement can be extremely difficult in those with major burns involving the extremities. Therefore, central venous catheters have become standard practice in major burns. Particular attention should be given to the use of various available cannulation sites, depending on the size of the patient, as well as taking into consideration the clinical condition of the burn wounds. The rate of catheter-related bloodstream infections in burn patients is estimated to be 20 per 1000 catheter days.[102] Therefore, compulsory site care is required. Because it is more difficult to relocate lines in severely burned than in nonburned patients, guidewire exchange is acceptable unless there is clinical evidence of infection, such as erythema, drainage from the site, or bacteremia.

Central venous line placement is associated with potentially serious complications. In order to reduce the risk of bleeding complications, many burn centers rely on fluoroscopic or ultrasound guidance during the insertion of central venous catheters.

Bleeding complications associated with central venous access vary in location and can be local, mediastinal, intrathoracic, or pericardial. Local hemorrhage typically occurs in patients with a coagulopathy and can be controlled with local pressure. Hemorrhage into the thoracic space can occur at the time of catheter insertion, but it can also be seen when the catheter erodes through the vein wall. The most common situation leading to venous wall perforation occurs during the insertion of the percutaneous introducer sheath over a guidewire. As the sheath is introduced, it can fail to negotiate the path of the vein and traumatize the vein wall. Consequently, blood may accumulate into the mediastinum, pleural space, or pericardium.

If the injury is small, it should resolve on its own. However, in cases of a larger venous tear, rapid bleeding into the thoracic cavity can occur, and emergency thoracotomy may be necessary. Bleeding or infusion of fluid into the pericardial space can rapidly compromise cardiac function and result in hemodynamic collapse. Pericardial tamponade typically presents with hypotension, muffled heart sounds, and distended neck veins (Beck's triad). However all components of the classic triad of symptoms are rarely present, and a physician must have a high index of suspicion in order to recognize this condition early. Echocardiography can confirm the clinical suspicion, and pericardiocentesis or pericardial window is therapeutic.[103]

DISTAL LIMB ISCHEMIA

Arterial monitoring is frequently required in patients with major burns. Although radial and femoral arterial catheters are routinely placed without significant complications, they can be associated with problems such as hematoma, thrombosis, and pain. Occasionally the common femoral artery is considered for access, given its larger caliber. Because the femoral artery is the major blood supply to the lower extremity, this site should be approached with caution for fear that thrombosis could lead to distal limb ischemia.[104] Especially in pediatric burn patients, the femoral artery is small, and the catheter within the vessel can result in near complete occlusion of blood flow to the distal limb. However reported complication rates after catheterization of the femoral artery in burn patients are low (1.9%) while providing a more accurate measure of hemodynamic parameters (Table 37.2).[105] Nonetheless, complications can be devastating, ranging from transient distal limb ischemia to amputation. Management of distal limb ischemia starts with removal of the catheter along with systemic heparinization. If there is no full recovery after 24 hours, surgical intervention is warranted. Should conservative management fail, exploration of the femoral artery with thrombectomy, fasciotomy, and completion arteriography is recommended. Although rare, amputation may be required if flow is not re-established and tissue salvage is not possible.

Thoracic Complications

PNEUMOTHORAX

Several factors increase the risk of pneumothorax in burn patients; these factors can be related to the traumatic injury itself (barotrauma associated with explosions or blast injuries, concomitant rib fractures, etc.) or associated with the treatment of burns (barotrauma secondary to positive pressure mechanical ventilation, iatrogenic injuries during placement of central venous catheters, etc.). Additionally pneumothorax can occur following electrical injury; the exact mechanisms responsible for pneumothoraces in electrical injuries are debatable, and a blast-like injury due to a high-voltage electric arc is one of the proposed explanations.[106,107]

Pneumothoraces are classified into small or large based on the separation from the pleural surface (lung edge) to the chest wall. A pneumothorax is considered small if the distance is less than 3 cm.[108] Typically, stable patients with a small pneumothorax (<3 cm) are managed conservatively with observation and oxygen supplementation. Conversely, patients who are symptomatic and/or have a large pneumothorax (>3 cm) require thoracostomy. However, several operations and the possible need for reintubation are common scenarios in the hospital stay of severely burned patients. Thus, conservative management of pneumothorax, regardless of size, is not recommended. The placement of a small-caliber (8–14F) pigtail tube is advocated; it is a

Table 37.2 Complications of Femoral Arterial Catheterization[105]

	Age (yr)	Weight (kg)	% TBSA Burn/3rd	Catheter Size (Fr.)	Cather Site Burn	Burns to Limb	Operator	*Onset of Ischemia (Hr)*	Surgical Exploration†
1	2.2	17.7	36-5/36-5	3	No	Yes	Anesthesiologist	6	Yes
2	0.9	12.5	95/95	3	No	Yes	Surgeon	12	Yes
3	2.0	12.7	51/51	3	No	No	Surgeon	4	Yes
4	0.5	6.5	18/1	2.5	No	No	Surgeon	24	No
5	2.1	15.8	70/70	3	No	Yes	Surgeon	4	No
6	12.4	36-3	48/20	3	No	No	Surgeon	12	No
7	2.2	13.5	62/58	3	Yes	Yes	Surgeon	4	No
8	1.7	13.1	64/59	3	No	Yes	Surgeon	6	No
9	2.7	13.7	69/18	3	No	Yes	Surgeon	4	No
10	3.8	15.1	57/5	3	No	Yes	Surgeon	6	No
11	6.3	22.0	87/87	3	Yes	Yes	Anesthesiologist	6	No
12	1.9	13.3	47/47	3	No	No	Anesthesiologist	4	Yes

*Hours after catheter placement.
†All patients received IV heparin therapy.

less invasive procedure compared to a standard chest tube. Pigtail catheters cause less pain and muscle spasms, with a potential to decrease atelectasis and risk of pneumonia. Although the use of large-bore chest tubes (24–28F) is advocated for patients who need mechanical ventilation,[108] current practice trends and recent studies support the use of pigtail catheters in burn patients.[109–111]

EMPYEMA

Parapneumonic effusions, or empyemas, are pleural effusions located in anatomical contiguity to bacterial pneumonia.[112] Most of the empyemas are small and resolve after antibiotic therapy. However, complicated empyemas, characterized by bacterial invasion of the pleural space, may occur. Burn patients are particularly susceptible to the development of empyema owing to high bacterial colonization and impaired immune defenses.

Common clinical features include cough, fever, pleuritic chest pain, dyspnea, and sputum production. In general, the presenting symptoms, other than pleuritic pain and duration of fever, are not helpful in determining which patients have pneumonia versus pneumonia with empyema. Patients with empyema may report a longer course, with several days of fever and malaise rather than hours. The presence of empyema is first suggested by a chest radiograph showing a pleural-based opacity that has an abnormal contour or does not flow freely on lateral decubitus views. When these features are noted, additional imaging with ultrasound allows for identification of loculations and helps to rule out the presence of a solid mass. Optimal evaluation of an empyema or loculated effusion requires a chest CT scan with intravenous contrast. The use of contrast enhances the pleural surface and assists in delineating pleural fluid loculations.[113]

Management of empyema includes appropriate antibiotic therapy and a drainage procedure (tube thoracostomy, video-assisted thoracoscopic surgery [VATS], open decortication or open thoracotomy). Choice of procedure will be influenced by cavity size, loculations, and pleural thickness.[114] Goals of treatment consist of sterilization of the empyema cavity, complete pleural fluid drainage, and obliteration of the empyema cavity by lung expansion. The intrapleural administration of fibrinolytic agents is debatable; however a recent double-blind randomized crossover trial reported that intrapleural instillation of alteplase was associated with lower treatment failure compared to placebo.[115] In the pediatric population, randomized controlled trials have demonstrated that VATS has no therapeutic or recovery advantages over fibrinolysis. Conversely, VATS is associated with increased costs and longer parenteral antibiotic administration. With the implementation of a standardized protocol, only 16% of these patients are expected to require VATS after fibrinolysis.[116–118] These results have promoted the adoption of fibrinolysis as the first therapeutic option for the treatment of empyema in children.

Urologic Complications

Urologic complications following thermal injury are rare. Direct injury to the external genitalia only comprises 1.7% of cases but has increased morbidity, with elevated risk of infections. More importantly, it is an independent predictor of mortality.[119] Furthermore, these injuries should prompt the burn care team to carefully assess the events leading up to the injury. One study found that child abuse was the cause in 46% of cases involving males and 48% of cases involving females.[120] Surgical repair of urologic complications is rarely reported. Electrical injury resulting in bladder rupture, urinary fistula, and erectile dysfunction have been reported in small studies and case reports.[121–123] The presence of these injuries should be managed by a

multidisciplinary approach with consultation with pediatric surgery and urology specialists.

Conclusion

When presented with patients with multiple organ injuries, the protocols for ATLS should be initiated first, followed by a systematic approach to the management of any and all other injuries. Complications requiring operative management in the setting of a burn injury are common and can compound an already overwhelming physiological response. When there is an exaggerated systemic inflammatory response, associated complications are often clinically masked, promoting delays in diagnosis that result in worsened outcomes. Surgical issues and complications in this patient population are often unavoidable, and clinicians must be thorough in the evaluation of patients with a significant burn injury.

Complete references available online at
www.expertconsult.inkling.com

Further Reading

Gasior AC, Knott EM, Sharp SW, et al. Experience with an evidence-based protocol using fibrinolysis as first line treatment for empyema in children. *J Pediatr Surg*. 2013;48(6):1312-1315.

Kirkpatrick AW, Ball CG, Nickerson D, D'Amours SK. Intraabdominal hypertension and the abdominal compartment syndrome in burn patients. *World J Surg*. 2009;33(6):1142-1149.

Ng JWG, Cairns SA, O'Boyle CP. Management of the lower gastrointestinal system in burn: a comprehensive review. *Burns*. 2016;1-10.

Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. *Am J Gastroenterol*. 2013;108(4):478-498.

References

1. Dougherty W, Waxman K. The complexities of managing severe burns with associated trauma. *Surg Clin North Am*. 1996;76(4):923-958.
2. Hawkins A, Maclennan PA, McGwin G, Cross JM, Rue LW. The impact of combined trauma and burns on patient mortality. *J Trauma*. 2005;58(2):284-288.
3. Santaniello JM, Luchette FA, Esposito TJ, et al. Ten year experience of burn, trauma, and combined burn/trauma injuries comparing outcomes. *J Trauma*. 2004;57(4):696-700.
4. Brandt CP, Yowler CJ, Fratianne RB. Burns with multiple trauma. *Am Surg*. 2002;68(3):240-243, discussion 243.
5. Soto JA, Múnera F, Morales C, et al. Focal arterial injuries of the proximal extremities: helical CT arteriography as the initial method of diagnosis. *Radiology*. 2001;218(1):188-194.
6. Williams FN, Jeschke MG, Chinkes DL, et al. Modulation of the hypermetabolic response to trauma: temperature, nutrition, and drugs. *J Am Coll Surg*. 2009;208(4):489-502.
7. Banks RO, Gallavan RH, Zinner MH, et al. Vasoactive agents in control of the mesenteric circulation. *Fed Proc*. 1985;44(12):2743-2749.
8. Hassoun H, Kone B, Mercer D, et al. Post-injury multiple organ failure: the role of the gut. *Shock*. 2001;15(1):1-10.
9. Jones WG, Minei JP, Barber AE, Fahey TJ, Shires GT. Splanchnic vasoconstriction and bacterial translocation after thermal injury. *Am J Physiol*. 1991;261(4 Pt 2):H1190-H1196.
10. Tokyay R, Zeigler ST, Traber DL, et al. Postburn gastrointestinal vasoconstriction increases bacterial and endotoxin translocation. *J Appl Physiol*. 1985;74(4):1521-1527.
11. Pastores S, Katz D, Kvetan V. Splanchnic ischemia and gut mucosal injury in sepsis and the multiple organ dysfunction syndrome. *Am J Gastroenterol*. 1996;91(9):1697-1710.
12. Faries PL, Simon RJ, Martella AT, Lee MJ, Machiedo GW. Intestinal permeability correlates with severity of injury in trauma patients. *J Trauma*. 1998;44(6):1031-1036.
13. Li X, Akhtar S, Choudhry MA. Alteration in intestine tight junction protein phosphorylation and apoptosis is associated with increase in IL-8 levels following alcohol intoxication and burn injury. *Biochim Biophys Acta*. 2012;1822(2):196-203.
14. Magnotti LJ, Deitch EA. Burns, bacterial translocation, gut barrier function, and failure. *J Burn Care Rehabil*. 2005;26(5):383-391.
15. Ng JWG, Cairns SA, O'Boyle CP. Management of the lower gastrointestinal system in burn: A comprehensive review. *Burns*. 2016;1-10.
16. Ramzy PI, Wolf SE, Irtun O, et al. Gut epithelial apoptosis after severe burn: effects of gut hypoperfusion. *J Am Coll Surg*. 2000;190(3):281-287.
17. Samonte VA, Goto M, Ravindranath TM, et al. Exacerbation of intestinal permeability in rats after a two-hit injury: burn and *Enterococcus faecalis* infection. *Crit Care Med*. 2004;32(11):2267-2273.
18. Gan HT, Pasricha PJ, Chen JDZ. Blockade of p38 mitogen-activated protein kinase pathway ameliorates delayed intestinal transit in burned rats. *Am J Surg*. 2007;193(4):530-537.
19. Farro G, Gomez-Pinilla PJ, Di Giovangiulio M, et al. Smooth muscle and neural dysfunction contribute to different phases of murine postoperative ileus. *Neurogastroenterol Motil*. 2016;28(6):934-947.
20. Nullens S, Staessens M, Peleman C, et al. Beneficial effects of anti-interleukin-6 antibodies on impaired gastrointestinal motility, inflammation and increased colonic permeability in a murine model of sepsis are most pronounced when administered in a preventive setup. Stover CM (ed.). *PLoS ONE*. 2016;11(4):e0152914.
21. Ünlüer EE, Alican I, Yegen C, Yegen BÇ. The delays in intestinal motility and neutrophil infiltration following burn injury in rats involve endogenous endothelins. *Burns*. 2000;26(4):335-340.
22. Overhaus M, Tögel S, Pezzone MA, Bauer AJ. Mechanisms of polymicrobial sepsis-induced ileus. *Am J Physiol Gastrointest Liver Physiol*. 2004;287(3):G685-G694.
23. Ives A, Muller M, Pegg S. Colonic pseudo-obstruction in burns patients. *Burns*. 1996;22(8):598-601.
24. Estela CM, Burd DAR. Conservative management of acute pseudo-obstruction in a major burn. *Burns*. 1999;25(6):523-525.
25. Kadesky K, Purdue GF, Hunt JL. Acute pseudo-obstruction in critically ill patients with burns. *J Burn Care Rehabil*. 1995;16(2 Pt 1):132-135.
26. Chudzinski AP, Thompson EV, Ayscue JM. Acute colonic pseudoobstruction. *Clin Colon Rectal Surg*. 2015;28(2):112-117.
27. Edelman DA, Antaki F, Basson MD, et al. Ogilvie syndrome and herpes zoster: case report and review of the literature. *J Emerg Med*. 2010;39(5):696-700.
28. McNamara R, Mihalakis MJ. Acute colonic pseudo-obstruction: rapid correction with neostigmine in the emergency department. *J Emerg Med*. 2008;35(2):167-170.
29. Vanek V, Al-Salti M. Acute pseudo-obstruction of the colon (Ogilvie's syndrome). An analysis of 400 cases. *Dis Colon Rectum*. 1986;29(3):203-210.
30. Harrison ME, Anderson MA, Appalaneni V, et al. The role of endoscopy in the management of patients with known and suspected colonic obstruction and pseudo-obstruction. *Gastrointest Endosc*. 2010;71(4):669-679.
31. Weinstock LB, Chang AC. Methylnaltrexone for treatment of acute colonic pseudo-obstruction. *J Clin Gastroenterol*. 2011;45(10):883-884.
32. Harrison ME, Anderson MA, Appalaneni V, et al. The role of endoscopy in the management of patients with known and suspected colonic obstruction and pseudo-obstruction. *Gastrointest Endosc*. 2010;71(4):669-679.
33. Vidal MG, Ruiz Weisser J, Gonzalez F, et al. Incidence and clinical effects of intra-abdominal hypertension in critically ill patients. *Crit Care Med*. 2008;36(6):1823-1831.
34. Malbrain MLNG, Cheatham ML, Kirkpatrick A, et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. I. Definitions. *Intensive Care Med*. 2006;32(11):1722-1732.
35. Malbrain MLNG, Deeren D, De Potter TJR. Intra-abdominal hypertension in the critically ill: it is time to pay attention. *Curr Opin Crit Care*. 2005;11(2):156-171.
36. Sugrue M. Abdominal compartment syndrome. *Curr Opin Crit Care*. 2005;11:333-338.
37. Markell KW, Renz EM, White CE, et al. Abdominal complications after severe burns. *J Am Coll Surg*. 2009;208(5):940-947.
38. Ertel W, Oberholzer A, Platz A, Stocker R, Trentz O. Incidence and clinical pattern of the abdominal compartment syndrome after "damage-control" laparotomy in 311 patients with severe abdominal and/or pelvic trauma. *Crit Care Med*. 2000;28(6):1747-1753.
39. Kirkpatrick AW, Ball CG, Nickerson D, D'Amours SK. Intraabdominal hypertension and the abdominal compartment syndrome in burn patients. *World J Surg*. 2009;33(6):1142-1149.
40. Balogh Z, McKinley BA, Cocanour CS, et al. Supranormal trauma resuscitation causes more cases of abdominal compartment syndrome. *Arch Surg*. 2003;138(6):637-643.
41. Oda J, Yamashita K, Inoue T, et al. Resuscitation fluid volume and abdominal compartment syndrome in patients with major burns. *Burns*. 2006;32(2):151-154.
42. O'Mara MS, Slater H, Goldfarb IW, Caushaj PF. A prospective, randomized evaluation of intra-abdominal pressures with crystalloid and colloid resuscitation in burn patients. *J Trauma*. 2005;58(5):1011-1018.
43. Kron IL, Harman PK, Nolan SP. The measurement of intra-abdominal pressure as a criterion for abdominal re-exploration. *Ann Surg*. 1984;199.
44. Kirkpatrick AW, Brenneman FD, McLean RF, Rapanos T, Boulanger BR. Is clinical examination an accurate indicator of raised intra-abdominal pressure in critically injured patients? *Can J Surg*. 2000;43(3):207-211.
45. Sugrue M, Bauman A, Jones F, et al. Clinical examination is an inaccurate predictor of intraabdominal pressure. *World J Surg*. 2002;26(12):1428-1431.
46. Pickhardt PJ, Shimony JS, Heiken JP, Buchman TG, Fisher AJ. The abdominal compartment syndrome: CT findings. *AJR Am J Roentgenol*. 1999;173(3):575-579.
47. Hobson KG, Young KM, Ciraulo A, Palmieri TL, Greenhalgh DG. Release of abdominal compartment syndrome improves survival in patients with burn injury. *J Trauma*. 2002;53(6):1129-1133, discussion 1133-1134.
48. De Waele JJ, Hoste EAJ, Malbrain MLNG. Decompressive laparotomy for abdominal compartment syndrome – a critical analysis. *Crit Care*. 2006;10(2):1-9.
49. Cheatham ML. Nonoperative management of intraabdominal hypertension and abdominal compartment syndrome. *World J Surg*. 2009;33(6):1116-1122.

50. Burch JM, Moore EE, Moore FA, Franciose R. The abdominal compartment syndrome. *Surg Clin North Am*. 1996;76(4):833-842.
51. Cheatham ML, White MW, Sagraves SG, Johnson JL, Block EF. Abdominal perfusion pressure: a superior parameter in the assessment of intra-abdominal hypertension. *J Trauma*. 2000;49(4):621-626, discussion 626-627.
52. Mayberry JC, Goldman RK, Mullins RJ, et al. Surveyed opinion of American trauma surgeons on the prevention of the abdominal compartment syndrome. *J Trauma*. 1999;47(3):509-514.
53. Rodriguez N, Jeschke M, Williams F, Kmaolz L-P, Herndon DN. Nutrition in burns: Galveston contributions. *JPEN J Parenter Enteral Nutr*. 2011;35(6):704-714.
54. Mochizuki H, Trocki O, Dominioni L, et al. Mechanism of prevention of postburn hypermetabolism and catabolism by early enteral feeding. *Ann Surg*. 1984;200(3):297-310.
55. Herndon DN, Barrow RE, Stein M, et al. Increased mortality with intravenous supplemental feeding in severely burned patients. *J Burn Care Rehabil*. 1989;10(4):309-313.
56. Agarwala S, Dave S, Gupta A, Mitra D. Duodeno-renal fistula due to a nasogastric tube in a neonate. *Pediatr Surg Int*. 1998;14(1):102-103.
57. Newton M, Burnham W, Kamm M. Morbidity, mortality, and risk factors for esophagitis in hospital inpatients. *J Clin Gastroenterol*. 2000;30(3):264.
58. Marik PE, Zaloga GP. Gastric versus post-pyloric feeding: a systematic review. *Crit Care*. 2003;7(3):R46-R51.
59. Metheny NA, Meert KL, Clouse RE. Complications related to feeding tube placement. *Curr Opin Gastroenterol*. 2007;23(2):178-182.
60. Baskaya M. Inadvertent intracranial placement of a nasogastric tube in patients with head injuries. *Surg Neurol*. 1999;52(4):426-427.
61. Ferreras J, Junquera LM, García-Consuegra L. Intracranial placement of a nasogastric tube after severe craniofacial trauma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2000;90(5):564-566.
62. Raff T, Germann G, Hartmann B. The value of early enteral nutrition in the prophylaxis of stress ulceration in the severely burned patient. *Burns*. 1997;23(4):313-318.
63. Battal MN, Hata Y, Matsuka K, et al. Effect of a prostaglandin I2 analogue, beraprost sodium, on burn-induced gastric mucosal injury in rats. *Burns*. 1997;23(3):232-237.
64. Jia Y-T, Wei W, Ma B, et al. Activation of p38 MAPK by reactive oxygen species is essential in a rat model of stress-induced gastric mucosal injury. *J Immunol*. 2007;179(11):7808-7819.
65. Csendes A, Burgos AM, Smok G, et al. Latest results (12-21 years) of a prospective randomized study comparing Billroth II and Roux-en-Y anastomosis after a partial gastrectomy plus vagotomy in patients with duodenal ulcers. *Ann Surg*. 2009;249(2):189-194.
66. McClain T, Gilmore BT, Peetz M. Laparoscopic cholecystectomy in the treatment of acalculus cholecystitis in patients after thermal injury. *J Burn Care Rehabil*. 1997;18(2):141-146.
67. Theodorou P, Maurer CA, Spanholtz TA, et al. Acalculous cholecystitis in severely burned patients: incidence and predisposing factors. *Burns*. 2008;35(3):405-411.
68. Barie PS, Fischer E. Acute acalculous cholecystitis. *J Am Coll Surg*. 1995;180(2):232-244.
69. Flancbaum L, Choban PS. Use of morphine cholescintigraphy in the diagnosis of acute cholecystitis in critically ill patients. *Intensive Care Med*. 1995;21(2):120-124.
70. Mariat G, Mahul P, Prev N, et al. Contribution of ultrasonography and cholescintigraphy to the diagnosis of acute acalculous cholecystitis in intensive care unit patients. *Intensive Care Med*. 2000;26(11):1658-1663.
71. Mirvis S, Whitley N, Miller J. CT diagnosis of acalculous cholecystitis. *J Comput Assist Tomogr*. 1987;11(1):83-87.
72. Cornwell EE, Rodriguez A, Mirvis SE, Shorr RM. Acute acalculous cholecystitis in critically injured patients. Preoperative diagnostic imaging. *Ann Surg*. 1989;210(1):52-55.
73. Sosna J, Copel L, Kane RA, Kruskal JB. Ultrasound-guided percutaneous cholecystostomy: update on technique and clinical applications. *Surg Technol Int*. 2003;11:135-139.
74. Boland GW, Lee MJ, Leung J, Mueller PR. Percutaneous cholecystostomy in critically ill patients: early response and final outcome in 82 patients. *AJR Am J Roentgenol*. 1994;163(2):339-342.
75. England RE, McDermott VG, Smith TP, et al. Percutaneous cholecystostomy: who responds? *AJR Am J Roentgenol*. 1997;168(5):1247-1251.
76. Rivero HG, Lee JO, Herndon DN, et al. The role of acute pancreatitis in pediatric burn patients. *Burns*. 2011;37(1):82-825.
77. Ryan CM, Sheridan RL, Schoenfeld DA, Warshaw AL, Tompkins RG. Postburn pancreatitis. *Ann Surg*. 1995;222(2):163-170.
78. Jain R. Superior mesenteric artery syndrome. *Curr Treat Options Gastroenterol*. 2007;10(1):24-27.
79. Milner E, Cioffi W, McManus W, Pruitt B. Superior mesenteric artery syndrome in a burn patient. *Nutr Clin Pract*. 1993;8(6):264-266.
80. Reckler J, Bruck H, Munster A, Curreri P, Pruitt B. Superior mesenteric artery syndrome as a consequence of burn injury. *J Trauma*. 1972;12(11):979-985.
81. Kingham TP, Shen R, Ren C. Laparoscopic treatment of superior mesenteric artery syndrome. *JSLS*. 8(4):376-379.
82. Bohanon F, Nunez Lopez O, Graham B, Griffin L, Radhakrishnan R. A case series of laparoscopic duodenojejunostomy for the treatment of pediatric superior mesenteric artery syndrome. *Int J Surg Res*. 2016;S1(001):1-5.
83. Munene G, Knab M, Parag B. Laparoscopic duodenojejunostomy for superior mesenteric artery syndrome. *Am Surg*. 2010;76(3):321-324.
84. Kowal-Vern A, McGill V, Gamelli RL. Ischemic necrotic bowel disease in thermal injury. *Arch Surg*. 1997;132(4):440-443.
85. Groger A, Bozkurt A, Franke E, et al. Ischaemic necrosis of small and large intestine in a 2-year-old child with 20% partial thickness burns: a case report. *Burns*. 2005;31(7):930-932.
86. Wilson MD, Dziewulski P. Severe gastrointestinal haemorrhage and ischaemic necrosis of the small bowel in a child with 70% full-thickness burns: a case report. *Burns*. 2001;27(7):763-766.
87. Desai MH, Herndon DN, Rutan RL, Abston S, Linares HA. Ischemic intestinal complications in patients with burns. *Surg Gynecol Obstet*. 1991;172(4):257-261.
88. Crabtree SJ, Robertson JL, Chung KK. Clostridium difficile infections in patients with severe burns. *Burns*. 2011;37(1):42-48.
89. Jennings LJ, Hanumadass M. Silver sulfadiazine induced Clostridium difficile toxic megacolon in a burn patient: case report. *Burns*. 1998;24(7):676-679.
90. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. *Am J Gastroenterol*. 2013;108(4):478-498, quiz 499.
91. Venugopal AA, Johnson S. Fidaxomicin: a novel macrocyclic antibiotic approved for treatment of *Clostridium difficile* infection. *Clin Infect Dis*. 2012;54(4):568-574.
92. Nassour I, Carchman EH, Simmons RL, Zuckerbraun BS. Novel management strategies in the treatment of severe *Clostridium difficile* infection. *Adv Surg*. 2012;46(1):111-135.
93. Hall JF, Berger D. Outcome of colectomy for Clostridium difficile colitis: a plea for early surgical management. *Am J Surg*. 2008;196(3):384-388.
94. Neal MD, Alverdy JC, Hall DE, Simmons RL, Zuckerbraun BS. Diverting loop ileostomy and colonic lavage. *Ann Surg*. 2011;254(3):423-429.
95. Locher HH, Seiler P, Chen X, et al. In vitro and in vivo antibacterial evaluation of cadazolid, a new antibiotic for treatment of *Clostridium difficile* infections. *Antimicrob Agents Chemother*. 2014;58(2):892-900.
96. Endres BT, Bassères E, Khaleduzzaman M, et al. Evaluating the effects of surotomycin treatment on *Clostridium difficile* toxin A and B production, immune response, and morphological changes. *Antimicrob Agents Chemother*. 2016;60(6):3519-3523.
97. Bassères E, Endres BT, Khaleduzzaman M, et al. Impact on toxin production and cell morphology in *Clostridium difficile* by ridinilazole (SMT19969), a novel treatment for C. difficile infection. *J Antimicrob Chemother*. 2016;71(5):1245-1251.
98. Kociolek LK, Gerding DN. Breakthroughs in the treatment and prevention of *Clostridium difficile* infection. *Nat Rev Gastroenterol Hepatol*. 2016;13(3):150-160.
99. Gillespie P, Siddiqui H, Clarke J. Cannula related suppurative thrombophlebitis in the burned patient. *Burns*. 2000;26(2):200-204.
100. Khan EA, Correa AG, Baker CJ. Suppurative thrombophlebitis in children: a ten-year experience. *Pediatr Infect Dis J*. 1997;16(1):63-67.
101. Kniemeyer HW, Grabitz K, Buhl R, Wüst HJ, Sandmann W. Surgical treatment of septic deep venous thrombosis. *Surgery*. 1995;118(1):49-53.
102. Reed NL, Palmieri TL, O'Mara MS. Central venous catheter infections in burn patients with scheduled catheter exchange and replacement. *J Surg Res*. 2007;142(2):341-350.
103. Bowdle A. Vascular complications of central venous catheter placement: evidence-based methods for prevention and treatment. *J Cardiothorac Vasc Anesth*. 2014;28(2):358-368.

104. Graves PW, Davis AL, Maggi C, Nussbaum E. Femoral artery cannulation for monitoirng critically ill children: prospective study. *Crit Care Med*. 1990;18(12):1363-1366.
105. Mourot JM, Oliveira HM, Woodson LC, Herndon DN, Chung DH. Complications of femoral artery catheterization in pediatric burn patients. *J Burn Care Res*. 2009;30(3):432-436.
106. Gumus N. Pneumothorax followed by atelectasis after severe electrical burn. *J Burn Care Rehabil*. 2009;30(6):1050.
107. Lai C-C, Lin C-M, Xiao Q-C, Ding L-W. Pneumothorax: a rare complication of electric injury. *Burns*. 2008;34(1):125-126.
108. Baumann MH, Strange C, Heffner JE, et al. Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi Consensus Statement. *Chest*. 2001;119(2):590-602.
109. Liu C-M, Hang L-W, Chen W-K, Hsia T-C, Hsu W-H. Pigtail tube drainage in the treatment of spontaneous pneumothorax. *Am J Emerg Med*. 2003;21(3):241-244.
110. Chen C-H, Chen W, Hsu W-H. Pigtail catheter drainage for secondary spontaneous pneumothorax. *QJM*. 2006;99(7):489-491.
111. Sebastian R, Ghanem O, Diroma F, et al. Percutaneous pigtail catheter in the treatment of pneumothorax in major burns: the best alternative? Case report and review of literature. *Burns*. 2015;41(3):e24-e27.
112. Light RW, Girard WM, Jenkinson SG, George RB. Parapneumonic effusions. *Am J Med*. 1980;69(4):507-512.
113. Kearney SE, Davies CWH, Davies RJO, Gleeson FV. Computed tomography and ultrasound in parapneumonic effusions and empyema. *Clin Radiol*. 2000;55(7):542-547.
114. Scarci M, Abah U, Solli P, et al. EACTS expert consensus statement for surgical management of pleural empyema. *Eur J Cardiothorac Surg*. 2015;48(5):642-653.
115. Thommi G, Shehan JC, Robison KL, et al. A double blind randomized cross over trial comparing rate of decortication and efficacy of intrapleural instillation of alteplase vs placebo in patients with empyemas and complicated parapneumonic effusions. *Respir Med*. 2012;106(5):716-723.
116. St. Peter SD, Tsao K, Harrison C, et al. Thoracoscopic decortication vs tube thoracostomy with fibrinolysis for empyema in children: a prospective, randomized trial. *J Pediatr Surg*. 2009;44(1):106-111.
117. Gasior AC, Knott EM, Sharp SW, et al. Experience with an evidence-based protocol using fibrinolysis as first line treatment for empyema in children. *J Pediatr Surg*. 2013;48(6):1312-1315.
118. Gonzalez KW, Dalton BGA, Myers AL, Newland JG, St Peter SD. Antibiotic utilization based on primary treatment of pediatric empyema. *J Surg Res*. 2015;196(2):320-324.
119. Harpole BG, Wibbenmeyer LA, Erickson BA. Genital burns in the national burn repository: incidence, etiology, and impact on morbidity and mortality. *Urology*. 2014;83(2):298-302.
120. Angel C, Shu T, French D, et al. Genital and perineal burns in children: 10 years of experience at a major burn center. *J Pediatr Surg*. 2002;37(1):99-103.
121. Salehi SH, As'adi K, Naderan M, Shoar S, Saberi M. Assessment of erectile dysfunction following burn injury. *Urology*. 2016;93:112-116.
122. Chari PS, Bapna BC, Balakrishnan C. Electrical burns causing a urinary bladder fistula. Case report. *Plast Reconstr Surg*. 1978;61(3):446-448.
123. Miller FE, Peterson D, Miller J. Abdominal visceral perforation secondary to electrical injury: case report and review of the literature. *Burns Incl Therm Inj*. 1986;12(7):505-507.

38 Electrical Injuries

EILEEN BERNAL and BRETT D. ARNOLDO

Introduction

The harnessing of electricity may be the technical advance with the greatest impact on human life and culture in recorded history. The tools of modern life are increasingly powered by electricity, and life without it would be unrecognizable. There is, however, a price to be paid for this advancement. Electrical burn injuries are estimated to make up several thousand admissions to burn centers each year in the United States. The American Burn Association (ABA) 2016 Burn Incidence Fact Sheet, which is composed of registry statistics compiled by ongoing national health care and fire casualty surveys and the National Burn Repository, estimated 40,000 burn admissions of which 4% had a reported electrical etiology.[1] These injuries are the most devastating of all thermal injuries on a size-for-size basis and are the most frequent cause of amputations on the burn service.[2] These injuries are distributed in a bimodal fashion in regards to age. Work-related injuries are seen most commonly in adults. Together, electricians, power company linemen, and crane operators are especially at risk. Exposure to electricity made up 3% of all work-related deaths in 2013–2014 according to the United States Department of Labor; Bureau of Labor Statistics.[3] There is a 2:1 male-to-female ratio in childhood, but more than 90% of electrical injuries in adults are in men.[4-8] Children are more commonly injured in accidents in and around the home. Children younger than 6 years are more likely to encounter low-voltage outlets or electric cords. Older children have an increased incidence of high-voltage injuries by comparison because of their increased mobility and adventurousness.[9–11]

Electrical burn injuries have several unique acute manifestations that differ from other thermal injuries and require expertise in management. Decisions must be made early regarding cardiac monitoring and emergent or urgent exploration and decompression for compartment syndrome, as well as a more complex fluid management strategy to avoid the complications of acute kidney injury associated with myoglobinuria. These patients may need access to other specialty services such as plastic surgery consultation for possible early flap coverage to protect potentially viable tissue. In addition, physical medicine and rehabilitation services, with experience caring for patients with electrical injuries, are simply not available in nonburn centers. These injuries benefit from the multidisciplinary team approach and vast experience typically seen at ABA-verified burn centers.

Pathophysiology

Electrical current passing through tissue can cause injury by multiple distinct mechanisms. These include the direct action of electrical forces on proteins, cell membranes, and other biomolecular structures, as well as tissue injury mediated by the generation of heat.[12,13] The severity of injury is multifactorial and determined by voltage, current (amperage), type of current (alternating or direct), path of current flow, duration of contact, resistance at the point of contact, and individual susceptibility. These burns are somewhat arbitrarily classified as low (<1000 V) and high voltage (≥1000 V). Although the low-voltage injuries are generally more localized to the area of the contact point, the high-voltage injuries may be associated with both extension into deep tissue as well as a spreading out phenomenon to surrounding structures. So, although a low-voltage injury may penetrate deeper structures, the zone of injury is more limited. In contrast, high-voltage injuries, somewhat resembling crush injuries, tend to demonstrate a "tip of the iceberg" phenomenon, extending into deep structures (muscle or bone) as well as spreading out proximally and distally beneath the contact point.[14] The clinical implications of this will be discussed later, but from the surgeon's point of view, these injuries are potentially more urgent and occasionally emergent, but low-voltage injuries are not.

Domestic wiring in the United States operates on alternating current (AC) at 120 V. Therefore, nearly all burns occurring indoors are of the low-voltage type. Coworkers typically witness high-voltage injuries occurring indoors because these are more common in industrial or factory settings.

Unlike voltage, the actual amount of current is unknown. Current flow is related to the voltage by Ohm's law where:

$$\text{Current (I)} = \text{Voltage (E)}/\text{Resistance (R)}$$

Animal experiments have demonstrated that resistance varies continuously with time, initially dropping slowly then much more rapidly until arcing occurs at the contact sites. Resistance then rises to infinity and current flow ceases.[15] Temperature measurements taken simultaneously showed that the rate of temperature rise parallels changes in amperage. Interestingly, tissue temperature, a critical factor in the magnitude of tissue injury, does not increase distal to the contact points. Clinically, it is common to see relatively normal and intact digits in association with devastating tissue damage at the wrist and forearm that

ultimately results in amputation at the forearm level. Early and detailed discussion between the surgeon and patient and family can avoid confusion if the patient progresses to amputation.

In North America, the majority of all electricity used and the burn injuries it causes are the result of 60 cycle-per-second commercial AC, which reverses polarity 120 times per second. Exceptions where direct current (DC) is used for power are seen in industrial settings, as well as computers, light-emitting diodes (LEDs), solar cells, and electric vehicles. A series of events in American history, known as the War of the Currents, explains the dominance of AC over DC. Contributions from notables such as Thomas Edison, Nikola Tesla, and George Westinghouse led to concerns over commercial competition, electrical safety, and debates associated with the introduction of the electric chair. The degree of sordid detail surrounding these events can make for interesting tangential information during resident and medical student teaching sessions.[16,17]

Given the nature of AC and its rapid reversal of polarity and the relative inability to reconstruct the history with accuracy, the terms *entrance* and *exit* wounds are inaccurate and should be used with caution if at all. The term *contact point* is more appropriate. A thorough search for contact points should occur in all patients with electrical injuries because they may be few or many, obvious or well hidden (e.g., in the hair line).

The path of current, although often imprecise, can make a significant difference in outcome. Current potentially traversing the conduction system of the heart or a pathway including the central nervous system can alert the clinician to potential complications. AC causes tetanic muscle contractions, which may either throw the victim away from the source or draw him or her into a continued contact known as the "no-let-go" phenomenon. This occurs because both forearm flexors and extensors are stimulated by the current flow, but the flexors overpower the extensors, making the person unable to let go voluntarily. Given that humans most often explore their environment by grasping rather than tapping with the back of the hand, contact is usually prolonged. Altered levels of consciousness reported in about half of high-voltage victims also contributes to prolonged periods of contact.[18] Resistance, measured in ohms, at the point of contact varies from approximately 100,000 ohms for heavily calloused hands or feet during very dry winter weather to less than 2500 ohms when skin is damp.[11]

The classification of electrical injuries from a clinical point of view comes in four varieties: (1) the true electrical injury caused by the flow of current, (2) an arc injury resulting from the electric arc generated as the current passes from the source to an object, (3) flame injury caused by the ignition of clothing or surroundings, and (4) lightning strikes.

Electricity arcs at temperatures up to 4000°C and causes a flash-type injury without actual current flow through the body.[19] This is most commonly seen in electricians working with metal objects in close proximity to an electrical source. The victim may be thrown by the force and sustain trauma, including ruptured eardrums and any other variety of blunt force injuries. These injuries that occur without actual current flow may be classified like any other flame injury. However, the potential problem that arises is in the difficulty in ascertaining whether there was actual flow of current. As a result, most of these patients will be treated as having true electrical injuries.

The mechanism of electrical injury appears to be a multifactorial combination of thermal and nonthermal causes. Electricity flowing through tissue generates heat. Electrical current via ohmic conduction leads to Joule heating that can cause severe burn injury to the victim.[13] The burn injury is the result of damaging supraphysiological temperatures, which affect all proteins and cell membranes with Joule's law defining the amount of power (heat) delivered to an object:

$$\text{Power (J [Joules])} = \text{I}^2\ \text{(Current)} \times \text{R (Resistance)}$$

In increasing magnitude, tissue resistance is lowest from nerves, blood vessels, muscle, skin, and bone. Theoretically, current flow would be distributed in proportion to resistance, with tissues having the highest resistance generating the most heat. However, in animal models, the body tends to act as a single uniform resistance rather than a collection of different resistances. In other words, the body acts as a volume conductor, with the severity of injury being inversely proportional to the cross-sectional area of the involved body part.[15] Clinically, this is observed in particularly severe injuries at the level of the wrist and ankle. Deep tissue does appear to retain heat such that periosseous tissue, especially between two bones, will often have a more severe injury pattern than more superficial tissue. Clinically, this may be seen during exploration of the forearm wherein the superficial flexors are clearly involved and injured but the deeper pronator quadratus muscle appears to have a more severe injury. The associated macro- and microvascular injury appears to occur at the time of injury and is irreversible.[20] This vascular injury has been studied in a rabbit model in which optical microscopy demonstrated severe injury to blood vessels. Necrosis of vascular walls and thrombosis with destruction of arterial endothelium, pyknosis of vascular smooth muscle, and fibrinous exudates accompanying the thrombotic changes were noted. Progressive muscle necrosis over the first 72 hours after injury was also observed and thought attributable to vascular injury.[21] The study period followed the injury pattern for only 72 hours, but experienced clinicians can attest to a longer period of progression that may extend more than a week. These findings as well as clinical experience argue in favor of serial debridement and a conservative approach to definitive grafting. The pathophysiology, although not completely understood, also includes electroporation and electrochemical interactions in addition to thermal interactions.[22–24] These affect all tissue components, but the cell's plasma membrane appears to be the most important structure in determining the rate and quantity of tissue injury accumulation.[13] Electroporation is the formation of aqueous pores in lipid bilayers exposed to a supraphysiologic electrical field. The formation of these pores allows calcium influx into the cytoplasm and triggers a subsequent cascade leading to apoptosis. Particularly interesting, owing to characteristics of electric fields, it has been shown that cells of long length (skeletal muscle and nerve) are more vulnerable to electroporation.[13] Further experimental work

by Block et al.[23] in a Sprague-Dawley rat model confirmed that nonthermal effects alone could induce cellular necrosis. *Electroconformational denaturation of transmembrane proteins* refers to the changes in polarity of amino acids in response to exposure to electrical fields. Experimentally, voltage-gated channel proteins were found to change their conductance and ion specificity after exposure to a powerful pulsed field.[25]

Acute Care

Electrically burn-injured patients present some unique challenges in the acute setting. There are essentially three acute management concerns differentiating these patients from patients who were thermally injured without flow of electric current. In addition to the application of the basic principles of Advanced Trauma Life Support (ATLS), the three issues that need to be addressed in the "golden hour" are (1) which patients require electrocardiographic monitoring and for how long; (2) which patients are at risk for compartment syndrome and may need emergency surgical intervention (sometimes directly from the emergency department [ED]); and (3) how fluid resuscitation should proceed in the light of the preponderance of deep tissue injury that may not be appreciated on physical examination, particularly in the presence of pigmented urine.

Electrocardiographic Monitoring

All studies reviewed in a recent ABA guidelines paper confirmed that cardiac abnormalities, including dysrhythmias and myocardial damage, occur after both low- and high-voltage injuries, thus reinforcing the need for electrocardiography (ECG) as part of the initial evaluation in all patients.[26] The most frequent reason for death after electrical injury is cardiac.[27] Nonspecific ST changes are the most common ECG abnormality, and atrial fibrillation the most common dysrhythmia,[28,29] but ventricular fibrillation is the most common case of death at the scene of injury.[30]

Direct myocardial injury may also result. This injury behaves more similar to a traumatic myocardial contusion than a true myocardial infarction, not having the hemodynamic or recurrence consequences of atherosclerotic myocardial infarctions. Housinger et al. have shown that creatine kinase (CK) and MB creatine kinase (MB-CK) levels are poor indicators of myocardial injury in the absence of ECG findings of myocardial damage, especially in the presence of significant skeletal muscle injury.[31–33] In contrast, Saracoglu et al. have shown that elevated levels of both are related to an increased mortality rate.[34] Myocardial damage and dysrhythmias are manifested very soon after injury.[35] Although cardiac troponins are the preferred biomarkers for detecting myocardial injury in most clinical settings, this has not been adequately studied in the setting of electrical injuries. A recent study using serum troponin levels and serial echocardiography in 20 patients surviving high-voltage injury concluded that this was not a useful diagnostic test for predicting impaired left ventricular contractility.[36] Orak et al. have found an additional biomarker, pro-B-type natriuretic peptide (pro-BNP), to be elevated in high-voltage electrical injury with use as a marker for both morbidity and mortality.[27] However, the interpretation of cardiac biomarkers is problematic and needs to be correlated with other clinical findings. All patients should be monitored during transport and in the ED. Rather than a policy of more prolonged cardiac monitoring for all patients, a selective policy makes most efficient use of expensive medical resources, without patient risk.[2,35]

Indications for cardiac monitoring include (1) loss of consciousness, (2) ECG abnormality or evidence of ischemia, (3) documented dysrhythmia either before or after admission to the ED, (4) cardiopulmonary resuscitation (CPR) in the field, and (5) patients with other standard indications.[30] Therefore, asymptomatic and stable patients who have normal initial ECG findings and are without any risk factors do not need inpatient cardiac monitoring.[37]

No published studies have directly studied the appropriate duration of telemetry monitoring, but most series indicate 24–48 hours.[38–40] Our institutional bias is to monitor for approximately 24 hours after injury in patients with an indication. Low-voltage injuries not meeting the criteria for cardiac monitoring and no other indication for admission can be safely discharged from the ED. This is not applicable to high-voltage injuries, although retrospective evidence indicates that dysrhythmias will occur early, if at all, in these patients.[35]

Myoglobinuria

The presence of pigmented (darker than light pink) urine in a patient with an electrical burn indicates significant muscle damage with potentially ongoing ischemia. Myoglobinuria and hemoglobinuria secondary to rhabdomyolysis present a risk of acute renal failure and must be cleared promptly.[41,42] Whereas low levels are of little clinical concern, grossly visible urinary pigmentation requires a rapid response to minimize tubular obstruction. Titrating resuscitation fluid (Ringer's lactate) to maintain urine output double the goal rate of the standard burn patient, or approximately 100 mL/h in an adult, is the goal of therapy. The required urinary output is generally very high for several hours after injury followed by a significant reduction in urine requirements, as venous return from the injured part to the central circulation is thrombosed. Therapy continues until the urine appears clear. Other therapeutic options include the prevention of oliguria using loop diuretics, alkalinization of the urine with either a bolus or continuous infusion of sodium bicarbonate, normalization of serum electrolytes, and decompression of compartment syndromes.[43] Alkalinization and osmotic diuresis are not supported by level I evidence, but many burn centers have successfully adopted their use in various forms. Failure to clear pigment from the urine is generally an indication of significant muscle necrosis or ongoing ischemia. This should prompt a thorough evaluation of the likely current path and underlying muscle damage because failure of therapy can often be taken as an indication for operative intervention for decompression versus debridement or amputation.

Compartment Syndrome and Initial Operative Intervention

Patients with low-voltage electrical injuries are at low risk of compartment syndrome. The authors have not had to decompress any patients with low-voltage injuries for compartment syndrome in their combined burn experience. In contrast, high-voltage injuries require vigilance in regards to clinical decision making. Treatment may include ED to operative suite urgency, underscoring the need for these to be seen in centers with 24-hour surgical capability.

Multiple explanations for the pathophysiology of acute compartment syndrome exist, but in all cases, the final common pathway is cellular anoxia.[44] Damaged muscle and swelling in the investing fascia of the extremity may cause increased pressure compromising blood flow such that metabolic demand exceeds delivery. Venous outflow is jeopardized, leading to a decreased arteriovenous pressure gradient that ultimately can cause arteriolar collapse.[45,46] Loss of pulses is one of the last signs in true compartment syndrome, which is different from the early loss of pulses seen in a circumferentially burned extremity requiring escharotomy. Compartment pressure measurement is generally considered an adjunct in electrical injuries and is often an extra step that may not add to what is generally an obvious diagnosis. These injuries are rarely subtle. In the past, a very aggressive approach to fasciotomy was recommended, but significant morbidity may accompany this approach. Amputation rates in the early literature were generally reported in the range of 35% to 40%.[47–51] Mann et al. argued for a conservative course of management calling for fasciotomy in the patient with the usual clinical signs of compartment syndrome—progressive nerve dysfunction or failure of resuscitation.[52] The ABA guidelines paper indications for surgical decompression were in agreement with this management strategy.[26] In a review of the National Burn Repository, Pannucci et al. found early fasciotomy to be a marker for increased disease severity. Among patients who underwent early fasciotomy after electrical injury, 7.5% developed deep vein thrombosis, and 49% required amputation during their initial hospitalization.[53] Elevated CK levels have been correlated to the extent of muscle damage with some authors advocating early decompression and aggressive surgical management in patients with markedly elevated CK levels.[17] In the experience of the authors, high-voltage electrical injuries requiring decompression have significant clinical findings, making adjuncts such as CK levels and compartment pressures moot. They add little to the diagnostic evaluation other than for educational purposes in a training environment. Again, these injuries are generally dramatic. This tends to alleviate consternation regarding the decision to perform urgent exploration or fasciotomy; vigilance, however, must be maintained for the first 24 to 48 hours.

Fasciotomies are best performed in the operating room under general anesthesia.[54] Lower leg fasciotomy is a common procedure and should be within the skill set of all general surgeons. The upper extremity fasciotomy is less common and yet another reason to refer patients with these injuries to a specialized burn center. We favor a lazy-S incision with the caveat that formal forearm fasciotomy from elbow to wrist may not be needed given that the most

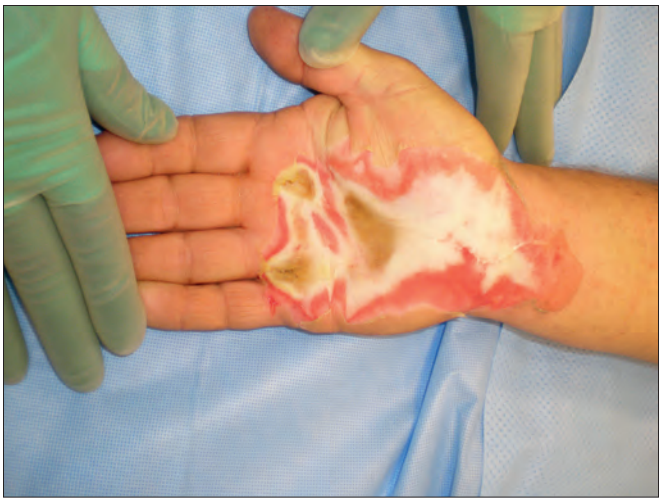

Fig. 38.1 High-voltage injury with neurologic deficit on examination.

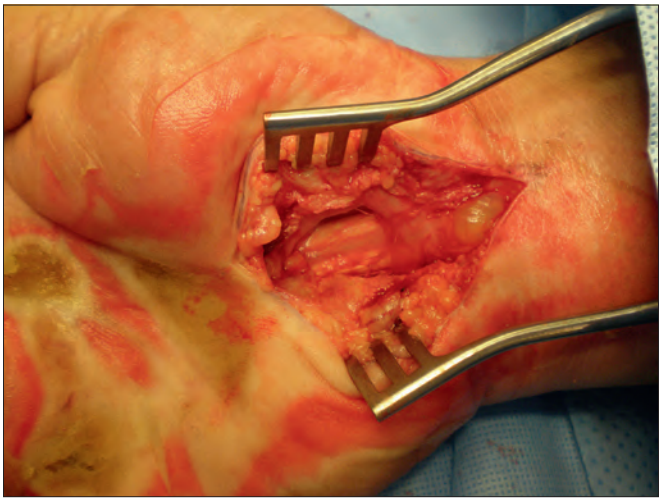

Fig. 38.2 Carpal tunnel release.

significant injury is often at the wrist with variable degree of spread. Beginning the skin incision distally and extending it as indicated is a reasonable approach. On occasion, all that may be required is a carpal tunnel release with a short proximal extension (Figs. 38.1 and 38.2).

Coverage of the wound may include wet to moist mafenide acetate 5% solution or a biologic such as porcine heterograft. The initial operation is followed by a second look in 24 to 48 hours, and depending on the degree of injury, serial debridement may follow. Fasciotomy wound closure is often not possible and skin grafting for wound coverage is common. Rarely will any amputation be indicated as the first operative procedure, and a more conservative approach is usually indicated. The clearly mummified, contracted extremity is one exception, however.

Further Surgical and Wound Considerations

For high-voltage injuries that do not require urgent surgical intervention, initial wound care and observation are

appropriate. Patients with small surface area low-voltage injuries that do not meet criteria for cardiac monitoring and do not have excessive pain control needs can either be discharged or observed depending on local capabilities such as ease of follow up or distance traveled to the burn center. Local wound care can be performed with 11.1% mafenide acetate cream (Sulfamylon) on thick contact points, given the excellent penetration and spectrum of coverage. Other involved areas may be treated by any number of topical agents, including silver sulfadiazine, bacitracin, or one of the silver-containing dressings. Surgical excision is begun 2 to 3 days postburn, either as a second-look operation after fasciotomy or as a first procedure in patients not requiring an urgent procedure. Obviously, necrotic tissue is removed, and tissue of questionable viability retained for reevaluation every several days until all nonviable tissue is ultimately removed. A very conservative course of tissue removal and wound closure with a combination of skin grafts or flaps for soft tissue coverage gives the best functional result. The addition of the vacuum-assisted closure (VAC) device has greatly simplified the management of these wounds. Applying a VAC device over a wound that has questionable tissue remaining loses nothing. If there is a suspicion of infection, the VAC device can simply be removed; otherwise, it can be exchanged at scheduled intervals at the bedside or in the operating room. For extremity injuries, particularly the hand, early involvement of a plastic surgeon with experience in burn reconstruction can provide an important contribution to long-term function. However, surgical options such as local or regional flaps may be unavailable because of the large zone of injury, and a free flap may not be tolerated by a sick patient given the prolonged operative time required. In these cases, a distant pedicle flap may be appropriate.[55] These may include older techniques such as the Crane principle as described by Barrilo et al. or the use of random abdominal wall flap, groin flap, tensor fascia lata flap, or a cross-arm flap.

Multiple diagnostic modalities have been investigated in an attempt to speed up the process of identifying the extent of deep tissue necrosis. These include xenon-133 and technetium pyrophosphate scans as well as gadolinium-enhanced magnetic resonance imaging.[56–60] Albeit very sensitive and specific, diagnostic scans add little to direct clinical evaluation and are ultimately expensive and unnecessary. An ongoing program of physical therapy and functional splinting is begun the day of admission if practical and continued throughout the hospital stay. Serial neurologic examinations are performed and documented. Regional anesthesia is avoided to minimize medical legal complications if late neurologic dysfunction arises.

Problem Areas

Contact points on areas such as the scalp and torso add complexity to management. Scalp burns that spare the galea are managed by excision and grafting directly onto the galea. Wounds that penetrate or expose the outer table of the skull or deeper require a different approach. Exposure of nonviable calvarium has historically been approached by providing a viable wound bed after debridement of dead bone with an osteotome or a dental burr. Drilling multiple holes deep enough to cause bleeding from viable cancellous bone is a method to encourage granulation tissue, which eventually can be skin grafted. This is a prolonged process, and methods such as the use of wound VAC or Integra may accelerate the process. The best and most expedient option may be a rotational scalp flap over the burned area followed by a split-thickness skin graft to cover the adjacent defect[61] (Figs. 38.3–38.5). Larger scalp defects are approached with free flaps anastomosed to appropriate vessels outside the zone of injury.[62]

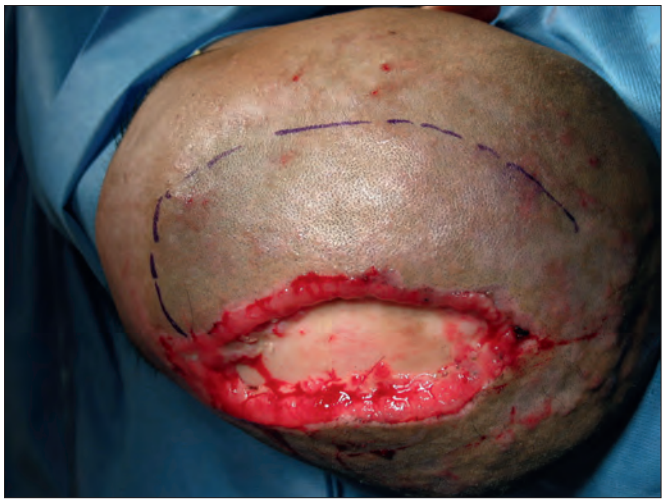

Fig. 38.3 Rotational flap planning.

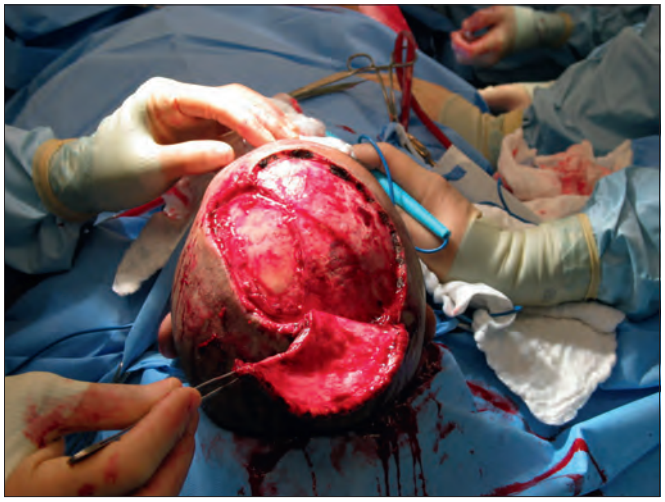

Fig. 38.4 Rotational flap creation.

Although significant electrical burn to the torso is seen less commonly than extremity wounds in both the high- and low-voltage categories, they can present special problems. Chest wall injuries may be particularly difficult to close, and early consultation with plastic surgery services may be helpful. Costal chondritis can be a long-term complication of these wounds. Visceral injuries are reportedly very rare and range from 0.4% to 1.7%.[63,64] The colon and small intestine are the most frequently affected, but gallbladder, liver, pancreas, stomach, and urinary bladder injuries have been described.[65] Vigilance for these potential

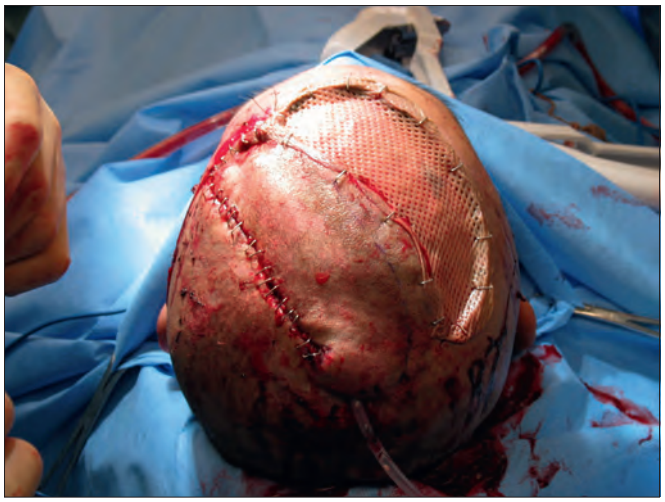

Fig. 38.5 Rotational flap with skin grafted defect.

injuries is required because they can occur in the absence of obvious contact points, and mortality rates are significant.[66,67] The relatively insensitive finding of feeding intolerance or a changing abdominal examination may be the only findings. Computed tomography (CT) may make the diagnosis and mandates laparotomy.

Lightning Injury

Lightning is the second leading cause of weather-related death in much of the world, but underreporting likely influences the data.[68–71] Approximately 100,000 thunderstorms occur in the United States each year, with lightning killing more people than any other weather phenomenon—about 80 fatalities per year—with Florida and Texas having the most deaths.[72–74] Although lightning strikes involve millions of volts of electricity, the spectrum of burn injury is extremely varied, from minimal cutaneous burns to significant burns equal in depth to commercial high-voltage electricity. Major cutaneous injury is rare unless a nearby object is turned incandescent, causing a flash and flame type of injury, as when a bag of golf clubs on the victim's back is struck. The pathognomonic sign of a lightning strike is a dendritic, arborescent or fernlike branching erythematous pattern on the skin. These Lichtenburg figures (also known as keraunographic markings) consist of extravasation of blood in the subcutaneous tissue that appears within an hour of injury and fades rapidly, much like a wheal-and-flare reaction.[75,76] Full-thickness isolated burns on the tips of the toes have also been reported as characteristic. Both findings are useful in determining the cause of injury in a patient found down under uncertain circumstances.[77]

Lightning may cause both respiratory and cardiac standstill, for which CPR is especially effective when promptly initiated,[78] although approximately 10% of lightning strikes prove to be fatal.[79] Patients may respond to resuscitation even when they appear dead and even when the interval between injury and resuscitation is prolonged. It is important to realize that dilated or nonreactive pupils are not necessarily a reliable sign of brain death in the early postinjury period, nor is Glasgow Coma Scale score a predictor of outcome.[80–82] The ears should be carefully examined because injuries are frequent, ranging from ruptured tympanic membranes (most common) to middle and inner ear destruction.[83] Electrical current injuries predominantly cause pure sensorineural hearing loss and may significantly increase a patient's lifetime risk of vertigo.[84] Associated ophthalmic injuries are varied; can be bilateral; and include the formation of thermal keratopathy, anterior uveitis, subcapsular cataract, vitreous hemorrhage, retinal detachment, central retinal artery and vein occlusion, cystoid macular edema, macular hole, and optic neuropathy.[81,85,86]

Neurologic complications are relatively common and include unconsciousness, seizures, paresthesias, and paralysis, which may develop over several days after injury. The term *keraunoparalysis* (Charcot's or temporary paralysis) has been used to describe the latter symptom complex, is associated with vasomotor disorders, and is characterized by complete tetraplegia and loss of sensory awareness of the trunk and all four extremities.[87] Fortunately, these are usually transient. Surgically treatable lesions, including epidural, subdural, and intracerebral hematomas, may occur, mandating a high index of suspicion for altered levels of consciousness.[74] The prognosis of many lightning-caused neurologic injuries is generally better than for other types of traumatic causes, although subtle neurologic changes may persist, suggesting a very conservative, watchful waiting and supportive approach with serial neurological examinations after an initial CT scan to rule out correctable causes. A study by Muehlberger et al. with follow-up to 12.3 years after injury showed that none of their 10 patients had long-term neurologic or psychological deficits.[88] However, posttraumatic stress disorder is common, occurring in about 30% of patients after lightning injury.[89]

Low-Voltage Injuries

Low-voltage (<1000 V) AC injury is usually localized to the points of contact. With prolonged contact, tissue damage may extend into deep tissues with little lateral extension, as seen in high-voltage (≥1000 V) wounds. These wounds are treated by excision to viable tissue and appropriate coverage based on wound depth and location.

Burns of the oral cavity are the most common type of serious electrical burn in young children.[90] Most of these injuries are the result of an unattended small child (commonly <4 years of age) chewing on an electrical cord. Injuries involving only the oral commissure are almost never excised because the extent of injury is difficult to predict. Simple wound care is performed as an outpatient procedure.[91,92] The most serious complication is bleeding from the labial artery, occurring 10–14 days after injury. Families are instructed to compress the labial artery digitally if bleeding occurs and to return to the ED. After healing, treatment varies according to the severity of injury. Gentle stretching and the use of oral splints give good cosmetic and functional results in most patients, with reconstructive surgery being reserved for the remainder. Severe microstomia is corrected by mucosal advancement flaps. Burns of the midportion of the mouth heal poorly and may require a more aggressive surgical approach.[93,94]

Complications

The primary early complications of electrical injury include renal, septic, cardiac, neurologic, and ocular manifestations. Neurologic deficits may be present on admission or develop days to weeks after injury.

Cataract formation is the most frequent ocular complication of electrical injury, although ocular manifestations may affect all portions of the eye.[95,96] The exact pathophysiology is unknown, but ocular changes may affect as many as 5–20% of patients with true electrical burns. Saffle et al. reported on seven patients with 13 cataracts, noting a high rate of bilateral involvement and little association with voltage or location of contact points, although often thought of as being more frequently associated with contact points of the head, neck, and upper trunk.[97] Of this series, 77% eventually progressed to surgical therapy, the results of which were uniformly good. Lag time before appearance may be as short as 3 weeks and as long as 11 years after injury.[98]

Neurologic complications are protean in their diversity and may present either early or late (as late as up to two years after injury). Neuromuscular defects including paresis, paralysis, Guillain-Barre syndrome, transverse myelitis, or amyotrophic lateral sclerosis can be caused by electrical injury.[99] Several studies put the incidence of post-electrical injury sequelae into perspective. Grube et al. reported on 64 patients with high-voltage burns, 67% of whom developed immediate central or peripheral neurologic symptoms.[18] One third had peripheral neuropathies, and one third of those were persistent. Furthermore, 12% had delayed onset of peripheral neuropathy, with 50% resolving. They reported no late-onset central neuropathies. Singerman et al. reported neurologic and psychological complication rates of 81.6% and 71%, respectively.[100] The most common neurologic symptoms were numbness (42%), weakness (32%), memory problems (32%), paresthesias (24%), and chronic pain (24%). The most common psychological symptoms were anxiety (50%), nightmares (45%), insomnia (37%), and flashbacks to the event (37%). Interestingly, the low-voltage injuries resulted in more long-term sequelae than high-voltage injuries. Further studies from the same center demonstrated only a 30% return to work after low-voltage electrical injuries.[101] In a study by Chudasama et al., the patients with high-voltage injuries had longer and more complex hospital stays and more frequent complications than patients with low-voltage injuries.[102] Despite this, the low-voltage group experienced similar rates of neuropsychiatric sequelae, limited return to work, and delays in return to work. Ko et al. reported on 13 patients with delayed onset of spinal cord injuries, postulating on a vascular cause of the deficits.[103] The most common peripheral defect is a peripheral neuropathy, with weakness being the most common clinical finding.[104] In general, resolution of early-onset lesions is much better than for late onset, spasticity is more frequent than flaccidity, and function is affected more than sensation.

Sympathetic overactivity, with changes in bowel habits and urinary and sexual function, is the primary autonomic complex complication. Although the exact mechanism of nerve injury has not been explained, both direct injury by electrical current or a vascular cause receive the most attention. To date, imaging studies, including angiography and magnetic resonance imaging, have not been helpful in either predicting or evaluating the extent of deficit. Very often, the patient's neuropsychological status is abnormal. In a study comparing electrical burn patients with non-burned electricians, Pliskin et al. showed significantly higher cognitive, physical, and emotional complaints not related to injury or litigation status.[105] A full neurologic examination must be performed on admission, documenting the initial presentation. Early involvement of an experienced, interested physiatrist is important in assessing long-term needs and participating in the creation of a therapy plan.

Heterotopic ossification occurring at the cut ends of amputation sites is unique to electrical burn patients. This occurs in about 80% of patients with long bone amputations but not in patients with disarticulations or small bone amputations. Helm et al. found ossification severe enough to require surgical revision of the bone end in 28%.[106] This is easily accomplished by opening the incision and using a bone rongeur to remove the soft heterotopic bone and reclosing the residual limb.

Although electrical burns comprise only about 4% of all burn injuries, they consume enormous amounts of resources, requiring a carefully planned team approach for optimal care.

Complete references available online at www.expertconsult.inkling.com

References

1. http://www.ameriburn.org/resources_factsheet.php. Accessed 9 May 2016.
2. Arnoldo BD, Purdue GF, Kowalske K, et al. Electrical injuries: a 20-year review. *J Burn Care Rehabil*. 2004;25(6):479-484.
3. http://www.bls.gov/news.release/cfoi.t01.htm. May 11, 2016.
4. Baxter CR, Waeckerle JF. Emergency treatment of burn injury. *Ann Emerg Med*. 1988;17(12):1305-1315.
5. Skoog T. Electrical injuries. *J Trauma*. 1970;10(10):816-830.
6. Cawley JC, Homce GT. Occupational electrical injuries in the United States, 1992-1998, and recommendations for safety research. *J Safety Res*. 2003;34(3):241-248.
7. Taylor AJ, McGwin G Jr, Davis GG, Brissie RM, Rue LW 3rd. Occupational electrocutions in Jefferson County, Alabama. *Occup Med (Lond)*. 2002;52(2):102-106.
8. Wick R, Gilbert JD, Simpson E, Byard RW. Fatal electrocution in adults—a 30-year study. *Med Sci Law*. 2006;46(2):166-172.
9. Baker MD, Chiaviello C. Household electrical injuries in children. Epidemiology and identification of avoidable hazards. *Am J Dis Child*. 1989;143(1):59-62.
10. Rabban JT, Blair JA, Rosen CL, Adler JN, Sheridan RL. Mechanisms of pediatric electrical injury. New implications for product safety and injury prevention. *Arch Pediatr Adolesc Med*. 1997;151(7):696-700.
11. Jain S, Bandi V. Electrical and lightning injuries. *Crit Care Clin*. 1999;15(2):319-331.
12. Lee RC. Cell injury by electric forces. *Ann N Y Acad Sci*. 2005;1066: 85-91.
13. Lee RC, Zhang D, Hannig J. Biophysical injury mechanisms in electrical shock trauma. *Annu Rev Biomed Eng*. 2000;2:477-509.
14. Artz CP. Electrical injury simulates crush injury. *Surg Gynecol Obstet*. 1967;125(6):1316-1317.
15. Hunt JL, Mason AD Jr, Masterson TS, Pruitt BA Jr. The pathophysiology of acute electric injuries. *J Trauma*. 1976;16(5):335-340.
16. http://energy.gov/articles/war-currents-ac-vs-dc-power. Accessed 8 April 2016.
17. Kopp J, Loos B, Spilker G, Horch RE. Correlation between serum creatinine kinase levels and extent of muscle damage in electrical burns. *Burns*. 2004;30(7):680-683.
18. Grube BJ, Heimbach DM, Engrav LH, Copass MK. Neurologic consequences of electrical burns. *J Trauma*. 1990;30(3):254-258.
19. Nichter LS, Braynt CA, Kenney JG, et al. Injuries due to commercial electric current. *J Burn Care Rehabil*. 1984;5:124-137.
20. Hunt JL, McManus WF, Haney WP, Pruitt BA Jr. Vascular lesions in acute electric injuries. *J Trauma*. 1974;14(6):461-473.
21. Jia-ke C, Li-gen L, Quan-wen G, et al. Establishment of soft-tissue-injury model of high-voltage electrical burn and observation of its pathological changes. *Burns*. 2009;35(8):1158-1164.
22. Bhatt DL, Gaylor DC, Lee RC. Rhabdomyolysis due to pulsed electric fields. *Plast Reconstr Surg*. 1990;86(1):1-11.
23. Block TA, Aarsvold JN, Matthews KL 2nd, et al. The 1995 Lindberg Award. Nonthermally mediated muscle injury and necrosis in electrical trauma. *J Burn Care Rehabil*. 1995;16(6):581-588.
24. Lee RC, Astumian RD. The physicochemical basis for thermal and non-thermal 'burn' injuries. *Burns*. 1996;22(7):509-519.
25. Chen W, Lee RC. Altered ion channel conductance and ionic selectivity induced by large imposed membrane potential pulse. *Biophys J*. 1994;67(2):603-612.
26. Arnoldo B, Klein M, Gibran NS. Practice guidelines for the management of electrical injuries. *J Burn Care Res*. 2006;27(4): 439-447.
27. Orak M, Ustundag M, Guloglu C, Gokhan S, Alyan O. Relation between serum Pro-Brain natriuretic peptide, myoglobin, CK levels and morbidity and mortality in high voltage electrical injuries. *Intern Med*. 2010;49(22):2439-2443.
28. Chandra NC, Siu CO, Munster AM. Clinical predictors of myocardial damage after high voltage electrical injury. *Crit Care Med*. 1990;18(3):293-297.
29. Das KM. Electrocardiographic changes following electric shock. *Indian J Pediatr*. 1974;41(316):192-194.
30. Arnoldo BD, Purdue GF. The diagnosis and management of electrical injuries. *Hand Clin*. 2009;25(4):469-479.
31. Housinger TA, Green L, Shahangian S, Saffle JR, Warden GD. A prospective study of myocardial damage in electrical injuries. *J Trauma*. 1985;25(2):122-124.
32. McBride JW, Labrosse KR, McCoy HG, et al. Is serum creatine kinase-MB in electrically injured patients predictive of myocardial injury? *JAMA*. 1986;255(6):764-768.
33. Dilworth DHD, Alford P. Evaluation of myocardial injury in electrical burn injuries. *J Burn Care Rehabil*. 1998;10:S239.
34. Saracoglu A, Kuzucuoglu T, Yakupoglu S, et al. Prognostic factors in electrical burns: a review of 101 patients. *Burns*. 2014;40(4):702-707.
35. Purdue GF, Hunt JL. Electrocardiographic monitoring after electrical injury: necessity or luxury. *J Trauma*. 1986;26(2):166-167.
36. Kim SH, Cho GY, Kim MK, et al. Alterations in left ventricular function assessed by two-dimensional speckle tracking echocardiography and the clinical utility of cardiac troponin I in survivors of high-voltage electrical injury. *Crit Care Med*. 2009;37(4):1282-1287.
37. Kramer C, Pfister R, Boekels T, Michels G. Cardiac monitoring always required after electrical injuries? *Med Klin Intensivmed Notfmed*. 2015.
38. Bailey B, Gaudreault P, Thivierge RL. Experience with guidelines for cardiac monitoring after electrical injury in children. *Am J Emerg Med*. 2000;18(6):671-675.
39. Wallace BH, Cone JB, Vanderpool RD, et al. Retrospective evaluation of admission criteria for paediatric electrical injuries. *Burns*. 1995;21(8):590-593.
40. Zubair M, Besner GE. Pediatric electrical burns: management strategies. *Burns*. 1997;23(5):413-420.
41. Bhavsar P, Rathod KJ, Rathod D, Chamania CS. Utility of serum creatinine, creatine kinase and urinary myoglobin in detecting acute renal failure due to rhabdomyolysis in trauma and electrical burns patients. *Indian J Surg*. 2013;75(1):17-21.
42. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. *Medicine (Baltimore)*. 2005;84(6):377-385.
43. Coban YK. Rhabdomyolysis, compartment syndrome and thermal injury. *World J Crit Care Med*. 2014;3(1):1-7.
44. Olson SA, Glasgow RR. Acute compartment syndrome in lower extremity musculoskeletal trauma. *J Am Acad Orthop Surg*. 2005; 13(7):436-444.
45. Elliott KG, Johnstone AJ. Diagnosing acute compartment syndrome. *J Bone Joint Surg Br*. 2003;85(5):625-632.
46. Burton AC. On the physical equilibrium of small blood vessels. *Am J Physiol*. 1951;164(2):319-329.
47. Achauer B, Applebaum R, Vander Kam VM. Electrical burn injury to the upper extremity. *Br J Plast Surg*. 1994;47(5):331-340.
48. d'Amato TA, Kaplan IB, Britt LD. High-voltage electrical injury: a role for mandatory exploration of deep muscle compartments. *J Natl Med Assoc*. 1994;86(7):535-537.
49. DiVincenti FC, Moncrief JA, Pruitt BA Jr. Electrical injuries: a review of 65 cases. *J Trauma*. 1969;9(6):497-507.
50. Luce EA, Gottlieb SE. True" high-tension electrical injuries. *Ann Plast Surg*. 1984;12(4):321-326.
51. Parshley PF, Kilgore J, Pulito JF, Smiley PW, Miller SH. Aggressive approach to the extremity damaged by electric current. *Am J Surg*. 1985;150(1):78-82.
52. Mann R, Gibran N, Engrav L, Heimbach D. Is immediate decompression of high voltage electrical injuries to the upper extremity always necessary? *J Trauma*. 1996;40(4):584-587, discussion 587-589.
53. Pannucci CJ, Osborne NH, Jaber RM, Cederna PS, Wahl WL. Early fasciotomy in electrically injured patients as a marker for injury severity and deep venous thrombosis risk: an analysis of the National Burn Repository. *J Burn Care Res*. 2010;31(6):882-887.
54. Fazi B, Raves JJ, Young JC, Diamond DL. Fasciotomy of the upper extremity in the patient with trauma. *Surg Gynecol Obstet*. 1987;165(5):447-448.
55. Barillo DJ, Arabitg R, Cancio LC, Goodwin CW. Distant pedicle flaps for soft tissue coverage of severely burned hands: an old idea revisited. *Burns*. 2001;27(6):613-619.
56. Clayton JM, Hayes AC, Hammel J, et al. Xenon-133 determination of muscle blood flow in electrical injury. *J Trauma*. 1977;17(4):293-298.
57. Fleckenstein JL, Chason DP, Bonte FJ, et al. High-voltage electric injury: assessment of muscle viability with MR imaging and Tc-99m pyrophosphate scintigraphy. *Radiology*. 1995;195(1):205-210.
58. Hammond J, Ward CG. The use of technetium-99 pyrophosphate scanning in management of high voltage electrical injuries. *Am Surg*. 1994;60(11):886-888.

59. Hunt J, Lewis S, Parkey R, Baxter C. The use of Technetium-99m stannous pyrophosphate scintigraphy to identify muscle damage in acute electric burns. *J Trauma*. 1979;19(6):409-413.
60. Ohashi M, Koizumi J, Hosoda Y, et al. Correlation between magnetic resonance imaging and histopathology of an amputated forearm after an electrical injury. *Burns*. 1998;24(4):362-368.
61. Hunt J, Purdue G, Spicer T. Management of full-thickness burns of the scalp and skull. *Arch Surg*. 1983;118(5):621-625.
62. Koul AR, Patil RK, Philip VK. Early use of microvascular free tissue transfer in the management of electrical injuries. *Burns*. 2008; 34(5):681-687.
63. Hussmann J, Kucan JO, Russell RC, Bradley T, Zamboni WA. Electrical injuries–morbidity, outcome and treatment rationale. *Burns*. 1995;21(7):530-535.
64. Haberal M, Ucar N, Bayraktar U, Oner Z, Bilgin N. Visceral injuries, wound infection and sepsis following electrical injuries. *Burns*. 1996;22(2):158-161.
65. Marques EG, Junior GA, Neto BF, et al. Visceral injury in electrical shock trauma: proposed guideline for the management of abdominal electrocution and literature review. *Int J Burns Trauma*. 2014;4(1):1-6.
66. Newsome TW, Curreri PW, Eurenius K. Visceral injuries: an unusual complication of an electrical burn. *Arch Surg*. 1972;105(3):494-497.
67. Reilley AF, Rees R, Kelton P, Lynch JB. Abdominal aortic occlusion following electric injury. *J Burn Care Rehabil*. 1985;6(3):226-229.
68. Holle RLR, Curran E. Distributions of lightning caused casualties and damages since 1959 in the United States. Paper presented at: 11th Conference on Applied Climatology1999; Boston, MA.
69. Ritenour AE, Morton MJ, McManus JG, Barillo DJ, Cancio LC. Lightning injury: a review. *Burns*. 2008;34(5):585-594.
70. R H. Bibliography on safety and demographics of lightning victims. Holle Meteorology & Photography. 2006.
71. Cherington MWJ, Boyson M, et al. Closing the gap on the actual numbers of lightning casualties and deaths. Paper presented at: 11th Conference on Applied Climatology American Meteorological Society, 1999; Boston, MA.
72. Lightning-associated deaths – United States, 1980-1995. *MMWR Morb Mortal Wkly Rep*. 1998;47(19):391-394.
73. Tribble CG, Persing JA, Morgan RF, Kenney JG, Edlich RF. Lightning injuries. *Compr Ther*. 1985;11(2):32-40.
74. Hiestand DGC. Lightning-strike injury. *J Intensive Care Med*. 1988;3:303-314.
75. Cherington M. James Parkinson: links to Charcot, Lichtenbergh, and lightning. *Arch Neurol*. 2004;61(6):977.
76. ten Duis HJ, Klasen HJ, Nijsten MW, Pietronero L. Superficial lightning injuries–their "fractal" shape and origin. *Burns Incl Therm Inj*. 1987;13(2):141-146.
77. Fahmy FS, Brinsden MD, Smith J, Frame JD. Lightning: the multisystem group injuries. *J Trauma*. 1999;46(5):937-940.
78. Moran KT, Thupari JN, Munster AM. Electric- and lightning-induced cardiac arrest reversed by cardiopulmonary resuscitation. *JAMA*. 1986;255(16):2157.
79. Rahmani SH, Faridaalaee G, Jahangard S. Acute transient hemiparesis induced by lightning strike. *Am J Emerg Med*. 2015;33(7):984 e981-984 e983.
80. Lee MS, Gunton KB, Fischer DH, Brucker AJ. Ocular manifestations of remote lightning strike. *Retina*. 2002;22(6):808-810.
81. Norman ME, Albertson D, Younge BR. Ophthalmic manifestations of lightning strike. *Surv Ophthalmol*. 2001;46(1):19-24.
82. Yi C, Liang Y, Jiexiong O, Yan H. Lightning-induced cataract and neuroretinopathy. *Retina*. 2001;21(5):526-528.
83. Bergstrom L, Neblett LW, Sando I, Hemenway WG, Harrison GD. The lightning-damaged ear. *Arch Otolaryngol*. 1974;100(2):117-121.
84. Modayil PC, Lloyd GW, Mallik A, Bowdler DA. Inner ear damage following electric current and lightning injury: a literature review. *Eur Arch Otorhinolaryngol*. 2014;271(5):855-861.
85. Handa JT, Jaffe GJ. Lightning maculopathy. A case report. *Retina*. 1994;14(2):169-172.
86. Dhillon PS, Gupta M. Ophthalmic manifestations postlightning strike. *BMJ Case Rep*. 2015;2015.
87. JM C. Des accidents nerveux provoque' par la fondre. *Bull Med*. 1889;3:1323-1326.
88. Muehlberger T, Vogt PM, Munster AM. The long-term consequences of lightning injuries. *Burns*. 2001;27(8):829-833.
89. Primeau M. Neurorehabilitation of behavioral disorders following lightning and electrical trauma. *Neurorehabilitation*. 2005;20(1):25-33.
90. Rai J, Jeschke MG, Barrow RE, Herndon DN. Electrical injuries: a 30-year review. *J Trauma*. 1999;46(5):933-936.
91. JGHS DI. Outpatient management of electric burns of the lip. *J Burn Care Rehabil*. 1984;5:465-466.
92. Leake JE, Curtin JW. Electrical burns of the mouth in children. *Clin Plast Surg*. 1984;11(4):669-683.
93. Pensler JM, Rosenthal A. Reconstruction of the oral commissure after an electrical burn. *J Burn Care Rehabil*. 1990;11(1):50-53.
94. Sadove AM, Jones JE, Lynch TR, Sheets PW. Appliance therapy for perioral electrical burns: a conservative approach. *J Burn Care Rehabil*. 1988;9(4):391-395.
95. Boozalis GT, Purdue GF, Hunt JL, McCulley JP. Ocular changes from electrical burn injuries. A literature review and report of cases. *J Burn Care Rehabil*. 1991;12(5):458-462.
96. Van Johnson E, Kline LB, Skalka HW. Electrical cataracts: a case report and review of the literature. *Ophthalmic Surg*. 1987;18(4):283-285.
97. Saffle JR, Crandall A, Warden GD. Cataracts: a long-term complication of electrical injury. *J Trauma*. 1985;25(1):17-21.
98. Mutlu FM, Duman H, Cil Y. Early-onset unilateral electric cataract: a rare clinical entity. *J Burn Care Rehabil*. 2004;25(4):363-365.
99. Petty PG, Parkin G. Electrical injury to the central nervous system. *Neurosurgery*. 1986;19(2):282-284.
100. Singerman J, Gomez M, Fish JS. Long-term sequelae of low-voltage electrical injury. *J Burn Care Res*. 2008;29(5):773-777.
101. Theman K, Singerman J, Gomez M, Fish JS. Return to work after low voltage electrical injury. *J Burn Care Res*. 2008;29(6):959-964.
102. Chudasama S, Goverman J, Donaldson JH, et al. Does voltage predict return to work and neuropsychiatric sequelae following electrical burn injury? *Ann Plast Surg*. 2010;64(5):522-525.
103. Ko SH, Chun W, Kim HC. Delayed spinal cord injury following electrical burns: a 7-year experience. *Burns*. 2004;30(7):691-695.
104. Haberal MA, Gurer S, Akman N, Basgoze O. Persistent peripheral nerve pathologies in patients with electric burns. *J Burn Care Rehabil*. 1996;17(2):147-149.
105. Pliskin NH, Capelli-Schellpfeffer M, Law RT, et al. Neuropsychological symptom presentation after electrical injury. *J Trauma*. 1998;44(4):709-715.
106. Helm PA, Walker SC. New bone formation at amputation sites in electrically burn-injured patients. *Arch Phys Med Rehabil*. 1987;68(5 Pt 1): 284-286.

39 Cold-Induced Injury: Frostbite

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History of Frostbite

Frostbite is a traumatic injury caused by the failure of normal protective mechanisms against the environment, resulting in freezing of tissue. Cold-induced injury remains surprisingly frequent in the United States owing to increasing interest in outdoor winter recreational activities as well as the common presence of homeless and socioeconomically disadvantaged individuals in large urban centers.[1,2]

The incidence of and circumstances surrounding frostbite have been documented in numerous military histories.[3] Hannibal lost nearly half of his army of 46,000 soldiers during a 2-week crossing of the Alps due to frostbite injury. During the Revolutionary War, Dr. James Thatcher recorded that Washington lost 10% of his army to cold-related casualties during the winter of 1778. Baron Dominique Jean Larrey produced the first systematic medical observations of frostbite while serving as Surgeon General of Napoleon's forces during the ill-fated invasion of Moscow in the Fall of 1812 and the subsequent retreat in a harsh Russian winter.[4] Because of the epidemic nature of frostbite in this campaign, Larrey was able to create seminal descriptions of frostbite and to identify the debilitating effects of daily refreezing that occurred with bonfire thawing and subsequent marching in frigid conditions; in addition, many soldiers burned their insensate frostbitten feet while attempting to rewarm them over bonfires. Larrey became convinced that the optimal therapeutic management consisted of friction massage with snow or ice, resulting in slow rewarming.[4] These recommendations were maintained as the standard of care for frostbite in military medicine for more than 100 years.

In the winter of 1941–1942, German troops sustained an estimated 250,000 frostbite injuries in the attempt to take Moscow, constituting the largest reported number of related frostbite injuries in history.[5] During World War II both German and Russian troops moved to a philosophy of rapid rewarming based on work conducted at the Kirov Institute in the 1930s.[5,6] Following World War II existing Russian and German works were translated into English and became the basis for rapid rewarming as the predominant Western paradigm. In 1960, Mills published the first major clinical experience with rapid rewarming and included a philosophy of total care for frostbite with his report.[7] Meryman subsequently edited a seminal text elucidating the scientific bases for frostbite injury.[8] Both military and civilian cold-induced injury data continued to accrue over the subsequent three decades in the absence of any significant clinical advances in the care of frostbite.[9–16] Frostbite continues to present a tremendous clinical challenge, with the greatest clinical advance coming only in the past decade with the use of thrombolytic therapy in early management.[17–19]

Pathophysiology and Classification of Frostbite

The injury associated with frostbite results from two broad mechanistic categories: the first is that of direct cellular damage and death due to the cold insult, and the second is the delayed process mediated by progressive tissue ischemia.[20–23] The immediate effects of frostbite are evidenced by formation of extracellular ice crystals that cause direct injury to the cell membrane, resulting in cellular dehydration due to a change in the osmotic gradient.[24] Rapid cooling results in intracellular freezing, causing more severe cellular damage and cell death, whereas a slower rate of cooling produces extracellular ice crystals. This slower process results in a transmembrane osmotic shift that draws water from within the cell and produces intracellular dehydration. This dehydration causes changes in protein and lipid conformation as well as changes in biochemical processes that are deleterious to intracellular homeostasis.[25–29] As the temperature continues to fall, intracellular crystals develop, with a loss of the linear relationship of temperature to metabolism, decreased DNA synthesis, and histamine response with skin flushing and development of a fluid-filled wheal.[13,30–33]

Microvascular pathophysiology may be even more important than the direct cold injury to the cell, a concept suggested by studies showing the survival of full-thickness skin subjected to freezing and thawing that progressed to necrosis when left in situ but survived when transplanted to a normal, uninjured recipient site.[23] Zacarian identified a number of processes that may play a role in the microcirculatory changes of frostbite. Transient vasoconstriction of both arterioles and venules with subsequent resumption of capillary blood flow appears to occur, and microemboli result from this course.[34] With thawing, the capillaries demonstrate restoration of blood flow that diminishes within minutes. Complete cessation of blood flow is often seen within 20 minutes of rewarming frozen tissue. Similar changes have been seen with random skin flap models after reperfusion, suggesting reactive oxygen species as mediators of injury.[35] Within 72 hours, significant deendothelialization and deposition of fibrin in the capillary bed occurs. Examination of the endothelial ultrastructure demonstrates swelling, fluid extravasation, endothelial cell dilation, and significant projection of the cell into the vascular lumen prior to cell lysis.[36] There is regional variation in the extent of injury, with low-flow venules being most

profoundly affected, resulting in the hypothesis that stasis also plays a role in this pathophysiologic process.[32]

The pathobiochemistry of frostbite has been closely compared to the inflammatory response in the burn wound.[37] Inflammatory mediators such as eicosanoids in burn blister fluid coupled with bradykinin and histamine release in the region of injury draw parallels with findings in cold-induced injury.[38–44] This has prompted investigators to hypothesize a frostbite soft tissue model similar to that of Jackson's for burns, including zones of necrosis and stasis.[45] Similar to their burn blister analysis, Robson and Heggers examined the fluid in frostbite blisters and found high levels of prostaglandin F_2 and thromboxane B_2.[37] These agents or their precursors have been implicated in vasoconstriction and leukocyte adherence. In addition, when refreezing follows thawing, the cellular damage caused by ice crystals and the subsequent inflammatory response are exaggerated.[46,47]

Clinical Findings and Classification of Frostbite Injury

In many situations, the patient is unaware that frostbite is occurring. The presence of hypothermia and the frequent use of mind-altering substances by frostbite patients may contribute to this problem. Typical distribution of injury is acral, with injuries to ears, nose, cheeks, and penis also being fairly common.[9,14,48] The patient may note insensitivity and clumsiness of the affected part. This complex of symptoms rapidly reverses upon rewarming. Severe pain occurs during and immediately after the rewarming process, is often described as throbbing in character, and typically requires parenteral opioids for relief.[49]

Because of the nature of freezing injury, classification has traditionally been based on physical examination findings that occur after rewarming. The most common presentation of *frostnip* is numbness and pallor of exposed skin. Frostnip does not include injury to the underlying dermis or soft tissues, so rewarming results in near-complete resolution of symptoms and physical findings. In contrast, true frostbite involves some degree of dermal and soft-tissue injury. Clinical appearance evolves over a period of time after rewarming, although the initial appearance may be deceptive because hyperemia is present in both frostbite and frostnip.[9,50] The development of skin blebs may require hours to days from the time of injury. After 12–24 hours, the character of the blebs usually becomes apparent and an assessment of the severity of involvement can allow for management planning for the injury.

Traditional classification of frostbite is similar to that of burn injury. First-degree injury is superficial, with hyperemia in the absence of vesicles or blebs. There may initially be an area of pallor with surrounding erythema that evolves into general edema and erythema without long-term sequelae. Second-degree injury has associated light-colored blisters and subsequent epidermal sloughing. This may correlate with partial dermal involvement but has a generally favorable prognosis. Third-degree frostbite typically has hemorrhagic blisters that evolve into thick, black eschar over 1–2 weeks. Fourth-degree injury involves bone, tendon, or muscle and uniformly results in tissue loss. Precision in depth of injury cannot be expected from visual inspection,

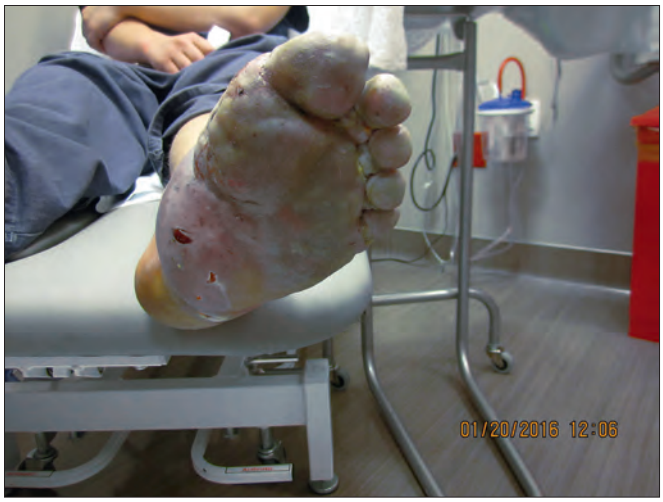

Fig. 39.1 Superficial frostbite injury with clear vesicles.

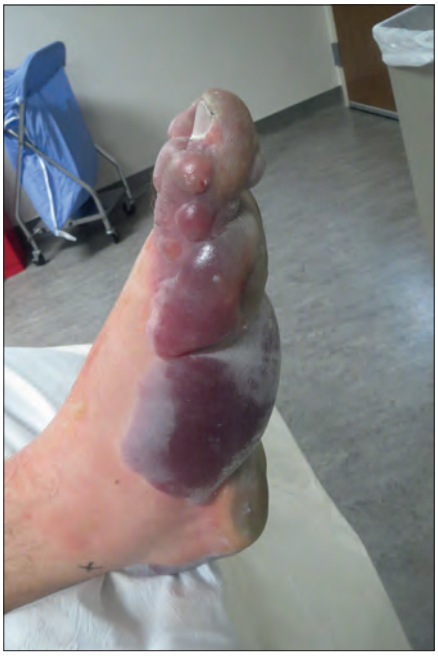

Fig. 39.2 Deep frostbite injury with hemorrhagic vesicles.

and some favor a more general classification of superficial (first- and second-degree injury, see Fig. 39.1) or deep (third- and fourth-degree, see Fig. 39.2) frostbite injury;[51,52] clinically, these can be delineated by clear vesicles, present with superficial injury or hemorrhagic blisters indicative of structural damage to the subdermal tissues.[52,53] Cauchy most recently proposed an alternative classification system based on risk of amputation that includes the extent of the lesion immediately after rewarming, findings from bone scan on day 2, and the presence of blisters on day 2.[54] Although this system has not come into widespread use, the relationship of objective findings to prognosis may prove helpful for future therapeutic trials in the management of frostbite.

Initial Management of Freezing Cold Injury

Prevention is obviously the ideal means of treatment for frostbite. Alcohol and drug intoxication heighten the risk for frostbite, most notably in urban populations and the mentally ill.[55,56] Although the cases of frostbite that occur in intoxicated, mentally ill, and homeless individuals are truly preventable only through broader social interventions, simple techniques exist for those who sustain frostbite secondary to involvement in cold-weather wilderness activities. Frostbite prevention measures in planned cold-weather wilderness activity include, but are not limited to, wearing appropriate clothing, which may include layers and wicking fabrics; keeping that clothing dry; responding appropriately to changing environmental conditions; and performing "cold checks" of at-risk or suspect areas.[57]

If frostbite is identified in the field, the greatest management priority is to not incur further injury. Jewelry should be removed if present in the affected area; rubbing the area with ice or snow is now known to incur further damage to fragile, injured tissue.[4,49,51,58,59] Injured areas should be mechanically protected from trauma because they are typically insensate and are at high risk for further injury.[49,51,58,60] The key decision that must be made in the field is whether thawing should be pursued prior to transfer to definitive care for the frostbite injury.[61] Based on the work of Mills at the Arctic Aeromedical Laboratory demonstrating the deleterious effects of thawing and refreezing on clinical outcomes from frostbite, rewarming in the field should not be pursued unless the ability to maintain the affected tissue in a thawed state is certain.[7,58,62] Systemic cold injury in the form of hypothermia often accompanies local frostbite injury, thus mandating that patients be carefully evaluated to verify that they are normothermic prior to initiating definitive frostbite management. Hypothermia causes peripheral vasoconstriction and diminished blood flow, processes that are exacerbated by the local cold injury. Most importantly, hypothermia can be life-threatening, as opposed to the digit or limb threat posed by frostbite.[63,64] Moderate to severe hypothermia, defined as a core temperature of less than 32°C, must be addressed prior to initiation of frostbite treatment.[48,50,57,62]

The traditional recommendations for rapid rewarming favor a water bath temperature of 40–42°C.[49,53,58,62] The State of Alaska guidelines recently changed the water bath recommendation to a temperature of 37–39°C because this does not substantially increase the time to rewarming but causes less pain for the patient.[51,57] The water bath for thawing should be maintained in this range with the water circulating around the involved tissue. The duration of rewarming is approximately 30 min, although clinical findings to determine the length of time for rewarming include the return of sensation and presence of flushing at the most distal aspect of the involved tissue.[51,61] Administration of narcotics is appropriate at the time of definitive rewarming because of the pain associated with the thawing process.[49] In addition, because these are tetanus-prone wounds, the patient's tetanus immunization should be verified and updated as appropriate. Finally, systemic antibiotics are recommended by some authors in patients with marked edema because of loss of the protective properties of the skin against skin flora when significant edema is present.[47,53,57,61,65–67]

Post-Thaw Evaluation and Management

Following rewarming, local care of the involved tissue is the first priority. Unroofing of blisters remains a matter of controversy.[67] Alteration in local chemokines through the presence of blister fluid, including high levels of $PGF_{2\alpha}$ and TXB_2 and diminished levels of PGE_2, result in vasoconstriction of the involved area, increased leukocyte adherence, and increased platelet aggregation, all of which cause progressive dermal ischemia.[13,37,41,44] However, concern also exists about removal of hemorrhagic blisters because of the damage to subdermal structures associated with these blisters, indicating that debridement may extend the soft-tissue damage in these areas.[52,53] A more practical justification for debridement of blisters is that it improves the visualization of underlying tissue, allowing the clinician to better assess the status of the wounds.[66]

Aloe vera has properties that counter the arachidonic acid cascade and therefore benefit the local care of frostbitten areas. Heggers demonstrated that the use of systemic NSAIDs and local aloe vera to address the inflammatory chemokines, coupled with systemic penicillin as prophylaxis against Gram-positive infection, resulted in demonstrably less tissue loss, a lower amputation rate, and shorter hospital stay versus patients managed with traditional topical antimicrobials.[13] Topical aloe vera alone was credited with clinically significant tissue salvage in these patients, resulting in preferential management with aloe vera rather than topical antimicrobials such as silver sulfadiazine or sulfamylon.[13,57,61,67] Topical wound care also should address mechanical protection of the affected areas, with careful padding, splinting, and elevation and/or compression to manage edema formation.[51,53,61,67]

NONSURGICAL THERAPIES

Pharmacologic management of the frostbite patient also includes systemic blockade of the arachidonic acid pathway to ameliorate the inflammatory response to the local cold injury. Historically aspirin was used and did demonstrate tissue survival improvement of greater than 20% in a rabbit ear model.[13] However aspirin blocks all arachidonate metabolites, including those that are beneficial for wound healing. Therefore, more recent recommendations center on the use of ibuprofen and specific blockade of TXA_2.[1,61,65,68]

Pentoxifylline, a phosphodiesterase inhibitor that is primarily used in claudication, has been shown to synergistically improve tissue viability in conjunction with topical aloe vera.[69] Pentoxifylline improves red blood cell flexibility, which may limit microvascular sludging and thereby diminish thrombus formation in small vessels. In addition, pentoxifylline may reduce blood viscosity, again contributing to improved tissue survival.[70] When pentoxifylline is used for post-thaw pharmacologic management, the current recommendation, based on a study of pedal frostbite, is 400 mg

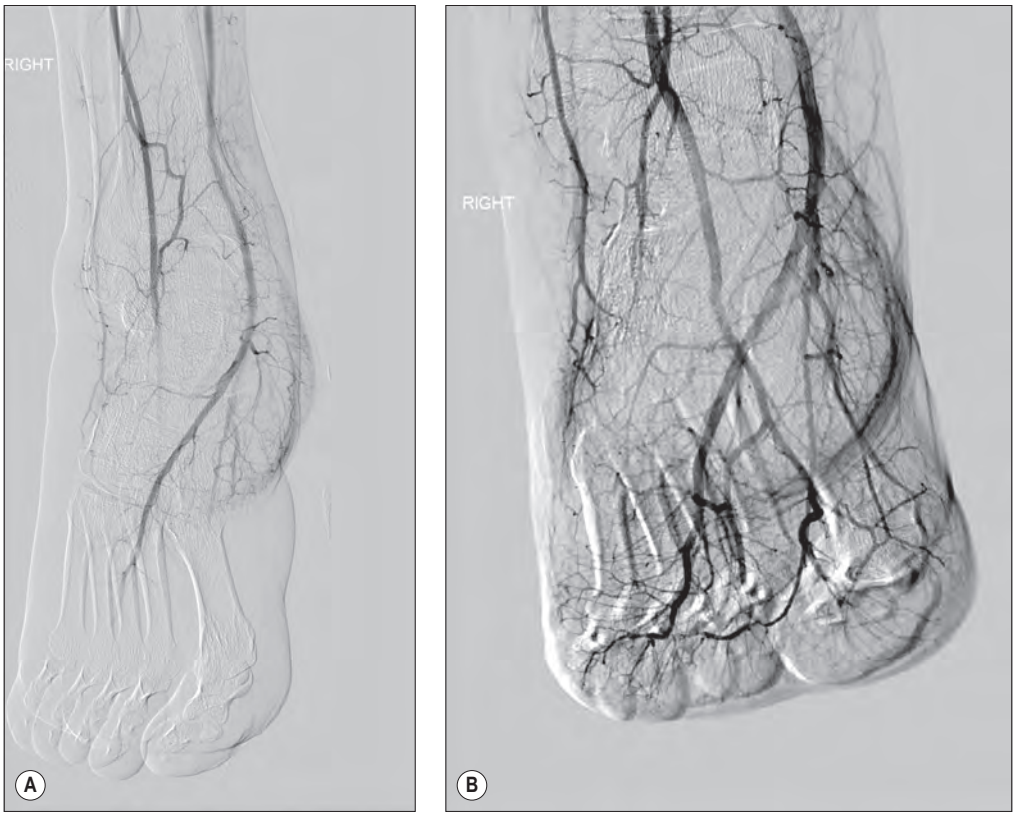

Fig. 39.3 **(A)** Angiogram of foot with deep frostbite prior to tissue plasminogen activator (t-PA). **(B)** Angiogram of foot with deep frostbite following 19 hours of t-PA.

t.i.d. for 2–6 weeks following injury.[70] Iloprost, a prostacyclin analog that also serves as a vasodilator, has interesting features that may be of benefit, although all data on its use are preliminary.[57,71] Although studies of pentoxifylline and iloprost are ongoing in Europe, current data are inadequate to recommend their use.

Thrombolytics have demonstrated the most notable clinical advance in the management of frostbite in the past 50 or more years. The first demonstration of possible utility for thrombolytics in frostbite management was an animal model using IV urokinase.[72] In 1992, a preliminary account indicated that thrombolytics were potentially better than slow rewarming for reducing amputation following frostbite injury.[73] Subsequent publications have shown improved digit salvage with the use of tissue plasminogen activator (t-PA) (see Fig. 39.3).[17,19,74–77] Unfortunately, t-PA only appears to be efficacious within 24 hours of thaw, meaning that this may not be an option for patients who are injured in extremely remote environments. Additionally, although digit salvage has been improved with thrombolytics, the long-term functional results of this salvage remain unclear, particularly the impact on neuropathic complications of freezing cold injury.

Surgical and chemical sympathectomy has largely fallen out of favor owing to clinical results that are mixed at best. Sympathectomy has not shown any improvement in tissue preservation in frostbite and may ultimately result in more proximal injury demarcation.[78,79] The two best-documented benefits of sympathectomy relate to long-term function, with improved cold tolerance and amelioration of the neuropathic pain and paresthesias that often present one of the greatest clinical challenges following freezing cold injury.[78,80] Therefore, the best use of sympathectomy may be in the longer-term management of otherwise disabling complications of frostbite.

Studies of hyperbaric oxygen (HBO) are limited but have some of the most promising functional results of an adjunctive therapy for frostbite. An early documented use of HBO for therapy in frostbite involved four Alpine mountaineers, all of whom presented 10 or more days following injury and all of whom demonstrated good tissue preservation with HBO.[81] Several subsequent case reports have demonstrated improved nutritive blood flow and/or complete maintenance of frostbitten areas following HBO therapy, even with delayed presentations.[82–85] The utility in delayed presentation combined with the potential for improved functional outcomes make HBO an extremely attractive therapy in frostbite. Multicenter trials of HBO would provide substantial progress toward understanding the role for this therapy in frostbite management.

IMAGING AND SURGICAL MANAGEMENT

Both scintigraphy and magnetic resonance imaging/angiography (MRI/MRA) have been recommended as diagnostic aids to improve the process of surgical management of frostbite. More than 20 years ago, Mehta identified three different patterns in triple-phase bone scanning that were useful indicators of outcome within 48 hours of injury.[86] Specifically, he found that perfusion and blood pooling

phases demonstrated at-risk tissue, and the bone phase showed deep tissue and bone infarction. Several studies have demonstrated excellent correlation between scintigraphic findings and surgical outcomes, although some authors claim that bone scan findings best correlate with surgical findings at 7–10 days following injury.[66,87,88] Confidence in scintigraphic findings by some practitioners has been adequate for them to derive a protocol using the findings to direct early surgery.[54,89] The use of MRI/ MRA initially seemed promising, allowing direct visualization of occluded vessels and possible better delineation of viable tissue than ^{99}Tc scanning.[90] However a subsequent study demonstrated that MRI was no better than bone scanning to identify anatomic sites for amputation and that the limited soft tissue present in digits hampered the utility of MRI.[65]

Because of a historical bias based on data showing that early surgery was potentially associated with worse outcomes, the adoption of scintigraphy with early operative intervention has been limited.[79] However, Greenwald developed a protocol with early scintigraphy followed by operative intervention at 7–10 days following injury.[89] Cauchy makes a plausible argument for intervention at 10–15 days post injury with a bone scan based on a shorter waiting time for the patient, lower infection risk, and earlier progression to rehabilitation; of note, Cauchy advocates repeat scanning at 7–10 days post injury if the injury is not clearly delineated on early (<48 hours) bone scan.[66] Nevertheless the prevalent clinical practice remains to time surgery anywhere from 4 weeks to 3 months following injury, once tissues have clearly demarcated to an experienced clinical eye.[49,67]

Conclusion

Frostbite has a long clinical history and remains a modern clinical challenge. Although the pathophysiology of freezing cold injury is well delineated, few advances from the traditional "frostbite in January, amputation in July" management approach have occurred. Thrombolytic therapy has shown benefit in digital salvage but requires early use and has unclear long-term functional outcomes. HBO has shown promise in terms of salvage and functional outcomes but so far has only been evaluated in case series. Vasodilation with pentoxifylline or iloprost merits ongoing study as a potential therapy for frostbite. Scintigraphy may provide a means to expedite the surgical management of frostbitten digits and extremities, but again has only been studied in limited settings. Large-scale multicenter evaluation of these varied evaluation and management techniques is required to demonstrate whether any of these practices will ultimately improve tissue salvage and functional outcomes.

Complete references available online at
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Further Reading

Bruen KJ, Ballard JR, Morris SE, et al. Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy. *Arch Surg*. 2007;142(6):546-551, discussion 551-553.

This retrospective, single-center review presented the largest series of frostbite patients managed with thrombolytic therapy. A reduction in incidence of digital amputation rates ranges from 41% to 10%.

Cauchy E, Marsigny B, Allamel G, et al. The value of technetium 99 scintigraphy in the prognosis of amputation in severe frostbite injuries of the extremities: a retrospective study of 92 severe frostbite injuries. *J Hand Surg Am*. 2000;25(5):969-978.

The Chamonix group provides a 12-year review including 92 patients, demonstrating the value of 99Tc scanning in frostbite evaluation and management. They use their experience to delineate an algorithm with potential use in future research on medical and surgical management of frostbite.

McCauley RL, Hing DN, Robson MC, et al. Frostbite injuries: a rational approach based on the pathophysiology. *J Trauma*. 1983;23(2):143-147.

This seminal article describes a limited single-center experience with frostbite. The University of Chicago Frostbite Protocol that is included is the foundation for multiple protocols that have been published subsequently.

State of Alaska. *State of Alaska Cold Injury Guidelines*. Juneau: State of Alaska; 2005.

These represent the most comprehensive guidelines for the management of all forms of cold injury. Frostbite guidelines include the spectrum of care, from management in the field through arrival at a hospital that can provide definitive care.

References

1. Edlich RF, Chang DE, Birk KA, Morgan RF, Tafel JA. Cold injuries. *Compr Ther*. 1989;15(9):13-21.
2. Purdue GF, Hunt JL. Cold injury: a collective review. *J Burn Care Rehabil*. 1986;7(4):331-342.
3. Schechter DC, Sarot IA. Historical accounts of injuries due to cold. *Surgery*. 1968;63(3):527-535.
4. Larrey DJ. *Memoirs of Military Surgery*. Vol. 2. Baltimore, MD: Joseph Cushing; 1814.
5. Killian H. *Cold Injury with Special Reference to the German Experience During World War II*. Germany: Aulendorf i Wurtt; 1952.
6. Ariev TJ. *Monograph on Frostbite*. Toronto: Defence Research Board of Canada; 1955.
7. Mills WJ, Whaley R. Frostbite: experience with rapid re-warming and ultrasonic therapy. *Alaska Med*. 1960;35(6).
8. Meryman HT. *Cryobiology*. New York: Academic Press; 1966.
9. Boswick JA Jr, Thompson JD, Jonas RA. The epidemiology of cold injuries. *Surg Gynecol Obs*. 1979;149(3):326-332.
10. Candler WH, Ivey H. Cold weather injuries among U.S. soldiers in Alaska: a five-year review. *Mil Med*. 1997;162(12):788-791.
11. Dembert ML, Dean LM, Noddin EM. Cold weather morbidity among United States Navy and Marine Corps Personnel. *Mil Med*. 1981;146(11):770-775.
12. Groom AF, Coull JT. Army amputees from the Falklands–review. *J R Army Med Corps*. 1984;130(2):114-116.
13. Heggers JP, Robson MC, Manavalen K, et al. Experimental and clinical observations on frostbite. *Ann Emerg Med*. 1987;16(9):1056-1062.
14. Lehmuskallio E, Lindholm H, Koskenvuo K, et al. Frostbite of the face and ears: epidemiological study of risk factors in Finnish conscripts. *BMJ*. 1995;311(7021):1661-1663.
15. Marsh AR. A short but distant war: the Falklands campaign. *J R Soc Med*. 1983;76(11):972-982.
16. Taylor MS, Kulungowski MA, Hamelink JK. Frostbite injuries during winter maneuvers: a long-term disability. *Mil Med*. 1989;154(8):411-412.
17. Bruen KJ, Ballard JR, Morris SE, et al. Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy. *Arch Surg*. 2007;142(6):543-546.
18. Sheridan RLL, Goldstein MA, Stoddard FJ Jr, et al. Case records of the Massachusetts General Hospital. Case 41-2009. A 16-year-old boy with hypothermia and frostbite. *N Engl J Med*. 2009;361(27):2654.
19. Twomey JA, Peltier GL, Zera RT. An open-label study to evaluate the safety and efficacy of tissue plasminogen activator in treatment of severe frostbite. *J Trauma*. 2005;59(6):1350-1355.
20. Eubanks RG. Heat and cold injuries. *J Ark Med Soc*. 1974;71(1):53-58.
21. Fuhrman FA, Crismon JM. Studies on gangrene following cold injury general course of events in rabbit feet and ears following untreated cold injury. *J Clin Invest*. 1947;26(2):236-244.
22. Quintanilla R, Krusen FH, Essex HE. Studies on frost-bite with special reference to treatment and the effect on minute blood vessels. *Am J Physiol*. 1947;149(1):149-161.
23. Weatherley-White RC, Sjostrom B, Paton BC. Experimental studies in cold injury. II. The pathogenesis of frostbite. *J Surg Res*. 1964;4:17-22.
24. Meryman HT. Mechanics of freezing in living cells and tissues. *Science*. 1956;124(3221):515-521.
25. Lovelock JE. Physical instability and thermal shock in red cells. *Nature*. 1954;173(4406):659-661.
26. Lovelock JE. The denaturation of lipid-protein complexes as a cause of damage by freezing. *Proc R Soc L B Biol Sci*. 1957;147(929):427-433.
27. Markert CL. Lactate dehydrogenase isozymes: dissociation and recombination of subunits. *Science*. 1963;140(3573):1329-1330.
28. Mazur P. Causes of injury in frozen and thawed cells. *Fed Proc*. 1965;24:S175-S182.
29. Mazur P. Studies on rapidly frozen suspensions of yeast cells by differential thermal analysis and conductometry. *Biophys J*. 1963;3:323-353.
30. Johnson BE, Daniels F Jr. Enzyme studies in experimental cryosurgery of the skin. *Cryobiology*. 1974;11(3):222-232.
31. Vanggaard L. Arteriovenous anastomoses in temperature regulation. *Acta Physiol Scand*. 1969;76(1):13A.
32. Zacarian SA, Stone D, Clater M. Effects of cryogenic temperatures on microcirculation in the golden hamster cheek pouch. *Cryobiology*. 1970;7(1):27-39.
33. Lewis T. *The Blood Vessels of the Human Skin and Their Responses*. London: Shaw and Sons, Ltd; 1927:147-150.
34. Zacarian SA. Cryogenics: The cryolesion and the pathogenesis of cryonecrosis. In: Zacarian SA, ed. *Cryosurgery for Skin Cancer and Cutaneous Disorders*. St. Louis: Mosby; 1985.
35. Bulkley GB. The role of oxygen free radicals in human disease processes. *Surgery*. 1983;94(3):407-411.
36. Rabb JM, Renaud ML, Brandt PA, Witt CW. Effect of freezing and thawing on the microcirculation and capillary endothelium of the hamster cheek pouch. *Cryobiology*. 1974;11(6):508-518.
37. Robson MC, Heggers JP. Evaluation of hand frostbite blister fluid as a clue to pathogenesis. *J Hand Surg Am*. 1981;6(1):43-47.
38. Back N, Jainchill M, Wilkens HJ, Ambrus JL. Effect of inhibitors of plasmin, kallikrein and kinin on mortality from scalding in mice. *Med Pharmacol Exp Int J Exp Med*. 1966;15(6):597-602.
39. Harms BA, Bodai BI, Smith M, et al. Prostaglandin release and altered microvascular integrity after burn injury. *J Surg Res*. 1981;31(4):274-280.
40. Heggers JP, Ko F, Robson MC, Heggers R, Craft KE. Evaluation of burn blister fluid. *Plast Reconstr Surg*. 1980;65(6):798-804.
41. Heggers JP, Loy GL, Robson MC, Del Beccaro EJ. Histological demonstration of prostaglandins and thromboxanes in burned tissue. *J Surg Res*. 1980;28(2):110-117.
42. Huribal M, Cunningham ME, D'Aiuto ML, Pleban WE, McMillen MA. Endothelin-1 and prostaglandin E2 levels increase in patients with burns. *J Am Coll Surg*. 1995;180(3):318-322.
43. Nakae H, Endo S, Inada K, et al. Plasma concentrations of type II phospholipase A2, cytokines and eicosanoids in patients with burns. *Burns*. 1995;21(6):422-426.
44. Robson MC, Del Beccaro EJ, Heggers JP. The effect of prostaglandins on the dermal microcirculation after burning, and the inhibition of the effect by specific pharmacological agents. *Plast Reconstr Surg*. 1979;63(6):781-787.
45. Jackson DM. The diagnosis of the depth of burning. *Br J Surg*. 1953;40(164):588-596.
46. Bhatnagar A, Sarker BB, Sawroop K, et al. Diagnosis, characterisation and evaluation of treatment response of frostbite using pertechnetate scintigraphy: a prospective study. *Eur J Nucl Med Mol Imaging*. 2002;29(2):170-175.
47. Petrone P, Kuncir EJ, Asensio JA. Surgical management and strategies in the treatment of hypothermia and cold injury. *Emerg Med Clin North Am*. 2003;21(4):1165-1178.
48. Valnicek SM, Chasmar LR, Clapson JB. Frostbite in the prairies: a 12-year review. *Plast Reconstr Surg*. 1993;92(4):633-641.
49. Jurkovich GJ. Environmental cold-induced injury. *Surg Clin North Am*. 2007;87(1):247-267, viii.
50. Orr KD, Fainer DC. Cold injuries in Korea during winter of 1950–51. *Med*. 1952;31(2):177-220.
51. State of Alaska. *State of Alaska Cold Injury Guidelines*. Services D of H and S, editor. Juneau, AK: State of Alaska; 2005.
52. Biem J, Koehncke N, Classen D, Dosman J. Out of the cold: management of hypothermia and frostbite. *CMAJ*. 2003;168(3):305-311.
53. McCauley RL, Hing DN, Robson MC, Heggers JP. Frostbite injuries: a rational approach based on the pathophysiology. *J Trauma*. 1983;23(2):143-147.
54. Cauchy E, Chetaille E, Marchand V, Marsigny B. Retrospective study of 70 cases of severe frostbite lesions: a proposed new classification scheme. *Wilderness Env Med*. 2001;12(4):248-255.
55. Kowal-Vern A, Latenser BA. Demographics of the homeless in an urban burn unit. *J Burn Care Res*. 2007;28(1):105-110.
56. Pinzur MS, Weaver FM. Is urban frostbite a psychiatric disorder? *Orthopedics*. 1997;20(1):43-45.
57. Imray C, Grieve A, Dhillon S. Cold damage to the extremities: frostbite and non-freezing cold injuries. *Postgr Med J*. 2009;85(1007):481-488.
58. Golant A, Nord RM, Paksima N, Posner MA. Cold exposure injuries to the extremities. *J Am Acad Orthop Surg*. 2008;16(12):704-715.
59. Syme D. Position paper: on-site treatment of frostbite for mountaineers. *High Alt Med Biol*. 2002;3(3):297-298.
60. Vogel JE, Dellon AL. Frostbite injuries of the hand. *Clin Plast Surg*. 1989;16(3):565-576.
61. McIntosh SE, Opacic M, Freer L, et al. Wilderness Medical Society practice guidelines for the prevention and treatment of frostbite: 2014 update. *Wilderness Environ Med*. 2014;25(4 suppl):S43-S54.
62. Grace TG. Cold exposure injuries and the winter athlete. *Clin Orthop Relat Res*. 1987;216:55-62.
63. Brown DJA, Brugger H, Boyd J, Paal P. Accidental hypothermia. *N Engl J Med*. 2012;367(20):1930-1938.

64. Zafren K, Giesbrecht GG, Danzl DF, et al. Wilderness Medical Society practice guidelines for the out-of-hospital evaluation and treatment of accidental hypothermia. *Wilderness Environ Med*. 2014;25(4):425-445.
65. Murphy JV, Banwell PE, Roberts AH, McGrouther DA. Frostbite: pathogenesis and treatment. *J Trauma*. 2000;48(1):171-178.
66. Cauchy E, Marsigny B, Allamel G, Verhellen R, Chetaille E. The value of technetium 99 scintigraphy in the prognosis of amputation in severe frostbite injuries of the extremities: A retrospective study of 92 severe frostbite injuries. *J Hand Surg Am*. 2000;25(5):969-978.
67. Mohr WJ, Jenabzadeh K, Ahrenholz DH. Cold injury. *Hand Clin*. 2009;25(4):481-496.
68. Britt LD, Dascombe WH, Rodriguez A. New horizons in management of hypothermia and frostbite injury. *Surg Clin North Am*. 1991;71(2):345-370.
69. Miller MB, Koltai PJ. Treatment of experimental frostbite with pentoxifylline and aloe vera cream. *Arch Otolaryngol Head Neck Surg*. 1995;121(6):678-680.
70. Hayes DW Jr, Mandracchia VJ, Considine C, Webb GE. Pentoxifylline. Adjunctive therapy in the treatment of pedal frostbite. *Clin Pod Med Surg*. 2000;17(4):715-722.
71. Cauchy E, Cheguillaume B, Chetaille E. A controlled trial of a prostacyclin and rt-PA in the treatment of severe frostbite. *N Engl J Med*. 2011;364(2):189-190.
72. Zdeblick TA, Field GA, Shaffer JW. Treatment of experimental frostbite with urokinase. *J Hand Surg Am*. 1988;13(6):948-953.
73. Skolnick AA. Early data suggest clot-dissolving drug may help save frostbitten limbs from amputation. *JAMA*. 1992;267(15):2008-2010.
74. Rakower SR, Shahgoli S, Wong SL. Doppler ultrasound and digital plethysmography to determine the need for sympathetic blockade after frostbite. *J Trauma*. 1978;18(10):713-718.
75. Johnson AR, Jensen HL, Peltier G, DelaCruz E. Efficacy of intravenous tissue plasminogen activator in frostbite patients and presentation of a treatment protocol for frostbite patients. *Foot Ankle Spec*. 2011;4(6):344-348.
76. Gonzaga T, Jenabzadeh K, Anderson CP, et al. Use of intraarterial thrombolytic therapy for acute treatment of frostbite in 62 patients with review of thrombolytic therapy in frostbite. *J Burn Care Res*. 2015.
77. Ibrahim AE, Goverman J, Sarhane KA, et al. The emerging role of tissue plasminogen activator in the management of severe frostbite. *J Burn Care Res*. 2015;36(2):e62-e66.
78. Bouwman DL, Morrison S, Lucas CE, Ledgerwood AM. Early sympathetic blockade for frostbite – is it of value? *J Trauma*. 1980;20(9):744-749.
79. Mills WJ Jr. Comments on this issue of Alaska Medicine – from then (1960) until now (1993). *Alaska Med*. 1993;35(1):70-87.
80. Taylor MS. Lumbar epidural sympathectomy for frostbite injuries of the feet. *Mil Med*. 1999;164(8):566-567.
81. Ward MP, Garnham JR, Simpson BR, Morley GH, Winter JS. Frostbite: general observations and report of cases treated by hyperbaric oxygen. *Proc R Soc Med*. 1968;61(8):787-789.
82. von Heimburg D, Noah EM, Sieckmann UP, Pallua N. Hyperbaric oxygen treatment in deep frostbite of both hands in a boy. *Burns*. 2001;27(4):404-408.
83. Finderle Z, Cankar K. Delayed treatment of frostbite injury with hyperbaric oxygen therapy: a case report. *Aviat Sp Env Med*. 2002;73(4):392-394.
84. Dwivedi DA, Alasinga S, Singhal S, Malhotra VK, Kotwal A. Successful treatment of frostbite with hyperbaric oxygen treatment. *Indian J Occup Environ Med*. 2015;19(2):121-122.
85. Kemper TCPM, de Jong VM, Anema HA, van den Brink A, van Hulst RA. Frostbite of both first digits of the foot treated with delayed hyperbaric oxygen:a case report and review of literature. *Undersea Hyperb Med*. 2014;41(1):65-70.
86. Mehta RC, Wilson MA. Frostbite injury: prediction of tissue viability with triple-phase bone scanning. *Radiology*. 1989;170(2):511-514.
87. Cauchy E, Chetaille E, Lefevre M, Kerelou E, Marsigny B. The role of bone scanning in severe frostbite of the extremities: a retrospective study of 88 cases. *Eur J Nucl Med*. 2000;27(5):497-502.
88. Salimi Z, Vas W, Tang-Barton P, et al. Assessment of tissue viability in frostbite by 99mTc pertechnetate scintigraphy. *AJR Am J Roentgenol*. 1984;142(2):415-419.
89. Greenwald D, Cooper B, Gottlieb L. An algorithm for early aggressive treatment of frostbite with limb salvage directed by triple-phase scanning. *Plast Reconstr Surg*. 1998;102(4):1069-1074.
90. Barker JR, Haws MJ, Brown RE, Kucan JO, Moore WD. Magnetic resonance imaging of severe frostbite injuries. *Ann Plast Surg*. 1997;38(3):275-279.

40 Chemical Burns

FELICIA N. WILLIAMS and JONG O. LEE

Introduction

Chemical burns represent a small percentage of burn injuries yet up to one third of burn-related deaths.[1] Many common household and industrial compounds have the potential to induce severe chemical burns. The American Association of Poison Control Centers' National Poison Data System 2014 annual report demonstrated 199,291 cases of exposure to cosmetic or personal care products; 198,018 household cleaning substances; 83,005 pesticides; 31,903 hydrocarbons; and 38,975 unspecified chemicals.[2] Exposure to specific chemicals, including acids, alkalines, peroxides, bleaches, and phenols, in 2014 totaled 38,594, which was up from the 38,552 cases of exposures in 2013.[3] The unfortunate reality concerning the ease of access to toxic products is evident in the presence of a rising number of pediatric exposures to chemical injuries. Most chemical burns involving children are secondary to common household products. Domestic chemical burn injuries are often due to poor labeling and storage, as well as secondary to intentional assault and suicide attempts. The most commonly affected areas of the body are the face, eyes, and arms and legs. As a result, the length of hospital stay and duration of healing tend to be greater with chemical burns. The majority of these deaths are related to the ingestion of chemical substances.[4] This chapter provides general principles for the treatment of chemical injuries.

Pathophysiology

All burn wounds, whether caused by chemical or thermal sources, have in common the denaturation of key structural and functional proteins. The structure of biological proteins involves not only a specific amino acid sequence but also a three-dimensional structure depending on weak forces, such as hydrogen bonding or van der Waals' forces. These three-dimensional structures impart biological activity to the proteins and are easily disrupted by outside influences, specifically chemical and thermal energy sources. Weak bonds are impaired by heat energy sources degrading and denaturing proteins. Moreover, any variations in pH or dissolution of surrounding lipids may neutralize a protein and disrupt its function. Direct chemical effects on a reactive group in a protein will similarly render it inactive.

The severity of a chemical burn injury is determined by several factors:[5]

- Concentration of chemical in contact or ingested
- Quantity of chemical agent
- Manner and duration of contact (skin or ingestion)
- Extent of penetration
- Mechanism of action of the chemical
- Physical state of agent (liquid, solid, gas).

There are six mechanisms of action for chemical agents in biological systems, classified by how they denature and damage proteins:[5,6]

1. *Reduction*: Reducing agents act by binding free electrons in tissue proteins, causing denaturation. In general, they do so by reducing the amide link. Examples include hydrochloric acid, nitric acid, alkyl mercuric compounds, ferrous iron, and sulfite compounds.[5,7]
2. *Oxidation*: Oxidizing agents are oxidized on contact with tissue proteins. These agents cause destruction by inserting oxygen, sulfur, or halogen atoms to structural and functional proteins. Byproducts are often toxic and continue to react with the surrounding tissue. Examples of oxidizing agents are sodium hypochlorite, potassium permanganate, chromic acid, and peroxide.[5]
3. *Corrosive agents*: Corrosive substances denature tissue proteins on contact and form eschar and a shallow ulcer. Examples of corrosive agents include phenols, cresols, white phosphorus, dichromate salts, sodium metals, lyes, sulfuric acid, and hydrochloric acid.
4. *Protoplasmic poisons*: These agents produce their effects by binding or inhibiting calcium or other organic ions necessary for tissue viability and function. These agents form esters with proteins and/or chelate calcium or other ions. Examples of protoplasmic poisons include "alkaloidal" acids; acetic acid; formic acid; and metabolic competitors and inhibitors such as oxalic acid, hydrofluoric acid, and hydrazoic acid.
5. *Vesicants*: Vesicant agents produce ischemia with necrosis at the site of contact. There is associated tissue cytokine release and blister formation. Examples include cantharides, dimethyl sulfoxide (DMSO), mustard gas (sulfur and nitrogen), and Lewisite.
6. *Desiccants*: These substances cause damage by dehydrating tissues and exothermic reactions, causing the release of heat into the tissue. Examples include sulfuric acid, muriatic acid, calcium sulfate, and silica gel.

Chemical burns are often described as acidic or alkali.[8] Acids act as proton donors in the biological system, and strong acids have a pH less than 2. Alkali, or basic, materials capable of producing injury typically have a pH greater than 11.5.[8] In general, alkaline materials cause more injury than acidic compounds. Whereas acids cause coagulation necrosis with precipitation of protein, the reaction to alkali is "liquefaction" necrosis, allowing the alkali to penetrate deeper into the injured tissue.[9] The presence of hydroxyl ions within these tissues increases their solubility, allowing alkaline proteinases to form when the alkalis dissolve the proteins of the tissues.[1] Organic solutions tend to dissolve

the lipid membrane of cell walls and cause disruption of cellular architecture as their mechanism of action. Inorganic solutions tend more to remain on the exterior of cells but may act as transporters to carry the above-mentioned agents that denature proteins or form salts with proteins themselves.[5]

General Principles of Management

The most important aspects of first aid for patients with chemical burns involve removal of the offending agent from contact with the patient—stop the burn. This requires removal of all potentially contaminated clothing and copious irrigation. Irrigation of chemical burns requires protection of healthcare providers to prevent additional injuries and additional patients. In addition, the wounds should not be irrigated by placing the patient into a tub, thereby containing the chemical and spreading the injurious material. Irrigation should be a large-volume shower or decontamination station and drained out of an appropriate drain. Immediate copious irrigation has been shown to reduce the extent and depth of injury, especially to eyes.[10] No measure of adequacy of lavage has been developed, but monitoring the pH from the effluent can provide quantifiable information as to adequacy of lavage. Thirty minutes to 2 hours of lavage is often necessary.

Safety data sheets (SDS) are mandated to be available for all chemicals present in the workplace. These can be valuable resources for potential systemic toxicity and adverse effects of an agent. Further assistance is available from regional poison control centers for household chemicals or unidentified agents.

The use of neutralizing agents is generally contraindicated. Neutralizing agents cause exothermic reactions, producing a thermal component along with a chemical injury. When the chemical agent is known and an appropriate antidote to support the physiologic changes incited by the original agent is known, some benefit to its use has been documented but has not been found to be superior to water for irrigation.[11–13] An example is calcium gluconate for hydrofluoric acid burns (discussed later in the chapter).

Treatment paradigms remain unchanged for burn and trauma patients with strict adherence to Advanced Trauma Life Support (ATLS)and Advanced Burn Life Support (ABLS) guidelines. After airway patency is assured, adequate air movement and hemodynamics should be maintained. Conventional thermal burn formulas are used for resuscitation at maintaining end-organ perfusion. Monitoring of urine output remains paramount to assessment of adequacy of end-organ perfusion and hence resuscitation. Systemic disturbances of pH are potential complications and must be monitored until acid–base disorder and electrolyte abnormalities are corrected.

The typical large-volume lavage required to adequately dilute chemical exposures puts the patient at potential risk for hypothermia, both from evaporative cooling losses and from the use of unwarmed lavage fluid. Principles of wound care for chemical burns are typically the same as for thermal burns. Early excision and grafting of obviously nonviable tissue is advocated, particularly in light of the observation that chemical burns tend to be deeper than they initially appear. As a result, they tend to heal more slowly.

Specific Agents

ACIDS

Acetic Acid

Acetic acid, also known as ethanoic acid, ethylic acid, and methane carboxylic acid, is a mild chelating agent. Solutions diluted to less than 40% concentrations, such as table vinegar and hair-wave neutralizing products, are usually harmless, but if used inappropriately, they may cause injuries. Chemical exposures may cause symptoms of upper and lower airway irritation, including cough, tachypnea, wheezing, nose and throat irritation, and pharyngeal and pulmonary edema. Other symptoms found are tooth erosion, conjunctivitis, headache, nausea, vomiting, impaired vision, abdominal pain, eye pain, and whitish discoloration of the skin.[5] In such cases, initial treatment involves irrigation.[14]

Carbolic Acid (Phenol)

Carbolic acid is a hydrocarbon derived from coal tar, which acts to cause damage secondary to its ability to induce denaturation and necrosis.[15,16] The most common adverse effects are dermatitis, abnormal pigmentation, and burns to the skin.[17] Concentrated amounts of phenol are caustic; therefore, prolonged skin contact causes partial- or full-thickness burns. These burns tend to become extensive before detection, secondary to the local anesthetic properties of phenol. Ingestion of as little as 1000 mg may be fatal. Systemic effects include ventricular arrhythmias,[18] pulmonary edema, stridor, and tachypnea. Locally, conjunctivitis, corneal edema or necrosis, and skin necrosis result.[16]

Acute poisonings are potentially fatal; hence, prompt action is necessary with copious irrigation. Polyethylene glycol (PEG; molecular weight 300 or 400 Da) has been shown to be of potential benefit, but large-volume lavage should not be delayed while PEG application is begun. Reports in the literature indicate that intravenous (IV) sodium bicarbonate may be of use to prevent some of the systemic effects of phenol.[19–26]

Chromic Acid

This acid causes nonpainful but corrosive ulcers upon contact with the skin.[27] Ulceration of the nasal septum and bronchospasm can occur with inhalation. This agent causes protein coagulation. Peak blood levels are thought to be achieved within 5 hours of exposure. Symptoms may occur with just 1% total body surface area (TBSA) burn, but a 10% burn or greater is often fatal owing to its systemic effects. Irrigation is the primary treatment for exposure, but in an industrial setting, washing with a dilute solution of sodium hyposulfite or water followed by rinsing in a buffered phosphate solution may be a more specific antidote. Dimercaprol may be used at 4 mg/kg intramuscularly every 4 hours for 2 days followed by 2–4 mg/kg/day for 7 days in total to treat the systemic effects. Dialysis in the first 24

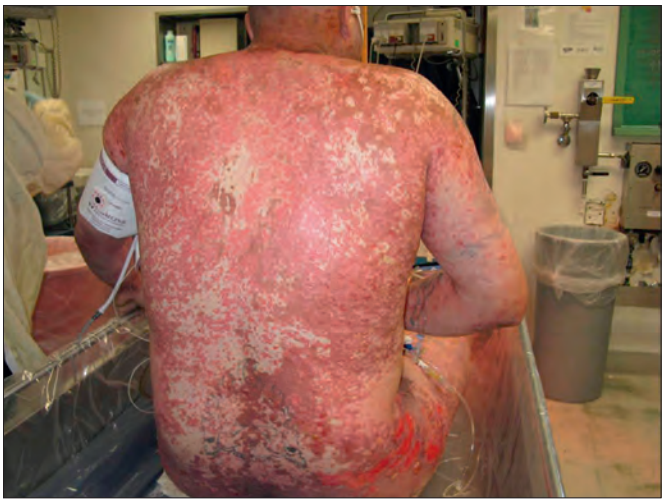

Fig. 40.1 Epichlorohydrin acid burn 3 days after admission.

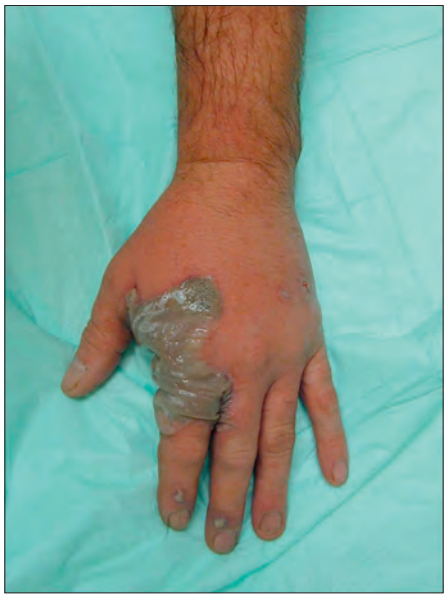

Fig. 40.2 Hydrochloric acid burn to the hand before blister removal.

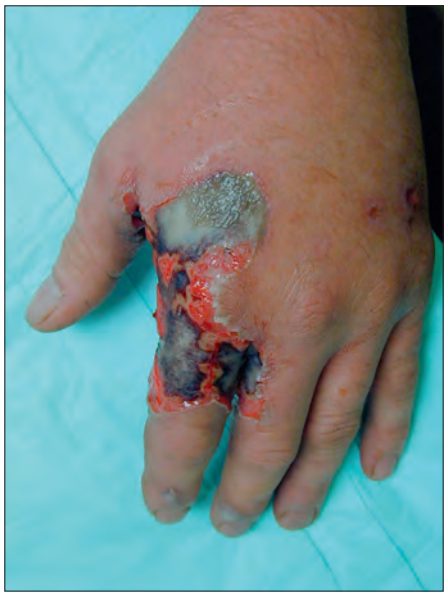

Fig. 40.3 Hydrochloric acid burn to the hand after blister removal.

hours is a reasonable means to remove circulating chromium and to address existing electrolyte imbalances. Exchange transfusion may be necessary. Various ointments containing products such as 10% calcium ethylenediaminetetraacetic acid (EDTA) or ascorbic acid are available for small superficial burns.[28,29] There have been case reports supporting the early excision of chromic acid burn to assist in preventing systemic toxicity.[28,30]

Epichlorohydrin Acid

Epichlorohydrin is a rare, corrosive carcinogen that is colorless and exudes a garlic-like odor. It is used in the production of glues, plastic, glycerols, and resins, as well as in paper reinforcement and water purification. It can also be converted into a binder used in the production of explosives. These burns may demonstrate a rapid progression to a full-thickness wound within hours. Management commences with copious irrigation and hemodynamic monitoring (Fig. 40.1).

Formic Acid

Formic acid is a strong inorganic acid used by glue makers and tanning workers. After contact, it creates an eschar, which does not prevent systemic absorption. After it is absorbed, metabolic acidosis, intravascular hemolysis with hemoglobinuria, renal failure, pulmonary complications, and abdominal pain with necrotizing pancreatitis usually occur.[31] All patients injured by formic acid should be hospitalized because of this multitude of potential systemic effects. Formic acid is the acid most commonly used in assaults, especially in developing countries, because of its easy availability.[32]

Hydrochloric Acid, Muriatic Acid, and Sulfuric Acid

Hydrochloric acid is one of the most commonly treated chemical burns. Hydrochloric acid and sulfuric acid are proton donors, which cause the pH in local tissues to drop to zero as hydrogen ions disassociate.[33] Coagulation necrosis and tissue ulceration occur, leading to consolidation of connective tissue and thrombosis of intramural vessels, ulceration, fibrosis, and hemolysis.[7] Many household cleaners contain dilute hydrochloric acid (3–6%) and sulfuric acid and its desiccant precursor (sulfur trioxide) in concentrations up to 80–99%. Muriatic acid is the commercial grade of concentrated hydrochloric acid. When in contact with the skin, it denatures proteins into their chloride salts. Copious irrigation and early excision are the treatments of choice. Hydrochloric acid fumes can cause inhalation injury with acute pulmonary edema (Figs. 40.2 and 40.3). Other symptoms found to occur are white or grayish discoloration of the skin and exposed mucosa. Patients may have eye, mouth, throat, and abdominal pain and injuries. They may experience hematemesis, vomiting, dizziness, headache, dyspnea, cough, tachypnea, pneumonia, laryngospasm, and ultimately respiratory failure.[5]

Hydrofluoric Acid

Hydrofluoric acid is a corrosive that is commonly used in industrial applications and computer processing. It is used as a cleaning agent in the petroleum industry, in the production of high-octane fuel, glass etching, germicides, dyes, tanning, and fireproofing material, as well as in rust removal. Hydrofluoric acid is particularly lethal owing to its properties both as an acid and as a metabolic poison. The acid component causes coagulation necrosis and cellular death. Fluoride ions then gain a portal of entry that chelates positively charged ions such as calcium and magnesium, resulting in hypocalcemia and hypomagnesemia.[34] This causes an efflux of intracellular calcium with resultant cell death. The fluoride ion remains active until it is completely neutralized by the bivalent cations. This may exceed the body's ability to mobilize calcium and magnesium rapidly enough, causing muscle contraction and cellular dysfunction. Fluoride ion also acts as a metabolic poison by inhibiting Na-K ATPase, allowing efflux of potassium.[35] Excess potassium subsequently causes shifts at nerve endings and is thought to be the cause of the extreme pain associated with hydrofluoric acid burns.[36–38] Patients may present with self-limiting symptoms such as nausea, vomiting, fever, whitish tissue with surrounding erythema, immediate profound abdominal, mouth and throat pain, skin edema, ulcers and necrosis or stridor, laryngeal edema, wheezing, tachypnea, tetany, and potentially fatal cardiac arrhythmias.[5]

Hydrofluoric acid burns are classified based on the concentration of the exposure.[39] Concentrations greater than 50% cause immediate tissue destruction and pain. Concentrations of 20–50% result in a burn becoming apparent within several hours of exposure. Injuries from concentrations less than 20% may take up to 24 hours to become apparent.

Death from hydrofluoric acid exposure is usually secondary to systemic toxicity. Systemic symptoms are secondary to acidosis, hypocalcemia, hypomagnesemia, and hyperkalemia, which can lead to ventricular fibrillation. Thus, electrolytes and cardiac rhythm should be monitored closely.[40] When cardiac dysrhythmias develop, it is difficult to restore a normal rhythm.[41] Compounding the problem of hypocalcemia, the fluoride ion may act as a metabolic poison in the myocardium to promote the irritability. The typical electrocardiographic change seen is Q–T interval prolongation. The fluoride ions can be removed by hemodialysis or cation exchange resins.[42]

Treatments for hydrofluoric acid exposure are designed to neutralize the fluoride ion and prevent systemic toxicity. Primarily, the wound should be copiously irrigated for 30 minutes. If the concentration of exposure is less than 20% or the duration of exposure is minimal, this may serve as the extent of treatment. For more serious exposures, topical, subcutaneous, or intraarterial mixtures of calcium gluconate can be used as a first option. The topical gel is a mixture of 3.5 g of 2.5% calcium gluconate and 5 oz of water-soluble lubricant. It should be applied to the wound four to six times each day for 3 to 4 days.[43] The mixture's penetration into the dermis is limited by its calcium component. This is improved with the use of DMSO, which has its own associated toxicity. Calcium gluconate injections into the area of the wound (0.5 mL/cm^2 of 10% calcium gluconate subcutaneously or intradermally) have also been used, with good results.[44] Intraarterial injections into the radial artery (10 mL of 10% calcium gluconate and 40 mL of 5% dextrose in water infused over 2–4 hours) can be used for management of burns to the hand, but in severe cases, palmar fasciotomy may be needed.[45,46] This injection should be performed within 6 hours of exposure to prevent tissue necrosis and minimize pain. It should continue until the patient is symptom free.

Nitric Acid

This is a strong oxidizing agent that can combine with organic proteins to produce organonitrates, which act as metabolic poisons. It is used in fertilizer management, casting iron and steel, and engraving. Upon skin contact, a yellow-brown stain develops on the skin and mucosa, with an eschar. Demarcation tends to occur slowly, causing difficulty in discerning burn depth. Initial treatment involves irrigation and the use of topical treatment.[47] In addition, patients may present with whitish tinge of the teeth, eye pain, oropharyngeal pain, or abdominal pain. Patients may have dyspnea, hematemesis, dizziness, cough, tachypnea, and even develop pneumonia and laryngospasm.[5]

Oxalic Acid

This is a potent metabolic poison that combines with calcium to limit its bioavailability, thereby limiting muscle contraction.[48] It is used industrially to remove rust and in bleaching products. Treatment consists of water irrigation and IV calcium, with continuous cardiopulmonary monitoring, as well as measurements of serum electrolytes and renal function.[48]

Phosphoric Acid

Phosphorus is an incendiary agent found in hand grenades, artillery shells, fireworks, and fertilizers.[18,49] White phosphorus ignites in the presence of air and burns until the entire agent is oxidized or the oxygen source is removed. The wounds are irrigated with water, and easily identifiable pieces of phosphorus are removed. Ultraviolet light can be used to identify embedded particles through phosphorescence. In addition, a solution of 0.5% copper sulfate can be applied, which will impede oxidation and turn the particles black to aid in their identification and removal. Hypocalcemia, hyperphosphatemia, and cardiac arrhythmias have been reported with phosphorus burns.[18,49] Patients may present with eye and respiratory tract irritation, blepharospasm, endophthalmitis, a sensation of a foreign body in the eye, lacrimation, photophobia, cornea perforation, and even ultimately blindness.[5]

ALKALIS

Strong alkalis have a pH of 12 or greater. Wounds caused by alkalis initially appear superficial but may often become full thickness in 2–3 days. This chemical creates a soluble protein by binding with lipids and proteins, thus allowing passage of hydroxyl ions into the tissue. Eventually, a soft, brownish, gelatinous eschar is created. Alkalis are very corrosive in nature and penetrate deeply. Examples of strong alkalis (lyes) include barium, sodium, ammonium, calcium, lithium, and potassium hydroxides. They are present in

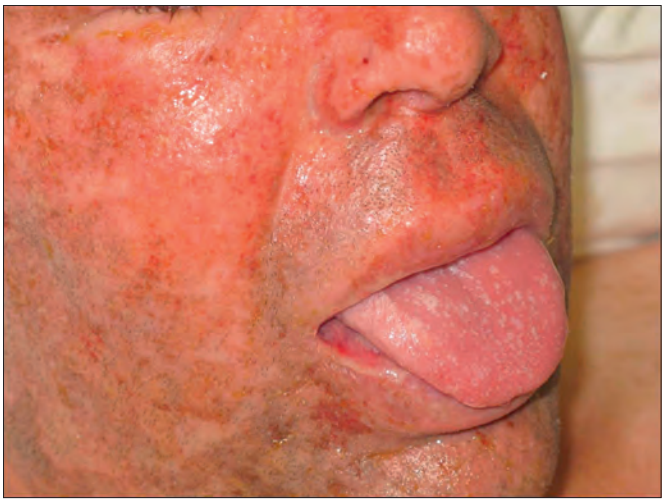

Fig. 40.4 Sodium hydroxide burn to the face and tongue.

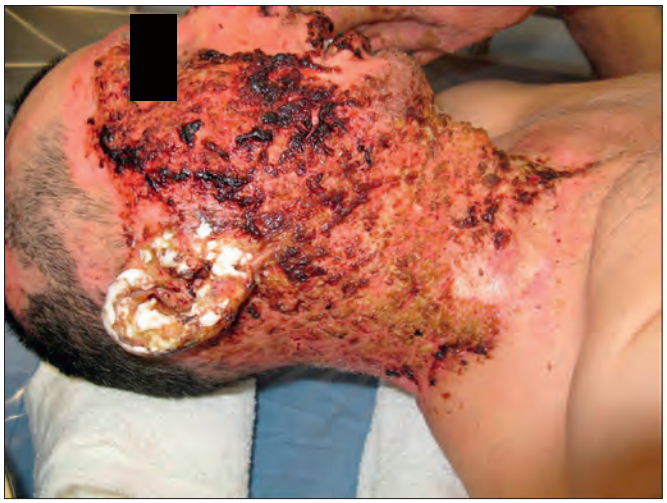

Fig. 40.5 Crude oil burn to the face.

many household cleaning solutions and have historically been ingested in suicide attempts, causing death secondary to airway occlusion.[17] Management of these burns necessitates immediate and copious irrigation.

Dry residues of alkali (e.g., lime) must be brushed away and then copious irrigation is undertaken. Attempts to neutralize alkali are not recommended. Alkaline injury to the eye is particularly devastating. These compounds rapidly penetrate the cornea, causing scarring and opacification, with associated perforation.[17]

CEMENT

Cement acts both as a desiccant and an alkali. Cement is calcium oxide, which becomes calcium hydroxide upon exposure to water. It usually contains lime, sand, and other metal oxides. The dry powder is very hygroscopic and will cause desiccation injury if not hydrated or washed away. Injury results from the action of the hydroxyl ion.[50]

METALS

Occupational injuries often occur to workers using molten metal, such as elemental metals, sodium, lithium, potassium, magnesium, aluminum, or calcium. After exposure, the use of water is contraindicated because it may result in an explosive exothermic reaction. Class D fire extinguishers or sand are ideal for management, but mineral oil is also an option (Fig. 40.4).

HYDROCARBONS

Hydrocarbons are corrosive agents, often contained within plants, animal fats, and fuel oils. Prolonged contact with petroleum distillates results in dissolution of lipid cell membranes, leading to cell death.[51] These burns tend to be superficial. Systemic toxicity usually involves respiratory depression. Heat loss from rapid evaporation of gasoline can cause the development of frostbite and dehydration. Early decontamination is most efficiently achieved with soap and water.

HYPOCHLORITE SOLUTIONS

These are potent oxidizers delivered in alkaline solution used as bleaches and household cleaners. Exposure to 30 mL of 15% solution is potentially fatal. Systemic manifestations of toxicity include vomiting, confusion, dyspnea, airway edema, cyanosis, cardiovascular collapse, and coma.[49] Treatment consists of copious irrigation.

ALKYL MERCURIC COMPOUNDS

Skin reaction with these substances releases free mercury, which can be found in blister fluid. With time, mercury is absorbed, leading subsequently to systemic effects. After blisters are debrided, repeat washing to lavage the blister fluid is necessary.

TAR

Tar, crude oil, and asphalt are various names for mineral products created from long-chain petroleum and coal or fossil hydrocarbons. This compound should be removed from the skin immediately. After it has cooled, the tar produces liquefaction injury and should be debrided from the skin, especially if obvious burn, blister, or tissue loss is apparent. Antibiotic ointments and household items such as baby oil, mineral oil, mayonnaise, and butter have been found to aid in its removal (Fig. 40.5).[52]

VESICANT CHEMICAL WARFARE AGENTS (MUSTARD, LEWISITE, NITROGEN)

These agents affect all epithelial tissues, including the skin, eyes, and respiratory epithelium. Symptoms described after exposure to mustard gas include burning eyes, a burning throat, and a feeling of suffocation.[43,46] This is followed by erythema of the skin within 4 hours and blister development within 12 to 48 hours. Severe pruritus develops, particularly in moist areas such as the axilla and perineum. When the blisters rupture, they leave painful, shallow ulcers. Exposure to larger quantities of these agents

produces coagulative necrosis of the skin, with either no blistering or "doughnut blisters" surrounding a central necrotic zone.[43,44,46]

Lewisite (2-chlorovinyl-dichloroarsine) is the best known arsine. It is more powerful than the mustards, and the symptoms occur sooner.

Phosgene oxime is another common agent in chemical warfare. It is the most widely used halogenated oxime and has the immediate effect of stinging, likened to contact with a stinging needle.[46] Affected areas quickly become swollen with blister formation, and eschars develop over the ensuing week. Wound healing is slow, typically over 2 months. Eye involvement is extremely painful and can result in permanent blindness. Inhalation leads to hypersecretion and pulmonary edema.

Clothing must be removed from the victim and large-volume lavage of the skin is undertaken. Eyes are irrigated with water or "balanced salt solution." Blisters are debrided and dressed with topical antimicrobials. Dimercaprol is a chelating agent that is an antidote for lewisite poisoning. There is no specific antidote for nitrogen mustard, but sodium thiosulfate and *N*-acetylcysteine may be helpful to reduce the effects if administered early.[46] The blister fluid from nitrogen mustard injuries does not contain active agent and is hence harmless.[47] Agranulocytosis or aplastic anemia can result from exposure to these agents.[24] In the appropriate setting, bone marrow transplantation may be considered.

Conclusion

Many chemical compounds can cause burn injury. The principal idea behind the treatment of chemical burns is early, copious irrigation. Wound care is the same as for thermal burns. Chemical burns tend to be deeper than they initially appear, often requiring skin grafting for management.

Complete references available online at
www.expertconsult.inkling.com

Further Reading

Chung JY, Kowal-Vern A, Latenser BA, et al. Cement-related injuries: review of a series, the National Burn Repository, and the prevailing literature. *J Burn Care Res.* 2007;28(6):827-834. *General overview of cement burns.*

Devereaux A, Amundson DE, Parrish JS, et al. Vesicants and nerve agents in chemical warfare. Decontamination and treatment strategies for a changed world. *Postgrad Med.* 2002;112(4):90-96. *General overview of vesicant chemical warfare agents.*

Harchelroad FP, Rottinghaus DM. Chemical Burns. In: *Emergency Medicine: A Comprehensive Study Guide*. 6th ed. 2004:200. *General review of chemical burns.*

Kuckelkorn R, Schrage N, Keller G, Redbrake C. Emergency treatment of chemical and thermal eye burns. *Acta Ophthalmol Scand.* 2002;80(1):4-10. *General review of chemical burns to eyes.*

Stuke LE, Arnoldo BD, Hunt JL, et al. Hydrofluoric acid burns: a 15-year experience. *J Burn Care Res.* 2008;29(6):893-896. *General overview of hydrofluoric acid burns.*

References

1. Palao R, Monge I, Ruiz M, Barret JP. Chemical burns: pathophysiology and treatment. *Burns*. 2010;36:295-304.
2. Mowry JB, Spyker DA, Brooks DE, McMillan N, Schauben JL. 2014 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 32nd Annual Report. *Clin Toxicol (Phila)*. 2015;53:962-1147.
3. Mowry JB, Spyker DA, Cantilena LR Jr, McMillan N, Ford M. 2013 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st Annual Report. *Clin Toxicol (Phila)*. 2014;52:1032-1283.
4. Watson WA, Litovitz TL, Rodgers GC Jr, et al. 2004 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med*. 2005;23:589-666.
5. Dinis-Oliveira RJ, Carvalho F, Moreira R, et al. Clinical and forensic signs related to chemical burns: a mechanistic approach. *Burns*. 2015;41:658-679.
6. Jelenko C 3rd. Chemicals that "burn". *J Trauma*. 1974;14:65-72.
7. Matshes EW, Taylor KA, Rao VJ. Sulfuric acid injury. *Am J Forensic Med Pathol*. 2008;29:340-345.
8. Leonard LG, Scheulen JJ, Munster AM. Chemical burns: effect of prompt first aid. *J Trauma*. 1982;22:420-423.
9. Yano K, Hata Y, Matsuka K, Ito O, Matsuda H. Effects of washing with a neutralizing agent on alkaline skin injuries in an experimental model. *Burns*. 1994;20:36-39.
10. Kuckelkorn R, Schrage N, Keller G, Redbrake C. Emergency treatment of chemical and thermal eye burns. *Acta Ophthalmol Scand*. 2002;80:4-10.
11. Cope O. The treatment of the surface burns. *Ann Surg*. 1943;117:885-893.
12. Cope VZ. What we learnt about burns in the war. *Clin J*. 1949;78:209-213.
13. Pike J, Patterson A Jr, Arons MS. Chemistry of cement burns: pathogenesis and treatment. *J Burn Care Rehabil*. 1988;9:258-260.
14. Fischer H, Caurdy-Bess L. Scalp burns from a permanent wave product. *Clin Pediatr (Phila)*. 1990;29:53.
15. Fisher AA. Irritant and toxic reactions to phenol in topical medications. *Cutis*. 1980;26:363-364, 90–92.
16. Lin TM, Lee SS, Lai CS, Lin SD. Phenol burn. *Burns*. 2006;32:517-521.
17. Sawhney CP, Kaushish R. Acid and alkali burns: considerations in management. *Burns*. 1989;15:132-134.
18. Bowen TE, Whelan TJ Jr, Nelson TG. Sudden death after phosphorus burns: experimental observations of hypocalcemia, hyperphosphatemia and electrocardiographic abnormalities following production of a standard white phosphorus burn. *Ann Surg*. 1971;174:779-784.
19. Casillas RP, Kiser RC, Truxall JA, et al. Therapeutic approaches to dermatotoxicity by sulfur mustard. I. Modulaton of sulfur mustard-induced cutaneous injury in the mouse ear vesicant model. *J Appl Toxicol*. 2000;20(suppl 1):S145-S151.
20. Dachir S, Fishbeine E, Meshulam Y, et al. Amelioration of sulfur mustard skin injury following a topical treatment with a mixture of a steroid and a NSAID. *J Appl Toxicol*. 2004;24:107-113.
21. Emami MH, Talaei M, Panahi Y, Saburi A, Ghanei M. Efficacy of omeprazole on cough, pulmonary function and quality of life of patients with sulfur mustard lung injury: A placebo-control, cross-over clinical trial study. *J Res Med Sci*. 2014;19:1027-1033.
22. Gu TY. Mechanism and treatment of sulfur mustard-induced cutaneous injury. *Chin J Traumatol*. 2014;17:345-350.
23. Kehe K, Thiermann H, Balszuweit F, et al. Acute effects of sulfur mustard injury – Munich experiences. *Toxicology*. 2009;263:3-8.
24. Laskin JD, Black AT, Jan YH, et al. Oxidants and antioxidants in sulfur mustard-induced injury. *Ann N Y Acad Sci*. 2010;1203:92-100.
25. Ruff AL, Dillman JF. Signaling molecules in sulfur mustard-induced cutaneous injury. *Eplasty*. 2007;8:e2.
26. Sabourin CL, Danne MM, Buxton KL, Casillas RP, Schlager JJ. Cytokine, chemokine, and matrix metalloproteinase response after sulfur mustard injury to weanling pig skin. *J Biochem Mol Toxicol*. 2002;16:263-272.
27. Ogawa M, Nakajima Y, Endo Y. Four cases of chemical burns thought to be caused by exposure to chromic acid mist. *J Occup Health*. 2007;49:402-404.
28. Cason JS. Report on three extensive industrial chemical burns. *Br Med J*. 1959;1:827-829.
29. Terrill PJ, Gowar JP. Chromic acid burns; beware, be aggressive, be watchful. *Br J Plast Surg*. 1990;43:699-701.
30. Matey P, Allison KP, Sheehan TM, Gowar JP. Chromic acid burns: early aggressive excision is the best method to prevent systemic toxicity. *J Burn Care Rehabil*. 2000;21:241-245.
31. Chan TC, Williams SR, Clark RF. Formic acid skin burns resulting in systemic toxicity. *Ann Emerg Med*. 1995;26:383-386.
32. Karunadasa KP, Perera C, Kanagaratnum V, et al. Burns due to acid assaults in Sri Lanka. *J Burn Care Res*. 2010;31:781-785.
33. Reilly DA, Garner WL. Management of chemical injuries to the upper extremity. *Hand Clin*. 2000;16:215-224.
34. Stuke LE, Arnoldo BD, Hunt JL, Purdue GF. Hydrofluoric acid burns: a 15-year experience. *J Burn Care Res*. 2008;29:893-896.
35. Mayer TG, Gross PL. Fatal systemic fluorosis due to hydrofluoric acid burns. *Ann Emerg Med*. 1985;14:149-153.
36. McIvor ME. Delayed fatal hyperkalemia in a patient with acute fluoride intoxication. *Ann Emerg Med*. 1987;16:1165-1167.
37. McIvor ME, Cummings CE, Mower MM, et al. Sudden cardiac death from acute fluoride intoxication: the role of potassium. *Ann Emerg Med*. 1987;16:777-781.
38. McIvor ME, Cummings CC, Mower MM, et al. The manipulation of potassium efflux during fluoride intoxication: implications for therapy. *Toxicology*. 1985;37:233-239.
39. Yolken R, Konecny P, McCarthy P. Acute fluoride poisoning. *Pediatrics*. 1976;58:90-93.
40. Anderson WJ, Anderson JR. Hydrofluoric acid burns of the hand: mechanism of injury and treatment. *J Hand Surg Am*. 1988;13:52-57.
41. Vance MV, Curry SC, Kunkel DB, Ryan PJ, Ruggeri SB. Digital hydrofluoric acid burns: treatment with intraarterial calcium infusion. *Ann Emerg Med*. 1986;15:890-896.
42. Caravati EM. Acute hydrofluoric acid exposure. *Am J Emerg Med*. 1988;6:143-150.
43. Miller FG. Poisoning by Phenol. *Can Med Assoc J*. 1942;46:615-616.
44. Saunders A, Geddes L, Elliott P. Are phenolic disinfectants toxic to staff members? *Aust Nurses J*. 1988;17:25-26.
45. Lazarus AA, Devereaux A. Potential agents of chemical warfare. Worst-case scenario protection and decontamination methods. *Postgrad Med*. 2002;112:133-140.
46. Devereaux A, Amundson DE, Parrish JS, Lazarus AA. Vesicants and nerve agents in chemical warfare. Decontamination and treatment strategies for a changed world. *Postgrad Med*. 2002;112:90-96, quiz 4.
47. Kolios L, Striepling E, Kolios G, et al. The nitric acid burn trauma of the skin. *J Plast Reconstr Aesthet Surg*. 2010;63:e358-e363.
48. Fitzpatrick KT, Moylan JA. Emergency care of chemical burns. *Postgrad Med*. 1985;78:189-194.
49. Summerlin WT, Walder AI, Moncrief JA. White phosphorus burns and massive hemolysis. *J Trauma*. 1967;7:476-484.
50. Chung JY, Kowal-Vern A, Latenser BA, Lewis RW 2nd. Cement-related injuries: review of a series, the National Burn Repository, and the prevailing literature. *J Burn Care Res*. 2007;28:827-834.
51. Klauder JV, Shelanski L, Gabriel K. Industrial uses of compounds of fluorine and oxalic acid; cutaneous reaction and calcium therapy. *AMA Arch Ind Health*. 1955;12:412-419.
52. Renz BM, Sherman R. Hot tar burns: twenty-seven hospitalized cases. *J Burn Care Rehabil*. 1994;15:341-345.

41 Radiation Injuries and Vesicant Burns

GABRIEL HUNDESHAGEN and STEPHEN M. MILNER

Radiation Injury: Introduction

In the aftermath of 9/11 and more recent acts of unrelenting terrorism, such as the mass killings in Paris, Brussels, and Orlando, the possibility of the use of nuclear weapons or crude nuclear devices in attacks on nuclear facilities and use of chemical agents cannot be ignored. Given the devastating medical consequences that would follow the use of such weapons, the training of medical personnel will be a crucial factor in the effective management of such casualties if the unthinkable ever occurs.

Only 4 months after Roentgen reported the discovery of X-rays, Dr. John Daniel observed that irradiation of his colleague's skull caused hair loss. Since this finding was reported in 1896, many biomedical effects of radiation have been described.[1] Knowledge of nuclear physics was rapidly amassed in the early part of the 20th century, leading eventually to the Manhattan project and the development of the atomic bomb. The use of this weapon over Japanese cities Hiroshima and Nagasaki in 1945 with at least 129,000 direct casualties and an extended amount of long-term sequelae stands as the most gruesome demonstration of the impact and threat that nuclear weapons hold. The past 50 years has also seen widespread deployment of energy-generating nuclear reactors and the expanding use of radioactive isotopes in industry, science, and health care.[2] In 2011, a tsunami following an earthquake near the Fukushima 1 power plant in Japan led to severe equipment failures and three nuclear meltdowns and the release of radioactive material with contaminative consequences.[3] This incidence was preceded by other major industrial accidents of note at Three Mile Island in Pennsylvania, Chernobyl in the Ukraine, and Goiania, Brazil, all of which have resulted in potential or real radiation injuries to hundreds of people. According to the latest National Council on Radiation Protection & Measurements report on radiation exposure to United States citizens, the most significant increase in ionizing radiation exposure, over the past 20 years, has been through medical imaging.[4]

Exposure to ionizing radiation can follow one of three patterns:

1. Small-scale accidents, or cumulative exposures, as might occur in a laboratory or from an X-ray device in a hospital setting
2. Large industrial accidents (such as those mentioned above), stretching the need for treatment beyond available resources
3. Detonation of a nuclear device in a military conflict in which resources are totally overwhelmed or unavailable and associated multiple and combined injuries also exist.

Terminology

Damage to biological tissue by ionizing radiation is mediated by energy transference. This can be the result of exposure to electromagnetic radiation (e.g., X-rays and gamma rays) or particulate radiation (e.g., alpha and beta particles or neutrons). The severity of tissue damage is determined by the energy deposited per unit track length, known as linear energy transfer (LET). Electromagnetic radiation passes through tissue almost unimpeded by the skin and is called low LET because little energy is left behind. In contrast, neutron exposure has high LET, resulting in significant energy absorption within the first few centimeters of the body. Alpha and low-energy beta particles do not penetrate the skin and represent a hazard only when internalized by inhalation, ingestion, or absorption through a wound.

The biological effect of ionizing radiation is measured by the radiation absorbed dose (rad). The newer SI unit of absorbed dose is the gray (1 Gy = 100 rad). Not all radiation is equally effective in causing biological damage, although it may cause the same energy deposition in tissue. For example, 1 Gy of neutron radiation will not have the same effect as 1 Gy of gamma or X-radiation. For this reason, a unit of dose equivalence was derived that allows radiations with different LET values to be compared. One such unit is the rem (acronym of roentgen equivalent man). The dose in rem is equal to the dose in rads multiplied by a quality factor (QF).[5] The QF takes into account the LET and has a different value for different radiations; for X-rays, it is 1.0, and for neutrons, it is 10. The international unit, now more widely in use, is the sievert (Sv). One sievert equals 100 rem; 1 rem equals 10 mSv. This allows radiations with different LET values to be compared because 1 Sv of neutron radiation has the same biological effect as 1 Sv of low LET gamma or X-radiation.

Incidence

The source of the most abundant type of biologically relevant electromagnetic radiation is the sun. Ultraviolet (UV) light with a wavelength of 315–400 nm (UVA), 280 to 315 nm (UVB), and 10–280 nm (UVC) would normally be absorbed by 98% in the atmosphere's so-called ozone layer, which extends at about 20 miles above sea level.[6] However, mostly because of human-made pollution and the resulting increase in local permeability of this protective layer, UV radiation can reach the surface of the skin and unfold its hazardous effects. Although not technically ionizing, UV light can severely irritate dermal structures in terms of first- and second-degree burns. Simultaneously,

Table 41.1 Major Radiation Accidents: Human Experience (1944–2016)

Location	Accidents (*n*)	Persons Involved (*n*)	Significant Exposures*	Fatalities
United States	271	1405	802	26
Non-United States	191	132,467	2183	102
Former Soviet Union†	(137)	(507)	(278)	(35)
Total	**462**	**133,872**	**2985**	**128**

*DOE/NRC dose criteria.
†Former Soviet Union Registry Data (not included in totals; data incomplete).
Source: REAC/TS Registry, 2016.

the formation of pyrimidine dimers in the DNA of dermal cells can be induced, which in the long term can result in malignancies.[6,7]

A significant radiation accident is one in which an individual exceeds at least one of the following criteria:[8]

- Whole-body doses equal to or exceeding 25 rem (0.25 Sv)
- Skin doses equal to or exceeding 600 rem (6 Sv)
- Absorbed dose equal to or greater than 75 rem (0.75 Sv) to other tissues or organs from an external source
- Internal contamination equal to or exceeding one-half the maximum permissible body burden (MPBB) as defined by the International Commission on Radiological Protection (this number is different for each radionuclide)
- Medical misadministration provided it results in a dose or burden equal to or greater than the criteria listed above.

Radiation accidents within the United States should be reported to the federally funded Radiation Emergency Assistance Center/Training Site (REAC/TS), where a Radiation Accident Registry System is maintained. It is operated by Oak Ridge Institute for Science and Education (ORISE) at Oak Ridge, Tennessee, and can be contacted by calling 865-576-1005 (website: http://orise.orau.gov/reacts). An emergency response team of physicians, nurses, health physicists, and support personnel provides consultative assistance on a 24-hour basis and has the capability of providing medical advice or treatment whenever a radiation accident occurs. If an accident involving radiation occurs outside the United States and local resources fall short in providing immediate advice, the REAC/TS hotline can be consulted internationally as well. The International Atomic Energy Agency (IAEA) provides a detailed publication concerning the immediate actions that should be taken in the event of large-scale radiation accidents, which can be found at http://www-ns.iaea.org/tech-areas/emergency/iec/frg/default.asp.

The number of accidents, the number of persons involved, and the number of fatalities, in the United States and worldwide are shown in Table 41.1. There have been a total of 128 fatalities recorded by the Registry worldwide (Dainiak N, personal communication and unpublished data, 2010).[8] The majority of the radiation deaths occurred as a result of the Chernobyl accident in 1986 (>40). The classification of radiation accident by device for the period 1944 until 2016 is shown in Table 41.2.

Table 41.2 Major Radiation Accidents Worldwide (1944–2016): Classification by Device

Type	Accidents (*n*)
Radiation devices	347
Sealed sources	222
X-ray devices	87
Accelerators	8
Radar generators	1
Radioisotopes	95
Diagnosis and therapy	50
Transuranics	25
Fission products	11
Tritium	2
Radium spills	1
Other	18
Criticalities	20
Critical assemblies	8
Reactors	6
Chemical operations	6
Total	462

Source: REAC/TS Registries, 2016.

The majority of radiation accidents involve radioactive sources used for industrial radiography. The next most frequent accidents are radioisotope accidents involving unsealed radioactive materials, such as tritium, fission products, radium, and free isotopes used for diagnosis and therapy. Uncommon criticality accidents occur when enough fissionable material, such as enriched uranium, is brought together to produce a neutron flux so high that the material undergoes a nuclear reaction.

The most devastating radiation injuries and fatalities yet seen, however, resulted from detonation of nuclear weapons at Hiroshima and Nagasaki during World War II. Since 1945, nuclear weapon technology has developed enormously, and current strategic thermonuclear warheads dwarf the weapons used in Japan.[9] The majority of radiation exposure occurred within the first minute of the explosion. There were no deaths attributed to the products left behind by the atomic explosions. As detailed by Kucan in 2004, the majority of radioactive fallout from these weapons was dispersed into the atmosphere because both were detonated several thousand feet in the air.[10]

Perhaps a more likely weapon of terrorism will involve the use of a radiological dispersal device (RDD). The term "dirty bomb" generally refers to a conventional explosive packaged with radioactive material that is scattered over a wide area when detonated. It is believed that these devices would probably elicit more harm by public fear and panic than by serious injury.[11]

In clinical practice, there are concerns that relatively low levels of radiation delivered over a long period of time might induce cancer or exert genetic or teratogenetic effects.

Table 41.3 The Effectiveness of Shielding Devices

Device	Transmission (%)
Lead apron	<10
Thyroid shield	<10
Leaded glasses	<10
Unleaded glasses	50
Human body	1
Human body wearing lead apron	0.1
Portable lead shields	<1

Although most of the literature that explores this issue refers to case studies, it confirms that exposure at a younger age increases the risk of cancer. Even more important, this risk is not reduced with time.[12] Exposure to radiation through computed tomography imaging is now commonplace, and healthcare personnel should not disregard the cumulative effects of these examinations, which can approximate levels seen in atomic bomb survivors (30 mSv).[13] Because distance and radiation intensity obey the inverse square law, radiation dose can be limited most effectively by increasing the distance from the source of radiation. Although the efficacy of shielding devices will be determined by the type and thickness of the material and the energy and type of radiation, Table 41.3 illustrates the effectiveness of these devices when used at diagnostic X-ray energies.

Cumulative doses of radiation can be recorded on radiation badges containing photographic emulsion. The personnel dosimeter is relatively cheap and accurate but has limitations. The smallest exposure that can be measured is 10 millirem; film badges can be exposed by heat, giving false readings, and they are analyzed only at monthly intervals.

Pathophysiology

The detonation of a nuclear device over a population center will produce an extremely hot, luminous fireball, which emits intense thermal radiation capable of causing burns and starting fires at considerable distance. This is accompanied by a destructive blast wave moving away from the fireball at supersonic speed and the emission of irradiation, mainly gamma rays and neutrons.[14] The result of a combination of thermal and radiation injuries can have a synergistic effect on the outcome. Several animal experiments have demonstrated a significant increase in mortality rate when a standard burn wound model is irradiated, over and above that expected from either injury alone.[15]

THERMAL EFFECTS

Exact information about the cause of fatalities in a nuclear blast is not available, but from the nuclear attack on Japan, it has been estimated that 50% of deaths were due to burns, and some 20% to 30% were flash burns.[16] The clinical picture may range from an erythema of exposed areas to a charring of the superficial layers of the skin. Secondary flame burns may be present after the ignition of the victim's clothing or environment. The physicians at Hiroshima and Nagasaki observed that the "flame" burn wound seemed to heal at first. However, between 1 and 2 weeks later, a serious relapse occurred. Wound infection set in; there was disorder in granulation tissue formation; and a gray, greasy coating would form on the wounds. Thrombocytopenia resulted in spontaneous bleeding both into the wound and elsewhere. Histologically, the normal collection of leukocytes delineating a necrotic area was found to be absent because of agranulocytosis, and gross bacterial invasion was evident; both of these changes obviously affected the prognosis of these otherwise relatively small injuries.[17]

RADIATION EFFECT

The transference of radiation energy can damage critical parts of the cell directly or indirectly by formation of free radicals. The primary targets are cellular and nuclear membranes as well as DNA.[18]

The morbidity of radiation depends on its dose, the dose rate, and the sensitivity of the cell exposed. Cells are most sensitive when undergoing mitosis so that those that divide rapidly such as bone marrow, skin, and the gastrointestinal (GI) tract are more susceptible to radiation damage. Radiation to an organ such as brain or liver, which has parenchymal cells with a slow turnover rate, results in damage to the more sensitive connective tissue and microcirculation.

The overall effect on the organism depends on the extent of the body surface involved, duration of exposure, and homogeneity of the radiation field. It is convenient to consider radiation injuries as localized or whole body (acute radiation syndrome).

Long-term effects of radiation exposure include the formation of cancer and wound-healing deficits. These have been studied in various venues including exposure to tanning beds, which have been linked to an increase in melanoma in young women of up to 75%. These changes are thought to be due to a defect in the p53 tumor suppressor pathway. Children are particularly at risk for radiation-induced injuries because they have a proportionally larger amount of replicating cells and will live long enough to see the effects of radiation, which can have upwards of a 30-year latency period.[19]

LOCALIZED INJURY

In a localized injury, a relatively small part of the body is affected without significant systemic effects.[20] The skin and subcutaneous tissue alone may be involved after exposure to low-energy radiation. Exposure to high-energy radiation may injure deeper structures.

Radiation damage depends on the dose of exposure and several progressive features are observed in skin: Erythema is equivalent to a first-degree thermal burn and occurs in two stages. Mild erythema appears within minutes or hours after the initial exposure and subsides in 2–3 days. The second onset of erythema occurs 2–3 weeks after exposure and is accompanied by dry desquamation of the epidermal keratinocytes. Epilation (loss of hair) may occur as soon as 7 days after injury. It is usually temporary with doses less than 5 Gy but may be permanent with higher doses.

Moist desquamation is equivalent to a second-degree thermal burn and develops after a latent period of about 3 weeks with a dose of 12–20 Gy. The latency period may be shorter with higher doses. Blisters form, which are susceptible to infection if not treated.

Full-thickness skin ulceration and necrosis are caused by doses in excess of about 25 Gy. Onset varies from a few weeks to a few months after exposure. Blood vessels become telangiectatic, and deeper vessels occlude. Obliterating endarteritis results in fibrosis, atrophy, and necrosis. Skin cancers may be evident after months or years.

One of the most closely studied local effects of radiation injury involves the treatment of breast cancer. It is well known that radiation therapy improves postmastectomy outcomes in women with multiple nodal involvement. This outcome comes at a cost as significantly increased rates of tissue contracture, hyperpigmentation, and asymmetry after all types of reconstruction paired with radiation.[20]

THE ACUTE RADIATION SYNDROME

The physiological effects of whole-body radiation are described as the acute radiation syndrome (ARS). The clinical course usually begins within hours of exposure. Prodromal symptoms include nausea, vomiting, diarrhea, fatigue, fever, and headache. There then follows a latent period, the duration of which is related to the dose. Hematopoietic and GI complications ensue. ARS can be subdivided into three overlapping subsyndromes, which are related to the dose exposure.

Hematopoietic Syndrome

This may occur after an exposure of 1–4 Gy. The bone marrow is the most sensitive, and pancytopenia develops. Opportunistic infections result from the granulocytopenia and spontaneous bleeding from thrombocytopenia. Hemorrhage and infection can cause death.

Gastrointestinal Syndrome

This requires a larger dose exposure usually in the range of 10–12 Gy. Severe nausea and vomiting associated with bowel cramps and watery diarrhea occur within hours of irradiation. There is a shorter latent period of 5–7 days, which reflects the turnover time of the gut epithelium (3–5 days). The epithelial damage results in loss of transport capability, bacterial translocation with septicemia, bowel ischemia, and bloody diarrhea. Large fluid imbalances can result in hypovolemia, acute renal failure, and anemia from both bleeding and the loss of erythropoiesis. Critical exposure will lead to rapid deterioration with unrelenting bloody diarrhea, fever, refractive hypovolemic shock, sepsis, and death.[21,22]

Neurovascular Syndrome

An exposure to a dose of 15–30 Gy or greater can cause an immediate total collapse of the vascular system superimposed on the aforementioned syndromes. This may be caused by the massive release of mediator substances, nitric oxide abnormalities, or destruction of endothelium.[21] This syndrome can progress rapidly with variable neurologic symptoms, respiratory distress, cardiovascular collapse, and death.

Table 41.4 Survival Rates With Major Resources Available

Burn alone	<70% TBSA	50% survival
Burn alone	>70% TBSA	Probably fatal
Burn plus radiation	<30% TBSA	May survive
Burn plus radiation	>30% TBSA	Probably fatal

TBSA, Total body surface area.

TRIAGE

Triage is the initial classification of casualties into priority groups for treatment and is essential in the management of large numbers of casualties. All first responders should take into account their own safety and remember that exposure to radiation is reduced by distance and shielding. Therefore, a perimeter should be established beyond which those without shielding should remain until the donning of personal protection equipment is complete. In most circumstances, ionizing radiation is not immediately life threatening, and after life-saving measures have been carried out and the patient stabilized, assessment of radiation exposure can proceed.[23]

If large-scale casualties are encountered, triage may, of necessity, seem to be draconian. Patients who are unlikely to survive should not be allowed to overwhelm available resources, so that adequate treatment reaches those most likely to survive. In conventional warfare with limited medical resources, 50% of soldiers with thermal injuries of up to 70% total body surface area (TBSA) are expected to survive (Table 41.4).

This survival rate should be bettered in a smaller civilian accident. Thus, patients with burns alone over 70% TBSA should receive expectant treatment, and those with burns under 20% can have their treatment delayed. If there has been a significant exposure to radiation as well as a thermal injury, individuals with over 30% TBSA burns are unlikely to survive without the use of major resources.[24]

Treatment

The treatment of any burn requires massive support from a dedicated team. This will be available for small accidents. With larger accidents or a nuclear attack, the number of victims could swamp the services; treatment facilities may be destroyed; normal supply channels would be drastically reduced, if present at all; production, distribution, and transportation of supplies may be greatly impaired; and local care workers may also be the victims.[2]

FIRST AID

The victims must be evacuated from the source of radiation to limit exposure. Normal resuscitation procedures must be followed. Contaminated clothing must be removed, and the skin wounds must be decontaminated by copious but gentle irrigation with water or saline. The goal of decontamination is to dilute and neutralize particles without spreading

them to unexposed areas. Thus, patients should not be immersed in tubs. Irrigation should be continued until a dosimeter such as a Geiger–Müller counter indicates a steady state or minimum radiation count has been reached.

Intact skin may also be irrigated with a soft brush or surgical sponge, preferably under a stream of warm tap water. If this is inadequate, a second scrubbing with mild soap or detergent (with a pH of 7) for 3–4 minutes is recommended. This is followed by application of povidone-iodine solution or hexachlorophene soap, which is then rinsed again for 2–3 minutes and dried. If the patient is known to have had exposure to less than 100 rem (1 Sv/Gy), he or she can be followed as an outpatient. Exposures greater than 100 rem (1 Sv/Gy) require full evaluation in the hospital. Patients with exposures greater than 200 rem (2 Sv/Gy) or who have symptoms of ARS should preferably be sent to specialist centers with facilities to treat bone marrow failure.[25]

ASSESSMENT

The assessment of thermal injury has been covered in preceding chapters. Exposure to radiation can be estimated clinically by noting the onset of symptoms of ARS, supported by biological parameters. A complete blood count, including platelets and differential count, should be performed immediately and repeated at 12–24 hours if indicated by a change in the absolute lymphocyte count. If the patient sustains a fall in lymphocyte count of 50% or a count less than 1×10^9/L in a time period of 48 hours postexposure, a moderate dose of radiation has been encountered.[26] Levels of serum amylase and diamine oxidase (produced by intestinal villi) may be useful biological dosimeters of the future. Amylase levels are only reliable when the salivary glands have been exposed, and diamine oxidase has not yet been fully assessed in humans. Lymphocyte chromosomal analysis allows for accurate measurement even at low levels of exposure. However, this test is impractical with large numbers of casualties.[27]

GENERAL CARE OF IRRADIATED PATIENTS

A history should be obtained from the patient or others. Factors such as age, concurrent medical problems, smoke inhalation, and multiple trauma will affect the prognosis. A full physical examination is carried out to exclude other injuries. Those exposed to lethal doses of radiation will exhibit early signs of radiation sickness and should be triaged accordingly.

All patients should be administered adequate analgesia. Opiates or opioids are the drugs of choice and must be titrated to effect and administered by the intravenous (IV) route. Early nausea and vomiting will be distressing and must be treated with available antiemetic drugs. Ondansetron may prove successful because it is used against similar symptoms encountered in radiotherapy and chemotherapy and can also be used in children.

Patients with thermal burns in excess of 40% TBSA or with associated inhalation or major trauma should be treated expectantly in the mass casualty situation. They should be made comfortable and given adequate analgesia, sedatives, or both if available and thought appropriate.

Table 41.5 Oral Resuscitation Formulas

Formula	Na	Cl	K^+	Buffer	Use
WHO ORS (1975)	90	80	20	30	Diarrhea
WHO ORS (2002)	75	65	20	10	Diarrhea
Fox's sodium lactate	161	0	0	161	Burns
Moyer's citrated NaCl	85	63	0	29	Burns
Monafo's HLS	300	200	0	100	Burns
Liquidsorb	60	44	4	28	Burns
Jiang's burn drink	48	28	0	20	Burns
Ricelyte	50	45	25	34	Burns
Ceralyte 90	90	80	20	30	Diarrhea and burns

HLS, Hypertonic lactated saline; *ORS,* oral resuscitation solution; *WHO,* World Health Organization.

Adapted from Kramer GC, Michell MW, Oliveira H, et al. Oral and enteral resuscitation of burn shock the historical record and implications for mass casualty care. *Eplasty* 2010;10:e56, with permission from ePlasty.

Resuscitation should be the same as that for an uncomplicated thermal injury. Any resuscitation formula can be used, but it must be closely monitored and adjusted as necessary to maintain an adequate urine output. Fluid losses from diarrhea and vomiting may be excessive and need to be replaced.

Oral Resuscitation

Intravenous fluids may be limited, and the victims may be advised to take oral fluids consisting of balanced salt solutions and maintain a large urine output. Studies in humans and animal models have shown that intestinal absorption remains intact in burn patients. Kramer et al. reviewed the use of oral resuscitation therapy in burn care and found 12 reports, most of which show equal outcomes to IV infusions. This solution should be readily available, cheap, easy to transport, and palatable (Table 41.5).[28,29] A study published by one of the authors shows a reduction in IV fluid requirements by 58% on average when Parkland formula-driven protocols are supplemented with oral resuscitation (Fig. 41.1).[30]

CARE OF BURN WOUNDS

After the patient has been cleaned, decontaminated, and debrided, the extent of any thermal burn and its depth can be ascertained more accurately.

Mild erythema may require little treatment; however, it is important to avoid further irritation of the skin by exposure to abrasive decontamination, irritating solutions, and sunlight. With a slightly higher radiation dose causing dry desquamation, a bland lotion and loose clothing to alleviate itching may be all that is required.

Deeper burns with moist desquamation are treated like conventional thermal injuries. Burns are best treated closed because of the high risk of sepsis in immunosuppressed patients whose wounds are susceptible to dehydration and colonization and invasion of organisms. Early tangential excision and split-skin grafting promotes early wound closure, decreases burn wound colonization and sepsis, and

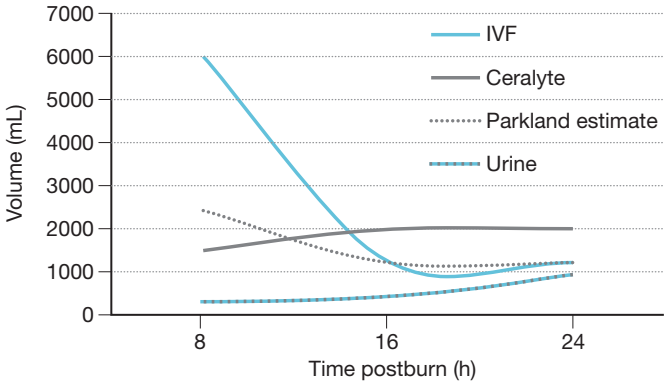

Fig. 41.1 The addition of oral resuscitation reduces overall intravenous fluid (IVF) requirements.

leads to shortened hospital stays.[31,32] Information regarding the grafting of radiation burns is not yet available but is probably best delayed. Dubos et al. performed early excision and grafting of burns in irradiated monkeys, showing that healing occurred fully by the end of the second week, although histologically, there was a slight delay in the healing process.[33] Blood loss in excess of 300 mL/% TBSA excised presents an increased anesthetic hazard and should be monitored closely. In irradiated tissue that is severely injured, definitive management often involves radical local resection and reconstruction with well-vascularized nonirradiated tissue, usually from a distant site. Research suggests injections of human mesenchymal stem cells may have a role in the treatment of local radiation-induced tissue injury.[34]

TREATMENT OF COMPLICATIONS

Hematologic

Blood and platelets are administered to maintain an adequate hemoglobin concentration and a platelet level of 20×10^9/L. If surgery is contemplated, this level should be raised to 75×10^9/L. All blood products should be irradiated to avoid graft-versus-host disease.

Bone marrow transplantation is the treatment of choice after total-body irradiation. It should be performed between 3 and 5 days postexposure as the immunosuppression is at its peak.

The proliferation and differentiation of residual hematopoietic stem and progenitor cells can be stimulated. Administration of antiapoptotic cytokine combinations such as stem cell factor, Flt-3 ligand, thrombopoietin, and interleukin-3 may assist recovery, if administered early.[35] Moreover, hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF) have been recommended based on improved survival rates in irradiated primates and reduced neutropenia in humans after accidental irradiation.[36,37]

Infection

The immunosuppression associated with irradiation makes the victim susceptible to exogenous and endogenous pathogens. Exogenous infection can be limited by adequate aseptic technique and nursing the patient in a sterile environment. Monitoring the patient adequately will allow the early diagnosis of sepsis and its treatment. The antibiotic chosen should reflect the current pattern of susceptibility and nosocomial infections in the particular unit at the time. Combination therapy will be required with profound neutropenia. Broad-spectrum antibiotics such as imipenem, ceftazidime, and ciprofloxacin can be considered. If Gram-positive infection is suspected, vancomycin or teicoplanin should be administered. In case of an inadequate response, an antifungal agent must be added.

SUMMARY

Treatment of radiation injury, whether or not it is combined with other injuries, requires specialized knowledge and resources. The combination of radiation injury with associated injuries appears to have a synergistic effect on outcome. Significant increases in mortality rates occur because of immunosuppression secondary to radiation exposure in patients already vulnerable to infections. For localized radiation injury, it is often difficult to assess the level of severity quickly and with accuracy because of the delay between exposure and appearances of lesions and because of hidden lesions in underlying tissues. Medical treatment deals with inflammation, moist desquamation, and chronic pain; the most favorable time for surgical intervention is difficult to specify. Full intensive care support is needed for whole-body irradiation causing ARS and is available only if small numbers are involved. Oral replacement therapy may be a feasible alternative to IV resuscitation of burns and could potentially save many lives in mass casualty situations. Those who survive and show signs of regeneration of tissues will warrant late surgical intervention. Aplastic anemia, immunosuppression, hemorrhage, and sepsis will be major problems for survivors. The improving therapy of bone marrow transplantation is the treatment of choice. Large numbers of casualties will necessitate expectant treatment only. In the event of a radiation mass casualty, resources will be limited, and treatment may depend on oral routes of resuscitation to maintain intravascular volume. Evacuation of survivors will take days, and a natural selection will take place.

Vesicant Burns

INTRODUCTION

Vesicant agents are characterized by their ability to produce cutaneous blisters resembling "burns." In the 1980s, the conflict between Iraq and Iran displayed the most open and widespread use of chemical weapons on a battlefield in recent decades. Although sulfur mustard is the most important vesicant militarily, the vesicant category includes other agents, such as lewisite and phosgene oxime. These compounds affect not only the skin but also all epithelial tissue with which they come into contact, particularly the eyes and respiratory tract. Although most physicians are unlikely to encounter casualties of chemical weapons, the proliferation of these agents has increased the risk to both military

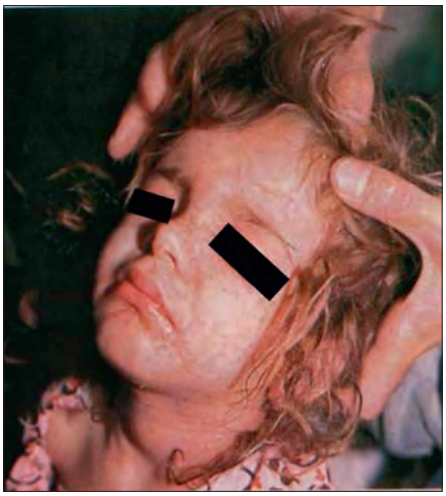

Fig. 41.2 Photograph of a child injured in the attack on Sardasht in 1987. (From Ghanei M, Aslani J, Khateri S, Hamedanizadeh K. Public health status of the civil population of Sardasht 15 years following large-scale wartime exposure to sulfur mustard. *J Burns Surg Wound Care* 2003;2(1):7-18, with permission from ePlasty, formerly *Journal of Burns and Wounds*.)

and civilian populations. They are likely to require expertise found in burn centers; for this reason, an account of the management of these injuries is included in this text.[38]

Chemical warfare was first introduced on a large scale during World War I, 100 years ago, when sulfur mustard (bis[2-chloroethyl]sulfide) and other agents were used extensively with devastating consequences in trench combat. The International Chemical Weapons Convention, an arms control treaty to ban and destroy chemical weaponry, was signed and ratified by 192 countries, entering into force in 1997, although the worldwide stockpile has not been deactivated and dismantled. The low technology required to manufacture the agents, easy stockpiling, and difficulty in detection cause vesicant agents to pose a continued major threat to civilians and military personnel.

MECHANISMS OF ACTION

The mechanism of action of mustard has eluded identification; however, most of the toxic effects are believed to be related to alkylation of DNA and critical target molecules. The DNA cross-links, which prevent replication and repair of DNA, ultimately lead to cell death. The dermal–epidermal separation, which causes the skin lesions, is believed to be due to release of proteases and other enzymes. Breakage of anchoring filaments connecting the basal cell layer to the basement membrane results in a blister with the basement membrane on its dermal side.[39]

CLINICAL FEATURES

Early symptoms ascribed to mustard gas include ocular photophobia and a feeling of suffocation associated with hoarseness and rhinorrhea with a burning throat.[40] After 4 hours, erythema is seen; in 12 to 48 hours, blistering appears accompanied by severe pruritus, which has a predilection for moist areas such as the axilla and perineum. The blisters tend to rupture, discharging an amber serous fluid and leaving painful shallow ulcers. Greater exposure produces coagulative necrosis of skin, with either no blistering or "doughnut blisters" surrounding a central necrotic zone.[39] This will be accompanied by severe conjunctivitis, corneal erosion, and necrotizing bronchitis. A secondary respiratory infection may develop over the next few days, coupled with associated bone marrow suppression, which may be fatal. Higher doses can lead to severe stem cell suppression, pancytopenia, and involvement of the GI tract with effects ranging from nausea and vomiting to severe hemorrhagic diarrhea. Excitation of the central nervous system, resulting in convulsions, has been reported.[41]

Lewisite (2-chlorovinyl-dichlorarsine) is the best known arsine. It is more powerful than the mustards, and symptoms occur sooner. Eye irritation is produced immediately, and sneezing, salivation, and lacrimation occur sooner. Nonlethal chronic exposure may lead to arsenical poisoning.

Exposure to phosgene oxime, the most common halogenated oxime, has the immediate effect of stinging, comparable to contact with a stinging nettle.[42] Within 1 minute, the affected area becomes swollen, and solid lesions resembling urticaria are seen. An eschar will form after 1 week, but healing is often delayed beyond 2 months. Contamination of the eyes is extremely painful and may result in permanent blindness. Inhalation causes irritation and coughing, hypersecretion, and pulmonary edema.[42]

Ghanei et al. reviewed 355 survivors and 108 deaths from exposure to sulfur mustard during an attack on Sardasht, Iran, in July of 1987. Their data revealed that mortality from exposure to this agent occurs in two waves. Initial deaths happened in the first 2–3 days after contact and were due mostly to respiratory involvement. The second wave of deaths occurred 1–3 weeks after contact and were attributed to respiratory distress syndrome or infection (pneumonia, septic shock, or wound infections). The authors suggest that patients should be kept in the intensive care unit (ICU) setting for the initial 4 weeks after contact and that antibiotic therapy be continued for at least the first 2 weeks of treatment.[43] Fig. 41.2 demonstrates numerous vesicles and a crusting rash after exposure to a sulfur mustard agent.

ACUTE TREATMENT FOR EXPOSURE TO A VESICANT AGENT

Butyl rubber gloves, boots, and a respirator are effective forms of prophylaxis. The first priority in treatment is to eliminate contact with the agent and initiate decontamination. During this procedure, attendants should also be suitably protected and contaminated clothing sealed in special containers to minimize self-endangerment. After clothing is removed, the skin is gently washed with soap and water.[44] At the initial encounter, eyes should be irrigated with copious quantities of water and the patient referred for ophthalmologic expertise.

Symptomatic relief is pivotal. Systemic analgesics can be started immediately and itching treated with sedatives (benzodiazepines or phenothiazines) and antipruritic agents. Dimercaprol (British antilewisite), a chelating agent, is a specific antidote for lewisite poisoning. It is of note that it is incompatible with silver sulfadiazine. It is available as an

ointment for skin lesions, as drops for eye applications (5–10% in oil), and in an intramuscular preparation for systemic toxicity. Other readily available chelating agents are:

- DMSA—mesodimercaptosuccinic acid
- DMPS—2,3-dimercapto-1 propanesulfonic acid sodium
- DMPA—N-(2,3-dimercaptopropyl) phthalamidic acid.

These have a high therapeutic index, are water soluble, and are effective orally. There is no specific antidote to mustard poisoning, and no pretreatments or treatments exist that provide practical or effective protection against mustard toxicity.[39,45]

Patients experiencing cutaneous injuries, erythema covering more than 5% TBSA in noncritical areas (face, hands, perineum) require hospitalization. The systemic fluid derangement is less severe than that seen with thermal burns; however, patients should be carefully monitored. Fluid requirements in Iranian casualties during the Iran–Iraq war appeared to have been relatively independent of affected TBSA.

Blisters should be deroofed and dressed with topical antimicrobials. The mustard blister fluid is harmless.[46] Favorable outcomes have now been demonstrated in a pig model by use of various debriding techniques and resurfacing with split-thickness skin grafts. Such methods have included laser, dermabrasion, sharp surgical excision, and enzymatic debridement.[38,47,48]

Respiratory injury requires symptomatic treatment according to its severity. Inhalation of high-dose steroids is controversial at present. Severe exposure will lead to agranulocytosis or aplastic anemia.[49] The pancytopenia seen after 7 days with the Iranian casualties did not appear to be helped by transfusion of relevant blood products. Bone marrow transplantation may prove useful, although of little practical value with large numbers of casualties. The effect of bone marrow stimulants such as oxymetholone and lithium carbonate is unknown but may be considered. Fluid replacement may be carried out dynamically with adequate cardiovascular monitoring. The maximum fluid loss occurs during blister formation and not necessarily in the first 24 hours.

LONG-TERM EFFECTS OF ACUTE EXPOSURE

Individuals who sustain mustard injury may experience difficulties after the initial effects of the injury have subsided. Destruction of melanocytes leave hypopigmented areas; otherwise, hyperpigmentation tends to predominate. Acute and severe exposure can also lead to chronic skin ulceration, scar formation, and the development of skin cancer.[39]

Recurrent or persistent corneal ulceration can occur after latent periods of 10–25 years. Chronic conjunctivitis and corneal clouding may accompany this delayed keratopathy.[50]

Clinical follow-ups on 200 Iranian soldiers who sustained injuries from mustard during the Iran–Iraq War indicate that about one third had experienced varied respiratory ailments, such as chronic bronchitis, asthma, recurrent pneumonia, bronchiectasis, and even tracheobronchial stenosis, more than 2 years after exposure. Some 12% of all British soldiers exposed to mustard in World War I were awarded disability compensation for respiratory disorders believed to have been caused by mustard exposures during combat.[51]

SUMMARY

The vesicant agents are perhaps poorly named because they have the ability to affect all epithelial surfaces, particularly the eyes and respiratory surfaces, and not just the skin. The most important vesicant is sulfur mustard, which acts as an alkylating agent, causing a series of clinical reactions ranging from vesicles to severe skin necrosis. Systemic effects are seen with high doses, and the combination of depressed bone marrow activity and respiratory involvement often proves fatal. There is no effective antidote, and treatment depends on prevention of contact and local therapy to achieve wound healing, which tends to be slow. There is no risk to the caregiver from the blister fluid, which contains no active agent. Treatment may require respiratory care in an ICU setting for upwards of 4 weeks, as well as several weeks of IV antibiotic therapy.

Complete references available online
www.expertconsult.inkling.com

Further Reading

Graham JS, Chilcott RP, Rice P, et al. Wound healing of cutaneous sulfur mustard injuries: strategies for the development of improved therapies. *J Burns Wounds*. 2005;4:e1.

Kramer GC, Michell MW, Oliveira H, et al. Oral and enteral resuscitation of burn shock: the historical record and implications for mass casualty care. *Eplasty*. 2010;10:pii, e56.

Kucan JO. Hiroshima and Nagasaki: Review of the consequences: implications in the post 9/11 world. *J Burns Surg Wound Care* [serial online]. 2004;3(1):8.

Nenot JC. Medical and surgical management for localized radiation injuries. *Int J Radiat Biol*. 1990;57:784.

References

1. Daniel J. Depilatory action of X-rays. *N Y Med Rec*. 1896;83:662.
2. Hirsch EF, Bowers GJ. Irradiated trauma victims: the impact of ionizing radiation on surgical considerations following a nuclear mishap. *World J Surg*. 1992;16(5):918-923.
3. Japanese Earthquake Update (19 March 2011, 4:30 UTC): IAEA Alert Log: Fukushima Daiichi Nuclear Accident [Internet]. 2011. Available from: https://web.archive.org/web/20110607091828/http://www.iaea.org/press/?p=1463. Cited 23 May 2016.
4. Mahesh M. NCRP Report Number 160: its significance to medical imaging. *J Am Coll Radiol*. 2009;6(12):890-892.
5. Mettler FA Jr, Kelsey CA Fundamentals of radiation accidents. In: Medical management of radiation accidents [Internet]. 1990. Available from: https://inis.iaea.org/search/search.aspx?orig_q=RN:22009703. Cited 11 July 2016.
6. Haigh JD. The sun and the Earth's climate. *Living Rev Sol Phys*. 2007;4(1):1-64.
7. Setlow RB, Carrier WL. Pyrimidine dimers in ultraviolet-irradiated DNA's. *J Mol Biol*. 1966;17(1):237-254.
8. Reference removed while revising
9. Eiseman B, Bond V. Surgical care of nuclear casualties. *Surg Gynecol Obstet*. 1978;146(6):877.
10. Kucan JO. Hiroshima and Nagasaki: Review of the consequences: implications in the post 9/11 world. *J Burns Surg Wound Care* [serial online]. 2004;3(1):8.
11. Zimmerman PD, Loeb C. Dirty bombs: the threat revisited. *Def Horiz*. 2004;(38):1.
12. Ron E. Cancer risks from medical radiation. *Health Phys*. 2003;85(1):47-59.
13. Goodman TR. Understanding the cancer-CT conundrum. *J Clin Gastroenterol*. 2010;44(7):469-474.
14. Lewis KN. Prompt and delayed effects of nuclear war. *Sci Am*. 1979;241(1):vp.
15. Brooks JW, Evans EI, Ham WT Jr, Reid JD. The influence of external body radiation on mortality from thermal burns. *Ann Surg*. 1952;136(3):533.
16. Glasstone S, Dolan PJ. *The Effects of Nuclear Weapons*. 3rd ed [Internet]. Washington, D.C. (USA): Department of Defense; Washington, D.C. (USA): Department of Energy; 1977. Available from: https://www.osti.gov/scitech/biblio/6852629. cited August 14 2017. Report No.: TID-28061.
17. Oughterson AW, Warren S. *Medical Effects of the Atomic Bomb in Japan*. Vol. 8. McGraw-Hill; 1956.
18. Neel JV. Update on the genetic effects of ionizing radiation. *JAMA*. 1991;266(5):698-701.
19. Fisher DE, James WD. Indoor tanning—science, behavior, and policy. *N Engl J Med*. 2010;363(10):901-903.
20. Nenot JC. Medical and surgical management for localized radiation injuries. *Int J Radiat Biol*. 1990;57(4):783-795.
21. Shadad AK, Sullivan FJ, Martin JD, Egan LJ. Gastrointestinal radiation injury: prevention and treatment. *World J Gastroenterol*. 2013;19(2):199-208.
22. Shadad AK, Sullivan FJ, Martin JD, Egan LJ. Gastrointestinal radiation injury: symptoms, risk factors and mechanisms. *World J Gastroenterol*. 2013;19(2):185-198.
23. Radiological Dispersal Device [Internet]. Available from: http://www.crcpd.org/RDD.htm. Cited 11 July 2016.
24. Becker WK, Buescher TM, Cioffi WG, McManus WF, Pruitt BA Jr. Combined radiation and thermal injury after nuclear attack. In: Treatment of Radiation Injuries [Internet]. Springer; 1990. p. 145–151. Available from: http://link.springer.com/chapter/10.1007/978-1-4899-0864-3_16. Cited 11 July 2016.
25. American Burn Association. American Burn Association Advanced Burn Life Support Provider Manual 2011. Chicago: American Burn Association.
26. Macvittie TJ. Commentary: Therapy of radiation injury. *Stem Cells*. 1997;15(S1):263-268.
27. Walker RI, Cerveny TJ, Alt LA. *Medical Consequences of Nuclear Warfare*. Vol. 2. Armed Forces Radiobiology Research Institute; 1989.
28. Kramer GC, Michell MW, Oliveira H, et al. Oral and enteral resuscitation of burn shock the historical record and implications for mass casualty care. *Eplasty* [Internet]. 2010;10(10). Available from: http://www.eplasty.com/images/PDF/eplasty10e56.pdf. Cited 11 July 2016.
29. Young L, Orosco R, Milner S. Double fire tragedy of Kenya. *Eplasty* [Internet]. 2010;10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2803767/. Cited 11 July 2016.
30. Milner SM, Greenough WB, Asuku ME, et al. From cholera to burns: a role for oral rehydration therapy. *J Health Popul Nutr*. 2011;29(6):648-651.
31. Burke JF, Bondoc CC, Quinby WC. Primary burn excision and immediate grafting: a method shortening illness. *J Trauma Acute Care Surg*. 1974;14(5):389-395.
32. Gray DT, Pine RW, Harnar TJ, et al. Early surgical excision versus conventional therapy in patients with 20 to 40 percent burns: a comparative study. *Am J Surg*. 1982;144(1):76-80.
33. Dubos M, Neveux Y, Monpeyssin M, Drouet J Impact of ionizing radiation on response to thermal and surgical trauma [Internet]. DTIC Document; 1983. Available from: http://oai.dtic.mil/oai/oai?verb=getRecord&metadataPrefix=html&identifier=ADP003859. Cited 11 July 2016.
34. Müller K, Meineke V. Advances in the management of localized radiation injuries. *Health Phys*. 2010;98(6):843-850.
35. Hérodin F, Drouet M. Cytokine-based treatment of accidentally irradiated victims and new approaches. *Exp Hematol*. 2005;33(10):1071-1080.
36. Waselenko JK, MacVittie TJ, Blakely WF, et al. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. *Ann Intern Med*. 2004;140(12):1037-1051.
37. Dainiak N, Ricks RC. The evolving role of haematopoietic cell transplantation in radiation injury: potentials and limitations. *Br J Radiol* [Internet]. 2014. Available from: http://www.birpublications.org/doi/full/10.1259/bjr/31003240. Cited 4 August 2016.
38. Graham JS, Chilcott RP, Rice P, et al. Wound healing of cutaneous sulfur mustard injuries: strategies for the development of improved therapies [Internet]. DTIC Document; 2005. Available from: http://oai.dtic.mil/oai/oai?verb=getRecord&metadataPrefix=html&identifier=ADA442459. Cited 11 July 2016.
39. Feister AJ Medical defense against mustard gas: toxic mechanisms and pharmacological implications [Internet]. CRC press; 1991. Available from: https://books.google.de/books?hl=de&lr=&id=BkBfb8vC_LgC&oi=fnd&pg=PA1&dq=50.%09Papirmeister+B,+Feister+AJ,+Robinson+SI,+et+al.+Pretreatments+and+therapies.+In:+Medical+defense+against+mustard+gas:+toxic+mechanisms+and+pharmacological+implications.+Boca+Raton:+CRC%3B+1990:243-287.&ots=E7P651kvUK&sig=WHA1GsBI690RwrNMGEl6IPjWjZI. Cited 11 July 2016.
40. Willems JL. Clinical management of mustard gas casualties. *Ann Med Mil Belg*. 1989;3(suppl 1):1-61.
41. PROMULGATION NLO. NATO Handbook on the Medical Aspects of NBC Defensive Operations AMedP-6 (B). Available from: http://oai.dtic.mil/oai/oai?verb=getRecord&metadataPrefix=html&identifier=ADA434662. Cited 11 July 2016.
42. McManus J, Huebner K. Vesicants. *Crit Care Clin*. 2005;21(4):707-718.
43. Ghanei M, Aslani J, Khateri S, Hamedanizadeh K. Public health status of the civil population of Sardasht 15 years following large-scale wartime exposure to sulfur mustard. *J Burns Surg Wound Care*. 2003;2(1):7-18.
44. Eldad A, Weinberg A, Breiterman S, et al. Early nonsurgical removal of chemically injured tissue enhances wound healing in partial thickness burns. *Burns*. 1998;24(2):166-172.
45. Weibrecht K, Rhyee S, Manuell ME, et al. Sulfur mustard exposure Presenting to a community emergency department. *Ann Emerg Med*. 2012;59(1):70-74.
46. Sulzberger MB, Katz JH. The absence of skin irritants in the contents of vesicles. *U S Nav Med Bull*. 1943;43:1258-1262.
47. Rice P The use of dermabrasion to accelerate the naturally slow rate of epidermal healing mustard injuries in pigs. In: Proceedings of the 1995 NATO Research Study Group 3 Meeting on Prophylaxis and Therapy Against Chemical Agents. 1995.
48. Graham JS, Schomacker KT, Glatter RD, et al. Bioengineering methods employed in the study of wound healing of sulphur mustard burns. *Skin Res Technol*. 2002;8(1):57-69.
49. Anslow WP, Houck CR. Systemic pharmacology and pathology of sulfur and nitrogen mustards. *Chem Warf Agents Relat Chem Probl*. 1946;1:470-478.
50. Blodi FC. Mustard gas keratopathy. *Int Ophthalmol Clin*. 1971;11(3):1-13.
51. Gilchrist HL A comparative study of world war casualties from gas and other weapons. US Government Printing Office; 1928.

42 Exfoliative Diseases of the Integument and Soft Tissue Necrotizing Infections

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Introduction

Acute, severe, exfoliative and necrotizing diseases of skin and underlying structures may cause significant morbidity and mortality in the afflicted patient. The problems associated with these diseases, such as wound infection, sepsis, inadequate nutrition, and pain, are similar to those seen in patients with major burns. Thus burn centers, with their multidisciplinary teams, have been advocated to provide the treatment and management for this unique, critically ill patient population. This chapter describes the pathophysiological processes of severe exfoliative skin disorders, their diagnosis, and the specialized treatment offered by burn centers.

Severe Exfoliative Disorders

This classification of exfoliative diseases of the skin and mucous membranes historically consisted of three specific maladies, distinguished by the amount of skin involvement: erythema multiforme major (EM), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). For the terms of this chapter, we are maintaining that approach. However, some recent classifications list EM as its own distinct disease entity separate from SJS and TEN and most commonly associated with the herpes simplex.[1] This new designation does not affect the classifications of SJS and TEN: Each are still determined by the extent of total body surface (TBSA) affected by the disease process. SJS is considered to affect <10% total body surface area (TBSA), whereas TEN covers >30% TSBA, leaving a zone of overlap between 10% and 30% TBSA, which is referred to as SJS/TEN.[1,2] The most common characteristics of these disease entities are defined in Table 42.1.[3,4]

Toxic Epidermal Necrolysis

EPIDEMIOLOGY

TEN represents the severe extreme of the spectrum of necrolytic disorders. A rare disease, the incidence of TEN in this country is estimated at 0.4–1.9 cases per million persons per year and that of SJS has been reported to be only slightly higher at 1–7 cases per million persons per year.[5–10] This incidence is similar to 1.89 cases of TEN per million persons per year reported for Europe in 1996, but higher than reported for Asia.[11,12] The overall rarity of this disease process has been, and continues to be, a barrier to research. However, over the past several decades, the concentration of physician experience with TEN into a limited set of regional burn centers has facilitated an increasing quantity and quality of active research.

These exfoliative disorders occur in all age groups; however the incidence is increased in the elderly and females.[3,13–17] In addition, TEN has been linked to certain infectious disease processes. The annual incidence of TEN in the human immunovirus (HIV)-infected population is 1000-fold higher than in the general public.[18] Whether this increase is due to their immunocompromised state or to the increased prescription of high-risk drugs, particularly sulfonamides, is debated.[19,20] However cases with no drug history or preceding illness have been reported. An additional infectious disease process associated with SJS/TEN is *Mycoplasma* pneumonia. Finally idiopathic cases not related to drugs account for 3–4% of TEN.[6,7]

Prognosis, Morbidity, Mortality

On the surface, these exfoliative disorders may mimic the symptoms of a partial-thickness thermal injury, specifically in relation to the involvement of the skin. However these diseases also affect all epithelial surfaces, thus increasing the risk and incidences of infections, other complications, and death. Patients suffering from particularly complicated cases of SJS may benefit from the expertise of a burn center, although these patients are generally referred on an as-needed basis. In contrast, those diagnosed with TEN carry a specific set of severe and complicated medical needs that are clearly best addressed in the context of a specialized burn center.

Mortality of TEN ranges from 25% to 80%, with morbidity being reported as high as 65%.[21] However reports are variable and usually based only on small patient populations.[17,22,23] Death may occur early in the course of the disease, with sepsis being the most frequent cause. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the predominant organisms involved.[17] Pulmonary embolism and gastrointestinal hemorrhage are other causes of death.

Mortality is increased significantly in those patients at the extremes of age and in relation to the percentage of

Table 42.1 Characteristics of Erythema Multiforme, Stevens–Johnson Syndrome, and Toxic Epidermal Necrolysis

	Erythema Multiforme	Stevens–Johnson Syndrome	Toxic Epidermal Necrolysis
Prodrome	Absent	High fever, malaise	High fever, malaise
Acute phase	4–8 days	4–8 days Sensation of skin burning or tenderness	Sudden onset, 1–2 days Sensation of skin burning or tenderness
Skin lesions	Symmetrical, primarily located on the extremities, some target lesions without blisters	Variable distribution, individual vesicles on an erythematous base <10% TBSA Nikolsky's positive	Diffuse generalized epidermal detachment, absence of target lesions, large confluent plaques >30% TBSA Nikolsky's positive
Mucosal involvement	Limited to one surface, usually oral	Severe, two or more surfaces involved	Severe, two or more surfaces involved
Histopathology	Dermoepidermal separation, mononuclear perivascular cell infiltrate, small areas of epidermal detachment associated with target lesions	Dermoepidermal separation, more intense dermal infiltrate, areas of epidermal detachment	Epidermal necrosis, dermoepidermal separation, minimal dermal inflammatory infiltrate, large areas of epidermal detachment
Recovery	1–4 weeks	1–6 weeks	1–6 weeks
Mortality	0%	0–38%	25–80%

Table 42.2 SCORTEN Scores and Mortality

SCORTEN (Sum of Scores)	Predicted Mortality
0–1	3.2%
2	12.1%
3	35.8%
4	58.3%
>5	90%

denuded skin and serum urea nitrogen levels.[17,22,24] Bastuji-Garin et al. in 2000 created the Score of Toxic Epidermal Necrolysis (SCORTEN), a scoring system to predict mortality in the adult population presenting with TEN. The scoring system uses seven independent risk factors to predict mortality by allotting 1 point for each variable:[25]

a. Age older than 40
b. Heart rate greater than 120 beats per minute
c. Comorbid malignancy
d. Epidermal detachment of greater than 10% of body surface area (BSA) on day 1
e. Blood urea nitrogen of greater than 28 mg/dL
f. Glucose of greater than 252 mg/dL
g. Bicarbonate less than 20 mEq/L.

The scoring system should be performed on day 1 and day 3 postadmission to maximize its predictive value. Mortality from TEN increases from 3.2% for a score of 0–1 to 90% for a score greater than 5 (Table 42.2).

While originally developed for adults, the scoring system has been validated in the pediatric population, but overall has been challenged for its lack of incorporating no more than one morbidity (malignancy) in its calculation.[26,27] While other investigators have developed formulas based on logistic regression analysis, the SCORTEN system is the most widely utilized.

SJS is associated with a mortality rate of 0–38%.[14,28] EM rarely causes death.[29]

ETIOLOGY

Keratinocyte apoptosis and secondary epidermal necrosis represent the pathopneumonic cellular process of TEN. The origins of the cellular process remain an active area of research, with an intricate meshwork of overlapping risk factors and processes starting to emerge as the picture sharpens. What has become clear is that the TEN disease process results from a complicated interaction of multiple processes and risk factors: genetic predisposition, environmental triggers, immunologic reaction, inflammatory mediators, and cellular apoptotic machinery.

Triggers and Risk Factors

TEN appears to be driven by immunological reactions to foreign antigens, often referred to as "triggers." Medications are by far the most commonly identified trigger, implicated in 77–94% cases of TEN. Antimicrobials, anticonvulsants analgesics, and nonsteroidal antiinflammatory agents of the oxicam type have been implicated.[6,16] Naturally the particular profile of TEN instigators will vary from population to population depending on the epidemiology of medication exposures in any given population.

Attempts to identify drugs suspected of having caused exfoliative necrolysis by skin test and laboratory tests seldom have been successful.[17] While some assays are trialed in research settings, there are currently no fully vetted, reliable methods available for identifying the inciting trigger in a patient with TEN. Historically the medication-specific trigger for any given case of TEN was ultimately a matter of speculation. However Sassolas et al. in 2010 developed an algorithm of drug causality for epidermal necrolysis termed ALDEN. The algorithm assigns a score of 1 to 10 for each drug based on six parameters.[32] The score is then categorized as very probable (>6), probable (4–5), possible (2–3),

unlikely (0–1), and very unlikely (<0) (Table 42.3).[32] The results of this algorithm were compared to a case-controlled analysis of the European Study of Severe Cutaneous Adverse Reactions (EuroSCAR) and found to have good accordance.[32,33] The use of ALDEN in the clinical setting may greatly improve the ability for clinicians and researchers to link medication-specific triggers and TEN.[32]

While advances have been made in correlating medications as the causative agent of TEN, the role of nonmedication triggers in the etiology of TEN remains murky. Upper respiratory tract infections, pharyngitis, otitis media, or viral illness are frequently reported as preceding or coinciding with the development of TEN in some patients.[13–15,34–36] *Mycoplasma pneumoniae* and herpes viruses (cytomegalovirus, Epstein–Barr virus, herpes simplex, and varicella zoster) have been implicated in the cause of EM and SJS, but not TEN.[14,37,38] Quantifying the association between TEN and antecedent viral syndromes is complicated by the rarity of TEN and the similarities between prodromal symptoms and other more common disorders. This leads to patients presenting with relatively prominent prodromal symptoms who are typically misdiagnosed as having a simple viral syndrome. Because of the delay between early prodromal symptoms and the more specific TEN rash, it is often impossible to determine in retrospect whether the pertinent symptoms were actually prodromal or if the patient had an antecedent viral infection. Furthermore, these prodromal symptoms are often treated with medications before the TEN diagnosis is considered. As such, medications used to treat prodromal symptoms are frequently misinterpreted as TEN triggers.

Table 42.3 Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN)

Criterion	Values	Rules to Apply	
Delay from initial drug component intake to onset of reaction (index day)	Suggestive +3 Compatible +2 Likely +1 Unlikely −1 Excluded −3	From 5 to 28 days From 29 to 56 days From 1 to 4 days >56 Days Drug started on or after the index day In case of previous reaction to the same drug, only changes for: Suggestive: +3: from 1 to 4 days Likely: +1: from 5 to 56 days	−3 to 3
Drug present in the body on index day	Define 0 Doubtful −1 Excluded −3	Drug continued up to index day or stopped at a time point less than five times the elimination half-life[a] before the index day Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a] but liver or kidney function alterations or suspected drug interactions[b] are present Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a], without liver or kidney function alterations or suspected drug interactions[b]	−3 to 0
Prechallenge/ rechallenge	Positive specific for disease and drug: 4 Positive specific for disease and drug: 2 Positive unspecific: 1 Not done/unknown: 0 Negative −2	SJS/TEN after use of same drug SJS/TEN after use of similar[c] drug or other reaction with same drug Other reaction after use of similar[c] drug No known previous exposure to this drug Exposure to this drug without any reaction (before or after reaction)	−2 to 4
Dechallenge	Neutral 0 Negative −2	Drug stopped (or unknown) Drug continued without harm	−2 or 0
Type of drug (notoriety)	Strongly associated 3 Associated 2 Suspected 1 Unknown 0 Not suspected −1	Drug of the "high-risk" list according to previous case–control studies[30–32] Drug with definite but lower risk according to previous case–control studiesd Several previous reports, ambiguous epidemiology results (drug "under surveillance") All other drugs including newly released ones No evidence of association from previous epidemiology stud with sufficient number of exposed controls[c] **Intermediate score = total of all previous criteria**	−1 to 3 **−11 to 10**
Other cause	Possible −1	Rank all drugs from highest to lowest intermediate score If at least one has an intermediate score >3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely)	−1
Final score			**−12 to 10**

<0, Very unlikely; 0–1, unlikely; 2–3, possible; 4–5, probable; ≥6, very probable.
ATC, anatomical therapeutic chemical; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.
[a]Drug (or active metabolite) elimination half-life from serum and/or tissues (according to pharmacology textbooks, tentative list available in complementary table), taking into account kidney function for drugs predominantly cleared by kidney and liver function for those with high hepatic clearance.
[b]Suspected interaction was considered when more than five drugs were present in a patient's body at the same time.
[c]Similar drug = same ATC code up to the fourth level (chemical subgroups), see Methods.

Genetics

Genetics clearly plays an important role in the pathophysiology of TEN, with multiple alleles identified as potent risk factors. Interestingly, the genetic risk factors identified thus far all appear to be trigger-specific. That is, a particular allele may place a person at risk for developing TEN in response to one drug, but not increase that same person's risk for developing TEN in response to a different medication.[39] The majority of those alleles identified thus far appear to increase risk through two separate mechanisms: drug–antigen metabolism and antigen presentation. As early as 1986, Shear et al. identified a pattern of "slow" sulfonamide metabolism in patients with a history of severe cutaneous sulfonamide reactions. Insights and technologies developed through the maturation of the field have allowed pharmacogeneticists to trace such associations with polymorphisms in genes encoding for components of the cytochrome P450 machinery. Investigators studying TEN patients' genotypes have assembled a sizable catalog of cytochrome P450C variants that convey an increased risk for developing TEN, with each polymorphism associated with a specific trigger agent.[40–46] The largest family of genes with a documented association with TEN include polymorphisms at a number of HLA loci that have been associated with drug-specific risks for TEN. These polymorphisms presumably alter the morphology of the HLA molecules on antigen-presenting cells, making them more or less inclined to "recognize" a particular antigen. The "antigen" may be the medication molecule, a drug metabolite, a byproduct of drug metabolism, or a hapten created by the binding of the drug, metabolite, or byproduct to another peptide.[47]

The clinical application of these genetic markers is complicated by the fact that their predictive value varies widely when applied to populations of different ethnic makeups. An example of this strong association between HLA, drug sensitivity, and ethnic background was discovered by Chung et al.[48] They demonstrated a strong association between HLA-B*1502, SJS, and carbamazepine in Han Chinese. This unique relationship was later observed in a Thai population, but was absent in the Japanese and European populations.[49–52] In fact, RegiSCAR, a large European study, suggested that HLA-B*1502 is not a marker for carbamazepine, sulfamethoxazole, lamotrigine, or NSAID oxicam-type-induced SJS or TEN.[52,53]

Although the HLA-B*1502 and carbamazepine association demonstrated significant ethnic variance, this is not the observation for all HLA–medication interactions. A second strong relationship among HLA, drug sensitivity, and SJS/TEN was observed for allopurinol and HLA-B*5801.[54] While the strength of the relationship continued to vary between ethnicities, the correlation persisted in Han Chinese, Japanese, Thai, and Europeans, unlike for HLA-B*1502 and carbamazepine.

In summary, for many of these markers, prevalence patterns make the marker too rare to function as a screening tool outside the context of specific ethnicities. Beyond issues of prevalence, some markers are associated with a TEN reaction in one population, but not in another: a phenomenon that likely traces to interactions between the "maker" allele and other genetic variables.

Immunopathology

Multiple lines of evidence point to T cells as critical effectors of the TEN process. T cells are the predominant cell type found in the blister fluid and exudate of patients with acute TEN.[55]

Suppression or cytotoxic T-cell infiltrates are observed in the epidermis in TEN.[56,57] The observation of blebbing of the keratinocyte plasma membrane in TEN is considered a reliable morphological finding of cytotoxic T-lymphocyte cytolysis.[57] Serum and exudate levels of markers of T-cell activation have been shown to correlate with disease activity and resolution.[58–61]

TEN is perhaps best understood as an immunologically mediated burn. For the most part, TEN resembles a classic type IV (delayed) hypersensitivity disorder. The delay between exposure and reaction, the critical role of T cells, and the accelerated reaction reported in cases of re-exposure to an initial trigger all favor this characterization.[39,62] While some have pointed to immunofluorescence microscopy findings of IgM and C3 deposited along the dermoepidermal junction and dermal vessels in cases of postherpetic SJS and EM as evidence of an associated type II hypersensitivity reaction, others attribute this to simple nonspecific exudation.[36,63–65] The exact antigen that activates the T-cell receptor varies depending on the specific trigger agent: the recognized moiety could be a molecule within the medication, a byproduct of agent metabolism, or a complex formed between an endogenous peptide and either of the preceding. Keratinocyte apoptosis is central to the pathogenesis of TEN. This event is thought to be mediated by ligand/receptor interaction of the tumor necrosis factor (TNF) superfamily (as TNF-α/TNF receptor or FasL/Fas interaction).[66,67] Through a series of experiments, Viard et al. observed, in vitro, that TEN patients expressed lytically active Fas ligand and that the action of this ligand could be blocked by both a monoclonal antibody and human immunoglobins.[68] In SJS, keratinocyte DNA fragmentation has been found in about 90% of cases associated with dermal perforin-positive lymphocytes.[39,69]

CLINICAL PRESENTATION

A prodromal phase of TEN is frequently identifiable in retrospect and usually characterized by some combination of low-grade fever, malaise, cough, conjunctivitis, and dysuria. These symptoms typically precede any cutaneous manifestation by 1–21 days, but usually last for 2–3 days.[1,14] This prodrome precedes the development of a frank rash, although patches of tender erythema and inflamed mucosal membranes are sometimes present. Skin involvement usually begins with subtle patches of tender erythema and localized morbilliform eruptions or discrete erythematous or purpuric macules. Later vesicles and large bullae emerge from areas of erythema, either en masse or via coalescence of initial morbilliform eruptions. On light digital pressure, the epidermis desquamates in sheets: Nikolsky's sign is positive (Fig. 42.1). The TEN rash is extremely painful, even when bullae are still intact. Generally, a lag period of 1–3 weeks is observed from initiation of drug until skin eruption, but this may be shorter, particularly in cases of re-exposure in a previously sensitized individual.[1,2,17]

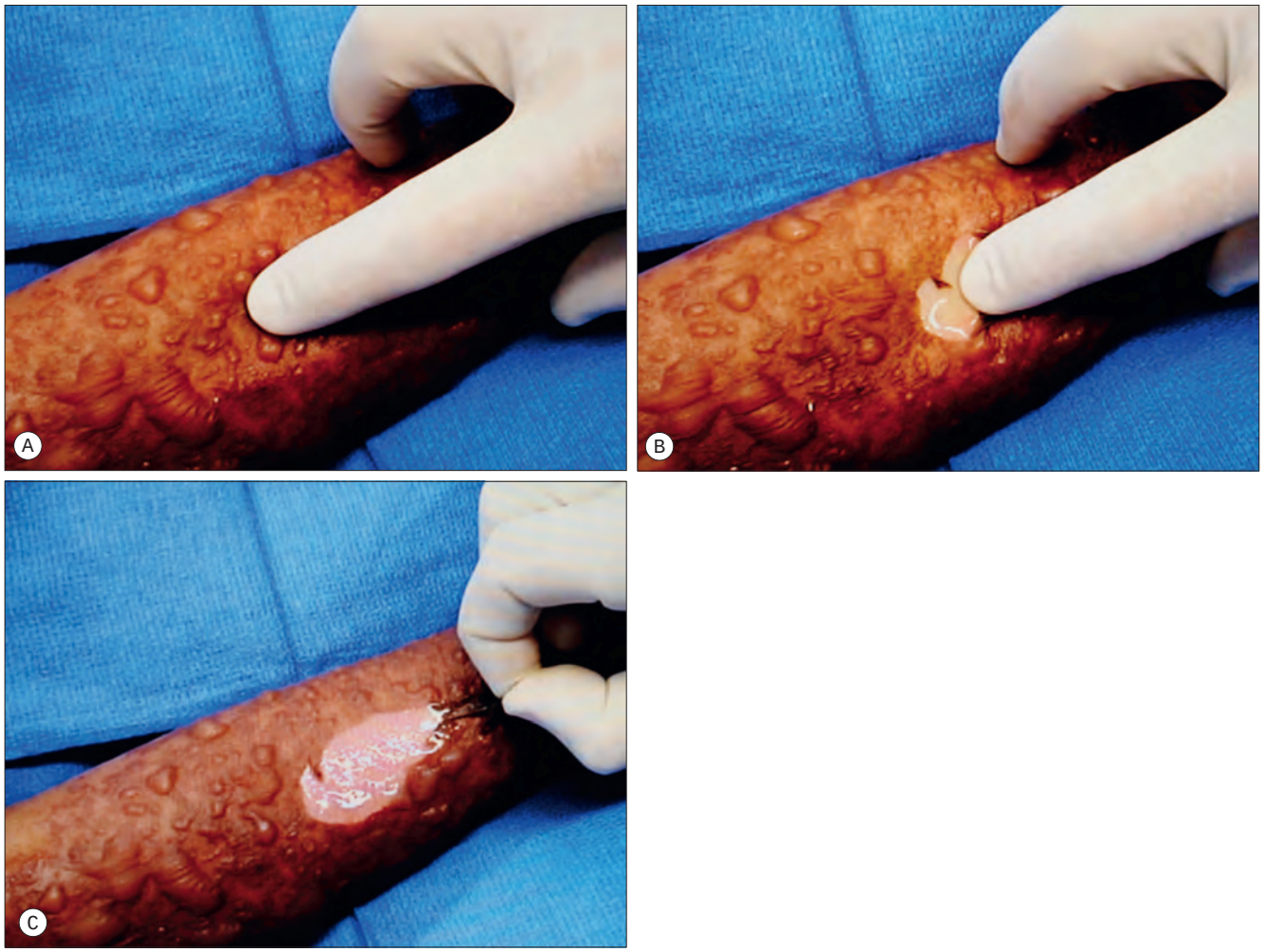

Fig. 42.1 (A–C) Nikolsky's sign. Epidermal separation induced by gentle pressure on the skin surface.

Mucosal involvement is extremely common in TEN, with two or more areas typically involved. These mucosal lesions are often most problematic in that they can cause significant immediate and long-term complications and typically persist (symptomatically) longer than cutaneous lesions.[6,16,17] Site involvement usually follows this order of frequency: oropharynx (93%), ocular (78%), genitalia (63%), and occasionally the anal mucosa.[70]

Mucosal involvement precedes skin lesions by 1–3 days in one-third of cases.[16,71] As such, any case presenting with skin involvement with no mucosal involvement should raise the suspicion for an alternative diagnosis. However it should be noted that detection of mucosal involvement often requires a significant index of suspicion: the fulminant skin findings can frequently distract from more subtle mucosal findings, such as enteral mucosal involvement and bronchial involvement, which are often more easily inferred from symptoms rather than direct visualization.

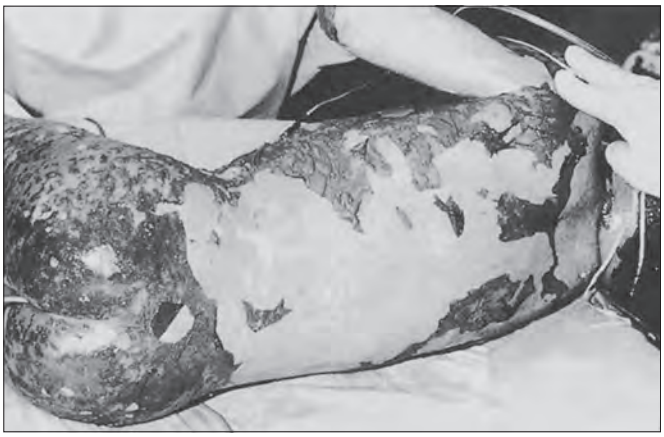

Fig. 42.2 Toxic epidermal necrolysis (TEN) is characterized by massive sloughing of the epidermal tissue.

DIAGNOSIS AND PROGNOSTIC EVALUATION

Histopathology

An early skin biopsy is essential for diagnosis. Skin manifestations vary from patient to patient and with the age of the lesion (Fig. 42.2). Advancing edges of the target lesions show scattered necrotic keratinocytes in the epidermis and only mild dermal inflammation. In older lesions and central zones of target lesions, the dusky appearance corresponds to areas of extensive keratinocyte necrosis, often with the formation of subepidermal

bullae and dermoepidermal separation. The surrounding erythematous zone shows papillary dermal edema, vascular dilation with endothelial cell swelling, and perivascular mononuclear cell infiltrate. Extravasated erythrocytes may be seen in the surrounding papillary dermis. The reticular dermis is normal.[17,22]

Epidermal and dermoepidermal suppressor or cytotoxic T lymphocytes, in addition to dermal infiltrates of helper T lymphocytes, have been demonstrated.[56,63,72] Hertl has confirmed that these epidermal cells are cytotoxic T cells.[73] Langerhans cells appear to be reduced in the epidermis, although numerous dermal macrophages are observed. A more intense dermal cell infiltrate is present in SJS, especially in postherpetic cases.[38] Dendritic lymphoid cells are observed, opposed to damaged dermal macrophages and necrotic keratinocytes. Furthermore, at the point where the cytoplasmic processes contact the keratinocyte, the plasma membrane of the keratinocyte is absent. Aberrant expression of HLA-DR on keratinocytes has been observed, a phenomenon that has been present in many other inflammatory skin disorders.[63,74]

COMPLICATIONS

TEN is frequently associated with serious complications. In many cases, the skin re-epithelializes from the dermal elements without significant scarring and with long-term affects typically limited to discoloration.[75] Scarring may be more prominent—and accompanied by contractures—if the disease progresses due to secondary infection or peripheral vasoconstriction from shock or vasopressor use. Nail plates are frequently lost and nail regrowth may be abnormal or absent.

Complications may also affect mucosal membranes throughout the body. One of the most severe long-term complications is ocular sequelae, which occurs in half of the survivors. Pseudomembranous or membranous conjunctivitis resulting from coalesced fibrin and necrotic debris can lead to ocular opacification, secondary infection, and blindness (Fig. 42.3).[4,76] Conjunctival scarring may also result in lacrimal duct destruction, leading to reduced tear production and keratoconjunctivitis sicca, a Sjögren-like syndrome. Finally, scar changes can lead to distortion of eyelid anatomy, which can result in ectropion, entropion, trichiasis, and symblepharon.[14,77]

Other systems that may be impacted include:

- *Oropharyngeal*: This is common and often results in pain on chewing, severe dysphagia, and odynophagia (Fig. 42.4). The mucositis is associated with an increase in secretions and sloughing mucosa, which can present an airway concern. Naturally, oropharyngeal involvement can interfere with oral intake, requiring direct enteral access for an alternate route of feeding. Buccal–gingiva epithelial fusing can occur, thus demonstrating the importance of good oral hygiene.
- *Respiratory*: Respiratory tract involvement occurs and is associated with increased mortality.[78,79] These complications include diffuse erythema to extensive confluent tracheal and bronchial erosion covered by fibrinous exudate. Epiglottal swelling necessitating intubation has also been reported. However bronchopneumonia has been found to be the most frequent complication, occurring in 50% of patients.[29,34,79]
- *Gastrointestinal*: The onset of intestinal symptoms generally occurs concurrently with the cutaneous lesions.[80] Epidermal and epithelial sloughing may extend into the gastrointestinal mucosa and may induce esophagitis with frequent subsequent stricture formation.[81] Gastrointestinal erosions macroscopically resemble ulcerative or pseudomembranous colitis, and massive hemorrhage requiring resection has been reported.
- *Urologic*: Male urethral involvement is fairly common, with visible involvement at the meatus. Long-term sequelae include urethral stricture and phimosis.
- *Gynecologic*: Vulvar involvement appears to be quite common in female patients, with reported incidences increasing over the past few decades as increasing

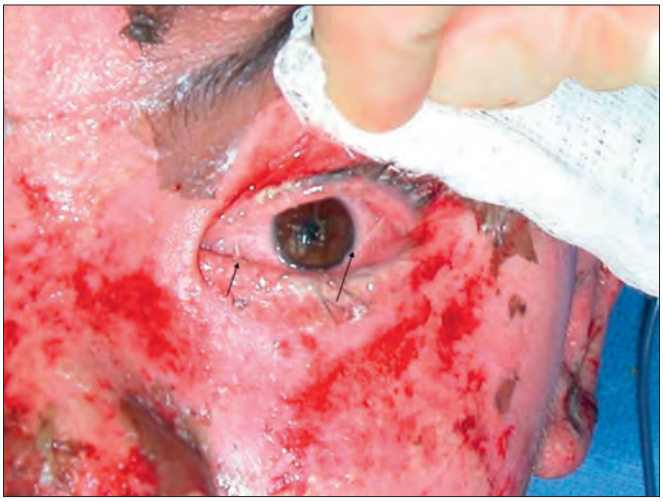

Fig. 42.3 Ocular involvement in toxic epidermal necrolysis (TEN) is common and can lead to blindness. Early and aggressive ocular care must be initiated to prevent pseudomembranes. (Arrows demonstrate membranous conjunctivitis.)

Fig. 42.4 Toxic epidermal necrolysis patient demonstrating significant oropharyngeal involvement.

awareness has resulted in improved detection and more frequent practice of routine screening exams. Mucosal erosions are clearly quite painful, and involvement of associated glandular structures can result in obstruction and dysfunction. Long-term sequelae can be particularly troublesome. Vaginal wall synechiae and clitoral hood adhesions can result in significant dyspareunia and sexual dysfunction.[82,83] Vaginal webbing and synechiae can result in dysfunctional menstruation with resultant infertility.[84–86] Consultation with a gynecologist is recommended for the majority of these cases.

Systemic and Other Nonmucocutaneous Complications

Although mucocutaneous erosions are the most common features of TEN/SJS, the disease may present with multisystem involvement. Renal manifestations like glomerulonephritis and acute tubular necrosis, as well as hepatitis and hepatocellular necrosis, have been described.[6,16,87] Hypoalbuminemia, asymptomatic hyperamylasemia, increased erythrocyte sedimentation rate, leukocytosis, thrombocytopenia, and normochromic and normocytic anemia are not uncommon.[29,78] Leukopenia is a frequent and poor prognostic sign.[6,17,34] This is due in part to depletion of the T helper/inducer lymphocyte population ($CD4^+$).[88] The white blood cell count generally returns to normal levels after 2–5 days. The cause of this immunosuppression is unclear.

MANAGEMENT

As previously stated, TEN is a life-threatening disease and is best managed in a burn ICU where a multidisciplinary approach, including goal-directed fluid resuscitation and nutritional support, is utilized.[23,34,35,89]

General Management and Resuscitation

Drugs suspected of having initiated the disease should be discontinued immediately. Administration of pain medication is of high priority, and antipyretic agents may be required. The use of broad-spectrum antibiotics should be carefully considered: Neutropenia is the only complication in which "prophylactic" antibiotics are indicated. Otherwise systemic antibiotics only should be used for documented infections or suspected sepsis.

Intravenous replacement of fluid losses through the exposed body surface is required. However, because patients do not develop the massive edema and fluid losses evident in burn patients, fluid resuscitation formulas commonly employed in the management of thermal injuries overestimate the actual need.[90,91] Ringer's lactate solution is given at a rate determined by close monitoring of the patient's condition, resuscitation indexes, and urine output. Once wound coverage is accomplished, fluid requirements usually decrease.

Central line placement should be avoided if possible to reduce the risk of infection and sepsis. To further minimize this risk, lines should be placed in areas of uninvolved skin. Invasive devices are removed as soon as possible, and oral and nasogastric routes are utilized at earliest convenience. Environmental temperature should be raised to 30–32°C to reduce metabolic energy expenditure. Heat shields and infrared lamps are beneficial in patients' rooms, bathrooms, and operating rooms.

Stress ulceration prophylaxis is advisable.

Immunomodulation Therapy

Because the pathophysiology of TEN appears to be initially immunologic, it is logical to consider immunosuppressive therapy as an early treatment modality. The following sections will briefly review the literature with regards to use of corticosteroids, cyclosporine A, intravenous immunoglobins, and thalidomide.

Corticosteroid Therapy. Corticosteroid treatment of TEN has produced much controversy. In relation to the delayed hypersensitivity reaction or antibody-dependent cytotoxicity theories of pathogenesis, corticosteroids would seem to be an appropriate form of medical therapy. However the practice of administering continuous high-dose corticosteroid in an attempt to stop the progression of the disease is widely rejected.[14,16,17,78,92,93] Rational assessment of the benefit of corticosteroids is not possible due to the lack of randomized, controlled, prospective trials. Many authors feel that steroids enhance the risk of sepsis, increase protein catabolism, delay wound healing, cause severe gastrointestinal bleeding, prolong hospitalization, and increase mortality.[29,34,90,94] One study found no decrease in the progression of SJS with steroids, but instead found significant morbidity.[94] In a prospective – although not randomized – study, increased survival (66%) was seen in matched patients who did not receive steroids compared to only 33% survival in those who did receive steroids.[34] Pediatric SJS patients treated with steroids had a longer hospital stay and a complication rate of 74% compared to 28% in those without steroids.[93] Another study demonstrated 80% mortality associated with steroid therapy, which was reduced to 20% when steroids were withheld. In several studies, patients with antecedent glucocorticoid therapy before the onset of TEN showed no significant survival benefit, and corticosteroid use itself has been linked to an increased risk for developing TEN.[11,31,95,96] Advocates of corticosteroid therapy suggest that improved results are possible when steroids are applied in a limited "pulse" dose early in the course to interrupt the active necrolytic process and limit complications. Kardaun et al. studied 12 patients over a 10-year period and suggested that short-term dexamethasone pulse therapy was safe and may contribute to a reduced mortality rate.[97] This was followed by the largest study of this approach, the EuroSCAR, which did identify a trend but not a statistically significant improvement with the early pulse of systemic corticosteroids.[98] Thus corticosteroid therapy remains controversial in this disease due to the absence of strong evidence of efficacy.

Cyclosporine A. Cyclosporine A is an agent that has the properties of both being a powerful immunosuppressant and an antiapoptotic. The mechanism of action is inhibition of the synthesis of interleukin-2 by selective inhibition of calcineurin, thus arresting the proliferation of T helper cells.[99] In the only case series, Arevalo et al. observed a significantly shorter time to disease arrest (24–36 h) and time to re-epithelialization when compared to historical

controls. This study was followed by a few small studies suggesting a potential benefit of cyclosporine A. In 2010, a phase II trial by Valleyrie-Allanore et al. found a treatment of 3 mg/kg per day of oral cyclosporine for 10 days followed by a tapering schema over the next month was not clinically significant.[100] However, mortality appeared to be reduced when compared to predictive mortality. Although intriguing, the currently published studies do not have similar methodologies, varying with regards to the dosage administered, route of administration, and duration of therapy. Furthermore, cyclosporine A therapy has been associated with a septicemia rate of 55%.[101] Therefore, a well-designed prospective clinical trial is warranted prior to advocating the use of cyclosporine A in the treatment of TEN.

Intravenous Immunoglobulin. Intravenous immunoglobulin (IVIG) has been suggested as a means of interrupting the autoimmune process fueling TEN. Furthermore, some have proposed that pooled human immunoglobins may contain a Fas blocking antibody, which would directly disrupt the keratinocyte apoptosis trigger.[102] Unfortunately, clinical data has been conflicting, creating difficulty in advocating IVIG treatment for TEN. To date, there have been 12 noncontrolled clinical studies examining the efficacy of IVIG in the treatment of TEN.[103–105] Interestingly, the data suggests that IVIG dosages of greater than 2 mg/kg may be superior to less than 2 mg/kg. Huang et al. performed a meta-analysis on the efficacy of IVIG therapy in TEN patients.[106] In adults, the high-dose IVIG group had a significantly lower mortality rate when compared to the low-dose IVIG group. However, the multivariate logistic regression model found the dosing of IVIG did not correlate with mortality when controlling for age, total BSA involvement, and delay in treatment.[21] This finding was supported by the largest clinical study to date, EuroSCAR, which failed to demonstrate efficacy of IVIG in the treatment of TEN.[98]

Despite these findings, some continue to advocate for the use of high-dose IVIG (3 mg/kg total dose give over 3–4 days) in the treatment of TEN based on the low complication risk and lack of alternative therapies. As in the case with cyclosporine A, a well-designed controlled multicenter clinical trial is warranted prior to advocating the use of human immunoglobins routinely in the treatment of TEN.

TNF-α Inhibitors, Thalidomide. The primary mechanism in the pathogenesis of TEN is keratinocyte apoptosis. Accordingly, TNF-α has been implicated in the pathogenesis of TEN. Thalidomide, a potent inhibitor of TNF-α, would appear to be a logical therapeutic agent in the treatment of TEN. Unfortunately, Wolkenstein et al. had to prematurely terminate a randomized clinical trial of thalidomide versus placebo in the treatment of TEN due to excess mortality in the treatment group.[107] Ten of 12 patients expired in the thalidomide group compared to three of 10 in the control group. The authors theorized that thalidomide may have paradoxically increased the production of TNF in the treatment group, a previously reported phenomenon of thalidomide administration. Therefore, thalidomide as a treatment for TEN should not be initiated owing to the detrimental effects, but this does demonstrate the usefulness of randomized, double-blinded, placebo-controlled clinical trials. Despite the failure of thalidomide, investigators are still exploring the use of TNF-α antagonists and inhibitors (infliximab, etanercept, etc.), in the treatment of TEN.[108,109] Unfortunately, these new therapies have only been reported in case reports and thus cannot be supported for routine use in this patient population.

Until these treatment modalities have proved their efficacy in controlled trials, the gold standard of treatment for TEN patients consists of a multidisciplinary approach as used in severe burns, focusing on wound care, infection control, and prevention of complications.

Surgical Approach. Débridement of necrotic epidermis and coverage of the large wound surface with biological or synthetic dressings have been advocated by several authors.[89,110,111] Sloughed epidermis should be removed in order to reduce bacterial growth and the risk for infection. The exposed and tender dermis should be covered. Débridement is best undertaken under general anesthesia as soon as diagnosis by histology is established. Blood loss associated with débridement is minimal, so over-resuscitation must be avoided.

Synthetic dressings, such as Biobrane, and biological dressings, such as homograft (cadaver allograft) and porcine xenograft skin, greatly reduce the pain, decrease fluid loss, and promote healing. Biobrane and similar products should be used with caution when covering wound areas greater than 40% TBSA secondary to the increasing incidence of local infections. Porcine xenograft adheres well to the skin and is commercially available in large quantities.[91,112] Homograft is more likely to become vascularized and therefore reduces the number of graft changes.[113] However this must be weighed against the potentially poor cosmetic results of vascularized homograft (Fig. 42.5). Grafted areas must be immobilized and protected from shear forces. In both adults and children, continuous rotation or air fluidized (Clinitron) beds frequently are used.

Topical Therapy. As separation occurs at the dermal–epidermal junction, varying depths of viable dermis remain. If this dermis can be protected from toxic detergents,

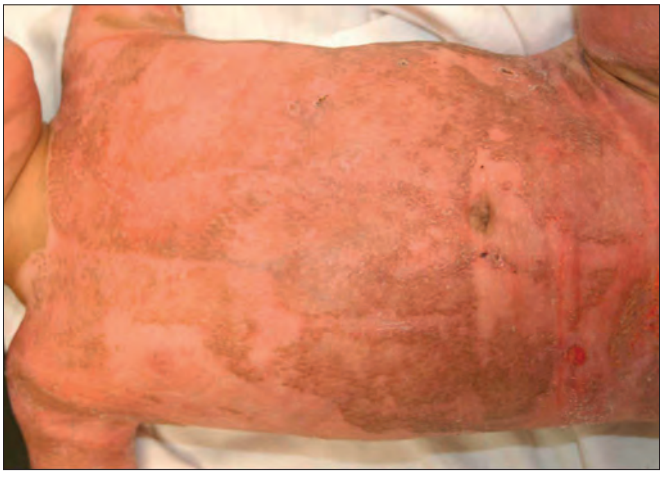

Fig. 42.5 Homograft vascularization occurring over a second-degree thermal injury, resulting in a poor cosmetic result.

desiccation, mechanical trauma, and wound infection, then rapid re-epithelialization by proliferation of basal keratinocytes from the skin appendages will occur.[90] Bacterial proliferation on the unprotected wound surface with invasive infection leads to full-thickness skin necrosis. Hydrotherapy and topical antimicrobials provide débridement and infection control that should be initiated early in the course of the disease. Effective topical antimicrobial agents include silver sulfadiazine cream, silver nitrate solution, chlorhexidine gluconate solution, and polymyxin-bacitracin ointment.[16,37,110] While silver sulfadiazine is widely used, concerns that its sulfonamide component can exacerbate the disease process remain a theoretic concern even though these concerns have not been confirmed in the literature. Additionally, an inhibitory effect on epithelialization and leukopenia requiring discontinuation has been observed. Alternatively silver nitrate solution does not contribute to the ongoing drug reaction, and epithelialization is not inhibited. For patients with contaminated wounds due to delayed initiation of treatment, silver nitrate soaks can reduce contamination and prepare the wound for eventual biological dressing. Silver nitrate solutions are hyponatremic and thus associated with approximately 350 mmol of sodium loss per day/m^2 treated. Serum electrolytes and osmolarity must be carefully monitored.

Chlorhexidine gluconate and polymyxin ointment are effective against Gram-negative organisms, including *P. aeruginosa*, with low incidence of sensitivity. Moreover, chlorhexidine gluconate also shows bactericidal effects against Gram-positive organisms.

Oropharyngeal mouth erosion resulting in severe dysphagia can be alleviated by the use of viscous lidocaine or cocaine rinses and thus ease oral administration of nutrients and fluids. Oral debris should be removed and the mouth rinsed or sprayed with antiseptic several times a day.[22] Oral nystatin prevents intestinal overgrowth of *Candida* and decreases the risk of *Candida* sepsis.[113]

Pulmonary involvement requires close supervision, with careful toileting including bronchoscopy, incentive spirometry, mobilization, and coughing to prevent infections and complications. If mechanical ventilatory support is necessary, the prevention of bronchopulmonary infection gains even more importance. Daily monitoring by blood assessment, including blood gas analysis, chest X-ray, and bacteriological culture, are required to initiate timely antibiotic therapy or ventilatory support. Measures to prevent thromboembolism, such as low-dose or low-molecular-weight administration of heparin, should be instituted on admission.

Ocular involvement should be assessed daily by an ophthalmologist. Conjunctival crusting can be minimized by the application of saline eye drops every hour. Any adhesions should be broken using a blunt instrument and bland eye drops or ointment applied frequently. Documented ocular infections are treated with organism-specific antibiotic therapy. Lacrimal duct obstruction may be detected early by performing Schirmer's test. There are a wide range of ophthalmic treatment options, a review of which would be beyond the context of this chapter. One reasonable, practical approach is the "Triple-TEN" protocol described by Tomlins et al., which includes (1) subconjunctival steroids to blunt local inflammation, (2) amniotic membrane application, and (3) insertion of a scleral shell spacer to prevent symblepharon formation.[115] Regardless of the specific treatment options taken, involvement of an ophthalmologist is clearly indicated.

Although it is not common in TEN, genitourinary mucosal involvement should be treated acutely with supportive care: pain control, hygiene, and topical treatments for pain relief and lubrication. Urinary catheterization needs to be weighed against the clinical stability and clinical scenario of the patient. Does the need for precise urine output outweigh the risk of increased infections that could occur with the placement of a catheter? Long-term sequelae include urethral stricture and phimosis, which can usually be managed with serial dilation and circumcision, respectively.

Vulvar involvement should also be managed proactively to minimize symptoms and (theoretically) attenuate the risk of long-term sequelae. The use of some topical medication options has been suggested, but none of these is considered the standard of care at this point. Mechanical treatments should be considered to prevent prolonged apposition of opposing inflamed mucosal surface to avoid fusion and synechiae. Vaginal dilators can be used to avoid fusion, although monitoring and regular changing are necessary to avoid infection. Finally, menstrual suppression should be considered to minimize the risk of vaginal adenosis.[114] Depending on the extent and severity of the involvement of the vaginal area, consider a consultation with a gynecologist.

Nutritional Support

Enteral nutrition should be initiated immediately once the patient is resuscitated. Due to the frequent presence of oral mucosal ulcerations, patients may be reluctant to take nutrition orally and thus require a nasogastric tube placement. Unlike burned patients who have significantly elevated metabolic rates, these patients appear to have metabolic rates only slightly above basal requirements. Weight stabilization and a positive nitrogen balance have been achieved in adults with 2500 kcal/day.[90,110]

Soft-Tissue Infections and Other Acute Skin Disorders

Staphylococcal scalded skin syndrome, necrotizing fasciitis, and purpura fulminans are examples of a group of conditions characterized by extensive soft-tissue loss, rapid onset of critical illness, and death. Early, accurate diagnosis is essential to initiate appropriate action, such as extensive surgical excision in the case of necrotizing fasciitis or crepitant soft-tissue infections. Burn care centers, with their acute and reconstructive capacities, have much to offer these patients with extensive skin loss.

STAPHYLOCOCCAL SCALDED SKIN SYNDROME

Staphylococcal scalded skin syndrome is the severe condition caused by exfoliative staphylococcal toxins and is characterized by systemic signs and symptoms and generalized involvement of the skin (Fig. 42.6). It is important to make a diagnosis early, particularly to differentiate it from TEN, which has a different management and much greater

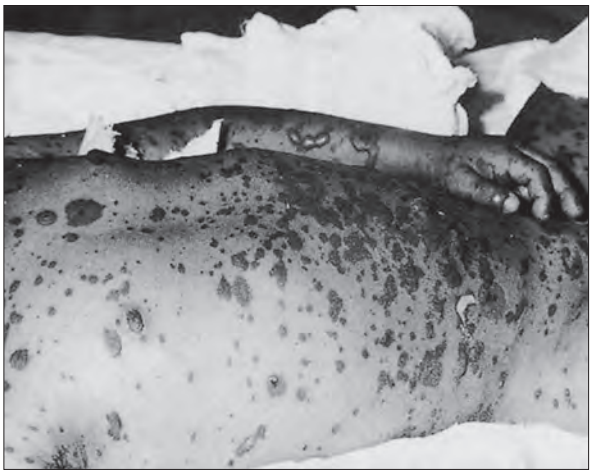

Fig. 42.6 Staphylococcal scalded skin syndrome is characterized by diffuse, erythematous lesions with bullae formation (see left forearm). Epidermis is shed in sheets with minimal abrasion. The wounds are partial thickness and heal without surgical intervention.

mortality. Staphylococcal scalded skin syndrome is predominantly a disease of infancy (Ritter's disease) and early childhood, with most cases occurring before the age of 5 years.[116] Newborn nurseries are often the sites of outbreaks. Attendant staff may be infected or colonized with *Staphylococcus aureus* strains producing epidermolytic toxin, thus emphasizing the importance of standard hygienic measures. Adult staphylococcal scalded skin syndrome is rare and usually associated with compromised renal function. Mortality is generally only 4%, but can be much higher in adults (40%) depending on underlying diseases.[116,117]

Pathology

Two distinct epidermolytic toxins (ETA and ETB), are responsible for the blistering in staphylococcal scalded skin syndrome.[81] ETA is heat-stable, whereas ETB is heat-labile and encoded by a bacterial plasmid. Most toxigenic strains of *S. aureus* are identified as group 2 phage.[118] The exfoliative toxin is metabolized and excreted by the kidneys, leading to a predisposition of patients with renal immaturity (children) or renal compromise. The exfoliative toxins produce blistering by disrupting the epidermal granular cell layers through interdesmosomal splittings but without epidermal necrosis and with very few inflammatory cells. The exact mechanism of action of the toxins has not been determined, although it is felt that the toxins directly affect desmosomes. One might be proteolytic disruption of desmosomes with the toxin or part of its sequence acting as a serine protease.[116,119,120]

Presentation

Onset may be marked by fever, malaise, and irritability. Scarlatiniform erythema is often accentuated in flexural and periorificial areas. The skin is generally tender to touch, and sheets of skin may peel away in response to minor trauma (Nikolsky's sign). Blisters appear within 24–48 hours of rupture, leaving a characteristic moist erythematous epidermal base. Severe mucosal involvement is not a typical feature.

Diagnosis

Diagnosis of staphylococcal scalded skin syndrome can be made rapidly with a skin biopsy. The characteristic intraepidermal level of splitting is seen, with the split occurring at the granular layer level (stratum granulosum) with no epidermal necrosis or inflammatory cells in the corium. Immunofluorescent studies of the skin are negative. A Tzanck preparation from a scraping of the base of a freshly denuded area will reveal the affected cell population (i.e., acantholytic keratinocytes).[118] Bullae, denuded skin, and blood are usually sterile, however, and staphylococci can usually be cultured from nares, conjunctiva, or pharynx.[121]

Management

With diagnosis, antibiotics should be started, and semisynthetic penicillinase-resistant penicillin analogs are indicated (e.g., meticillin or oxacillin) since the majority of group 2 staphylococci show resistance to penicillin. Administration of steroids to these patients is contraindicated.[118] After screening for colonization, decontamination of colonized areas, especially the nasopharyngeal region in patients and nursing staff, may be advisable to prevent further spread. Fluid resuscitation is usually required at a lesser volume compared to a burn patient with a similar involved BSA. Fluid substitution should be guided by urine output, hemodynamic parameters, and electrolyte and colloid status.

Until skin barrier function is restored, patients should receive appropriate wound dressings to prevent secondary wound infection. Topical agents are soothing and bacteriostatic. It needs to be pointed out that the wound initially is not colonized or infected, so alternatively, large areas can be more effectively managed with biological or synthetic dressings. They have the advantage of eliminating the need for frequent dressing changes, which can be particularly traumatic for young children. Mortality usually is low but may occur in very young and adult patients, usually from sepsis or electrolyte imbalance on the basis of underlying disease.[118] Complete wound healing is usually observed within 7 days, and scarring and altered pigmentation are not common.

NECROTIZING FASCIITIS AND BACTERIAL MYONECROSIS

Necrotizing fasciitis is a soft-tissue infection characterized by widespread necrosis of fascia and subcutaneous tissue, which may progress to muscle and skin necrosis. Overall mortality may still be as high as 50%.[111,122] Most cases of necrotizing fasciitis are due to polymicrobial infection including both anaerobic Gram-positive cocci and Gram-negative bacilli. *Streptococcus*, *Staphylococcus*, *Enterococcus*, and *Bacteroides* are commonly found. Infection with many bacterial species may result in bacterial myonecrosis. However, gas gangrene by *Clostridia* spp. results in severe systemic toxicity and higher mortality than necrotizing fasciitis. A deep contaminated wound frequently precedes the severe soft-tissue infection. Streptococcal myositis has a mortality rate of between 80% and 100%.[122,123] Risk factors for both necrotizing fasciitis and bacterial myonecrosis have been identified as diabetes mellitus, intravenous drug use,

age greater than 50 years, hypertension, and malnutrition/obesity. The presence of three or more of these risk factors was found to give a predictive mortality rate of 50% (Fig. 42.7).[124]

Diagnosis

Early diagnosis is of extreme importance and consequence. Initial presentation is deceptive because the findings may be localized pain and edema without discoloration of the skin. Later, induration and erythema may be evident. Paresthesia of overlying skin and eventual dusky discoloration and local blistering may occur in the later course. Severe toxemia may develop, usually out of proportion to the local signs. Severe systemic alterations are characteristic of myonecrosis. Gas inclusion may be evident in subcutaneous tissues on X-ray. Computed tomography (CT) and magnetic resonance imaging (MRI) may help in the diagnosis and provide information on the nature and extent of the infection.[125] Frozen section biopsies may provide early histological evidence of infection.[126] Gram stains and microbiological testing are very important diagnostic tools and guide antibiotic treatment. However, a definite distinction between necrotizing fasciitis, myonecrosis, and other soft-tissue infections often can only be established during surgery.

Management

The key to successful management of necrotizing infections is early diagnosis and radical surgical intervention. Surgical exploration involves complete excision of all necrotic tissues. If more than one operation for débridement of infected necrotic tissue is needed, mortality increases from 43% to 71%; this outcome drastically highlights the importance of adequate initial necrosectomy.[127] In patients with many risk factors, early amputation of the extremity, especially in cases of myonecrosis, should be considered. Broad-spectrum antibiotics are started preoperatively, although high-dose penicillin is appropriate for clostridial infections. However, antibiotic treatment is no substitution for surgical intervention. Adequate fluid resuscitation and nutritional support are also required. Wounds are packed open with antiseptic-soaked dressings, which need to be changed frequently. Kaiser and Cerra have reported unsatisfactory results with either early application of porcine xenografts or burn wound topical antimicrobials.[128] Complete control of local and systemic infection is required before wound closure is addressed.

As in burns, secondary infections must be prevented by proper wound management. Biological or synthetic dressings offer the advantages of decreased pain, decreased fluid loss, and prevention of secondary infection. Frequently large areas of skin and soft-tissue loss result from this disease and will eventually require extensive surgery to achieve adequate closure.

Some authors advocate the use of hyperbaric oxygen and claim that it results in decreased mortality and reduced need for débridement; however most of these reports are case reports or uncontrolled trials, and adequate prospective controlled trials in patients are still lacking.[129,130] In animals, hyperbaric oxygen therapy alone did not improve survival or bacterial colonization, but did show adjuvant

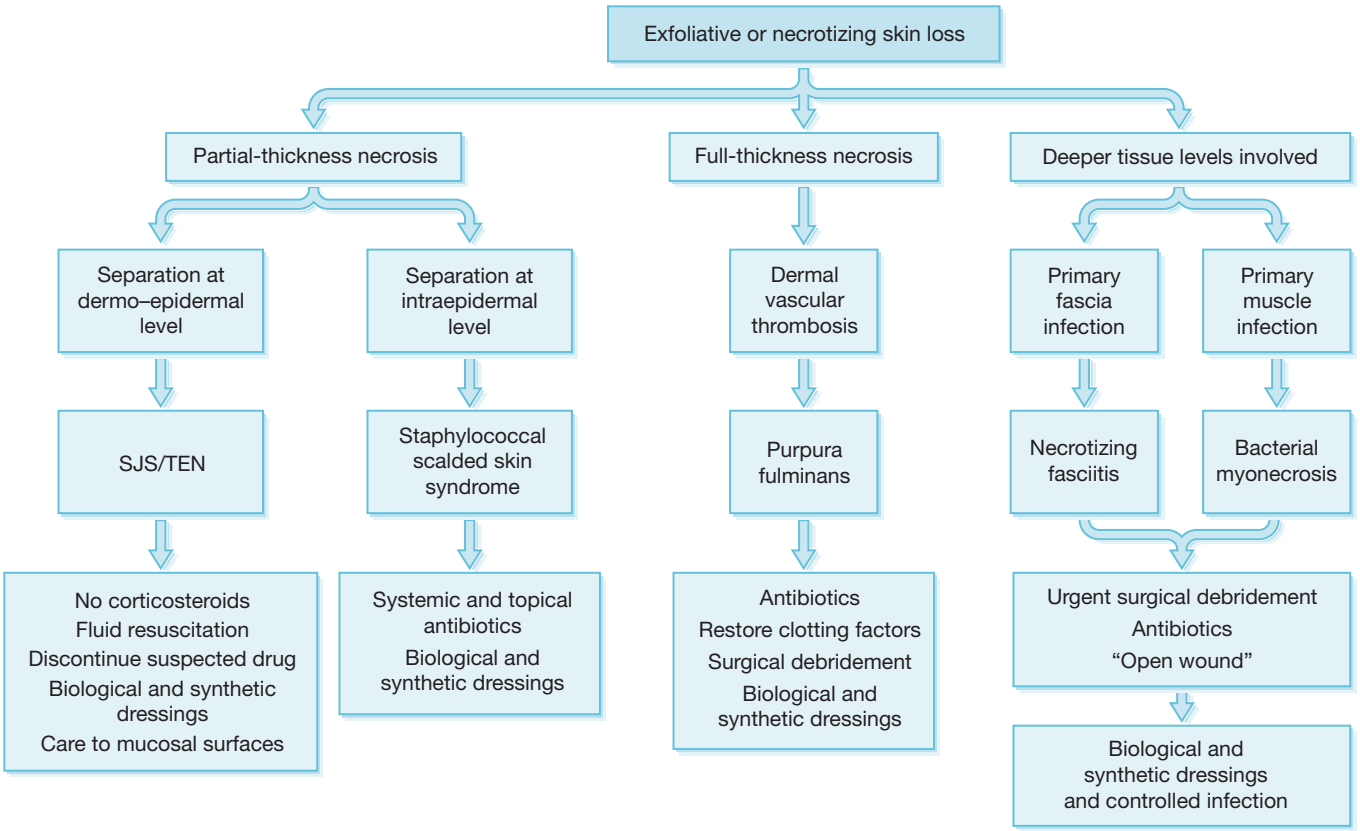

Fig. 42.7 Flowchart of management of exfoliative and necrotizing conditions of the skin.

effects to antibiotic treatment.[131] In summary, hyperbaric oxygen therapy, if available, should not delay radical surgical débridement and should be used as an adjunct to radical surgery and antibiotic therapy.[129,132]

PURPURA FULMINANS

Purpura fulminans is a term that describes an acute syndrome of rapidly progressive hemorrhagic necrosis of the skin due to dermal vascular thrombosis associated with vascular collapse and disseminated intravascular coagulation (DIC).[133] It may occur in individuals with dysfunction of the protein C anticoagulant system, with acute severe infection, or idiopathically without any coagulation dysfunction or infection.

It has been associated with systemic infection by *Meningococcus*, Gram-negative bacilli, *Staphylococcus*, *Streptococcus*, and *Rickettsia* organisms. Skin necrosis begins in a region of dermal discomfort, which rapidly progresses to evanescent flush, followed by petechiae. Hemorrhagic bullae progress to frank skin necrosis. The process generally involves the skin and subcutaneous tissues, without involvement of muscle. Skin involvement is frequently an early manifestation of the disease process. Skin biopsy will therefore allow an earlier diagnosis. Mortality in the acute phase is 18–40%.[134]

Management is directed at halting progression of the underlying infectious disease, preventing secondary infections, and removing nonviable tissue. Early heparin administration and replacement of clotting factors have proved useful to stop intravascular clotting.[134] Shock from blood extravasation and sepsis require extensive volume replacement. Limb vascular and compartmental pressure should be monitored closely to enable early escharotomy and/or fasciotomy, when needed. Skin lesions resulting only in blisters should be treated with topical antimicrobials (e.g., silver sulfadiazine) to prevent secondary infection. Nonviable tissue should be removed as soon as the patient's condition allows. Small areas can be covered with autografts but because large areas are frequently involved, allograft or xenograft skin coverage may be required. Limb amputations may be frequently required due to vascular compromise, as well as revisions for progression of disease.[135] Isolation of the affected patient, as well as monitoring and prophylactic treatment of patients and staff, may be necessary to prevent further spread and outbreaks of the disease, especially in the case of meningococcal infection.

CALCIPHYLAXIS

Calciphylaxis is a rare condition that is characterized by the development of extraskeletal calcifications resulting in tissue necrosis. Although the exact etiology is unknown, the condition appears to be most commonly associated with disorders that alter calcium/phosphate homeostasis. Thus the condition is usually diagnosed in individuals undergoing renal replacement therapy or who have recently undergone renal transplantation. Despite the close association with renal failure, Nigwekar et al. have identified a subgroup of individuals with the same pathological condition but without end-stage renal failure and coined the term "nonuremic calciphylaxis" (Fig. 42.8, Box 42.1).[136]

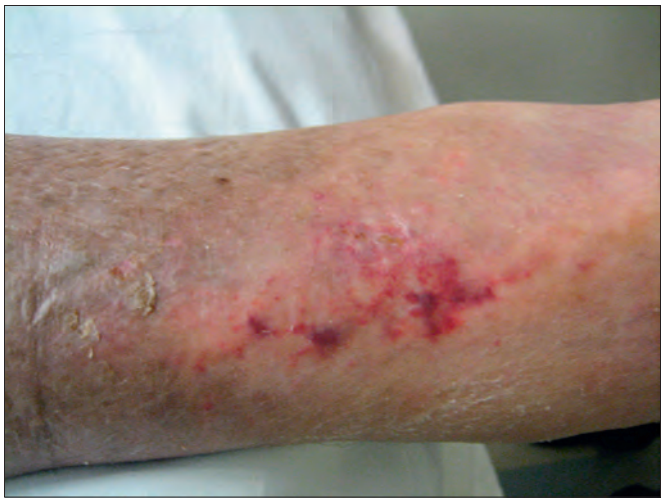

Fig. 42.8 Early calciphylaxis lesion. (Courtesy of Dr. Shawn Fagan.)

Box 42.1 Conditions Associated With Non-Uremic Calciphylaxis

- Primary hyperparathyroidism
- Breast cancer + chemotherapy
- Liver cirrhosis
- Cholangiocarcinoma
- Crohn's disease
- Rheumatic arthritis
- Systemic lupus erythematosus

First described by Bryant and White in 1898 and later investigated by Selye in 1962, it was not until 1976 that the true clinical significance of the syndrome was formally recognized by Gipstein et al. The clinical syndrome of calciphylaxis is characterized by:[137,138] (1) painful purpuric cutaneous lesions (Fig. 42.9), (2) histological evidence of systemic medial calcifications of arteries (tunica media), and (3) histological evidence of small-vessel mural calcification with or without endovascular fibrosis leading to vascular thrombosis and tissue necrosis.

As previously stated, the exact pathophysiology of calciphylaxis is unknown, although the best theory was offered by Selye et al. in 1962. Utilizing a rat model, he suggested that calciphylaxis was a condition of hypersensitivity caused by exposure to "sensitizing agents" (nephrectomy/parathyroid hormone) and "challengers" (egg albumin/metallic salts) over a defined period of time. Simply stated, calciphylaxis appears to be a clinical syndrome induced by a series of events that predispose the patient to extraskeletal calcifications. Most recently, Nigwekar et al. have suggested that the matrix protein GLA(MPG) may serve as a biomarker.[139] MPG is found in the walls of blood vessels and cartilage and functions to prevent calcium buildup. It requires activation by vitamin K to function well, and it is hypothesized that normal activation is impaired in calciphylaxis. Further studies are required to solidify the role of MPG in calciphylaxis, but the work appears promising.

Clinically, calciphylaxis affects approximately 1–4% of the population with underlying end-stage renal disease.[140]

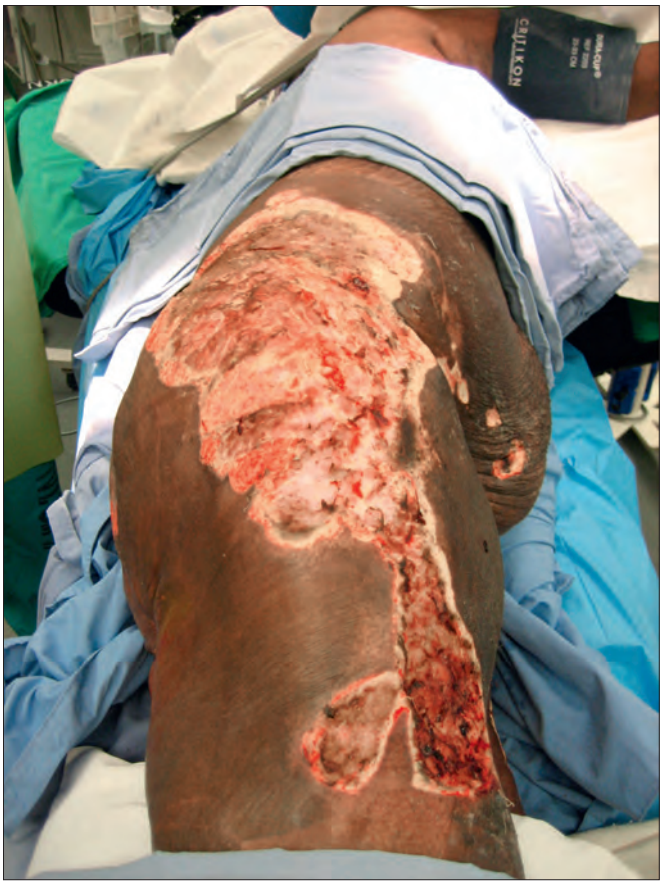

Fig. 42.9 Proximal calciphylaxis. (Courtesy of Dr. Shawn Fagan.)

The condition has been reported in age groups ranging from 6 months to 83 years of age. The condition appears to affect predominantly Caucasian women, with a female to male ratio of 3:1. Unfortunately the mortality rate associated with calciphylaxis is as high as 60–80% and appears to be related to the distribution of cutaneous lesions. Distal lesions have a reported mortality rate of 42%, whereas more proximal lesions (trunk, abdomen, buttocks, and proximal extremities) have a reported mortality rate approaching 72%. The association between mortality rates and lesion distribution may in fact be related to the degree of systemic involvement. The overall mortality rate from calciphylaxis appears to be closely related to the extent of internal organ involvement and development of sepsis from infected cutaneous lesions.

The diagnosis of calciphylaxis should be suspected in any patient with painful cutaneous lesions and a history supportive of the clinical syndrome. Although diagnostic lab testing and imaging are not helpful, the diagnosis can be formally established with a tissue biopsy.

Once the diagnosis is established, the treatment should be initiated using a multidisciplinary approach. The treatment should be based on improving the underlying condition, such as reformulation in hemodialysis or potentially administering sodium thiosulfate, which acts as an antioxidant and chelator of cations. Unfortunately, despite the best medical efforts, treatment usually becomes supportive from an analgesic and wound standpoint. Wound management should be aggressive to avoid local wound infections. The primary goal is to establish a healthy wound bed without evidence of disease progression prior to definitive closure.

Conclusion

Inflammatory and infectious conditions of the skin and underlying tissues represent a major diagnostic and therapeutic challenge. The team approach to their care is essential, and wound management is paramount. Burn centers are ideally suited to deal with patients with these conditions and should be considered as the appropriate site of referral for these critically ill patients.

Complete references available online at
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Further Reading

Becker DS. Toxic epidermal necrolysis. *Lancet*. 1998;351:1417-1420.
Cartotto R, Mayich M, Nickerson D, et al. SCORTEN accurately predicts mortality among toxic epidermal necrolysis patients treated in a burn center. *J Burn Care Res*. 2008;29(1):141-146.
Koh MJ, Tay YK. An update on Stevens–Johnson and toxic epidermal necrolysis in children. *Curr Opin Pediatr*. 2009;21:505-510.
Weenig RH, Sewell LD, Davis MD, et al. Calciphylaxis: natural history, risk factors, outcome. *J Am Acad Dermatol*. 2009;61(1):73-79.
Wilkins J, Morrison L, White CR. Oculocutaneous manifestations of the erythema multiforme/Stevens–Johnson syndrome/toxic epidermal necrolysis spectrum. *Dermatol Clin*. 1992;10:571-582.

References

1. Becker DS. Toxic epidermal necrolysis. *Lancet*. 1998;351:1417-1420.
2. Rasmussen JE. Erythema multiforme. Should anyone care about the standards of care? *Arch Dermatol*. 1995;131:726-729.
3. Patterson R, Dykewicz MS, Gonzales A, et al. Erythema multiforme and Stevens–Johnson syndrome: descriptive and therapeutic controversy. *Chest*. 1990;98:331-336.
4. Wilkins J, Morrison L, White CR. Oculocutaneous manifestations of the erythema multiforme/Stevens–Johnson syndrome/toxic epidermal necrolysis spectrum. *Dermatol Clin*. 1992;10:571-582.
5. Chan HC, Stern RS, Arndt KA, et al. The incidence of erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis. *Arch Dermatol*. 1990;126:43-47.
6. Roujeau JC, Guillaume JC, Fabre JP, et al. Toxic epidermal necrolysis (Lyell syndrome): incidence and drug etiology in France, 1981–1985. *Arch Dermatol*. 1990;126:37-42.
7. Schoepf E, Stuehmer A, Rzany B, et al. Toxic epidermal necrolysis and Stevens–Johnson syndrome: an epidemiologic study from West Germany. *Arch Dermatol*. 1991;127:839-842.
8. Naldi L, Locasti F, Marchesi L, et al. Incidence of toxic epidermal necrolysis in Italy. *Arch Dermatol*. 1990;126:1103-1104.
9. Strom BL, Carson JL, Halpern AC, et al. A population-based study of Stevens–Johnson syndrome: incidence and antecedent drug exposures. *Arch Dermatol*. 1991;127:831-838.
10. La Grenade L, Lee L, Weaver J, et al. Comparison of reporting of Steven Johnson syndrome and toxic epidermal necrolysis in association with selective COX-2 inhibitors. *Drug Saf*. 2005;28:917-924.
11. Rzany B, Correla O, Kelly JP, et al. Risk of Stevens Johnson syndrome and toxic epidermal necrolysis during the first weeks of antiepileptic therapy: a case control study on severe cutaneous adverse reactions. *Lancet*. 1999;353:2190-2194.
12. Chan HL. Toxic epidermal necrolysis in Singapore, 1989 through 1993: incidence and antecedent drug exposure. *Arch Dermatol*. 1995;333:1600-1607.
13. Halebian P, Corder V, Herndon D, et al. A burn center experience with toxic epidermal necrolysis. *J Burn Care Rehabil*. 1983;4:176-183.
14. Prendiville JS, Hebert AA, Greenwald MJ, et al. Management of Stevens–Johnson syndrome and toxic epidermal necrolysis in children. *J Pediatr*. 1987;115:881-887.
15. Kim PS, Goldfarb IW, Gaisford JC, et al. Stevens–Johnson syndrome and toxic epidermal necrolysis: a pathophysiologic review with recommendations for a treatment protocol. *J Burn Care Rehabil*. 1983;4:91-100.
16. Roujeau JC, Chosidow O, Saiag P, et al. Toxic epidermal necrolysis (Lyell syndrome). *J Am Acad Dermatol*. 1990;23:1039-1058.
17. Revuz J, Penson D, Roujeau JC, et al. Toxic epidermal necrolysis: clinical findings and prognostic factors in 87 patients. *Arch Dermatol*. 1987;123:1160-1166.
18. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Steven Johnsons syndrome or toxic epidermal necrolysis. *N Engl J Med*. 1995;333:1600-1607.
19. Goldstein SM, Wintroub BW, Elias PM, et al. Toxic epidermal necrolysis: unmuddying the waters. *Arch Dermatol*. 1987;123:1153-1155.
20. Widgerow AD. Toxic epidermal necrolysis – management issues and treatment options. *Int J Burn Trauma*. 2011;1(1):42-50.
21. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. *J Am Acad Dermatol*. 2013;69(2):187e1-187e16.
22. Revuz J, Roujeau JC, Guillaume JC, et al. Treatment of toxic epidermal necrolysis: Creteil's experience. *Arch Dermatol*. 1987;123:1156-1158.
23. Murphy JT, Purdue GF, Hunt JL. Toxic epidermal necrolysis. *J Burn Care Rehabil*. 1997;18:417-420.
24. Scully MC, Frieden IJ. Toxic epidermal necrolysis in early infancy. *J Am Acad Dermatol*. 1992;27:340-344.
25. Bastuji-Garin S, Fouchard N, Bertocchi M, Foujeau JC, Revuz J. Wokenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol*. 2000;115:149-153.
26. Beck A, Quirke KP, Gamelli RL, Mosier MJ. Pediatric toxic epidermal necrolysis: using SCORTEN and predictive models to predict morbidity when a focus on mortality is not enough. *J Burn Care Res*. 2015;36(1):167-177.
27. Von Wild T, Stollwerck PL, Namdar T, et al. Are multimorbidities underestimated in scoring systems of Steven-Johnson syndrome and toxic epidermal necrolysis like in SCORTEN? *E plasty*. 2012;12:321-331.
28. Cartotto R, Mayich M, Nickerson D, et al. SCORTEN accurately predicts mortality among toxic epidermal necrolysis patients treated in a burn center. *J Burn Care Res*. 2008;29(1):141-146.
29. Ruiz-Maldonado R. Acute disseminated epidermal necrosis type 1, 2 and 3: study of sixty cases. *J Am Acad Dermatol*. 1985;13:623-635.
30. Guillaume JC, Roujeau JC, Revuz J, et al. The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell syndrome). *Arch Dermatol*. 1987;123:1166-1170.
31. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med*. 1995;333:1600-1607.
32. Sassolas B, Haddad C, Mockenhaupt M, et al. ALDEN, an algorithm for assessment of drug causality in Stevens Johnson syndrome and toxic epidermal necrolysis: comparison with case control analysis. *Clin Pharm Ther*. 2010;88:60-68.
33. Mockenhaupt M, Viboud C, Dunant A, et al. Steven Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The Euro-SCAR-study. *J Invest Dermatol*. 2008;128:35-44.
34. Halebian PH, Madden MR, Finkestein JL, et al. Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. *Ann Surg*. 1986;204:503-511.
35. McGee T, Munster A. Toxic epidermal necrolysis syndrome: mortality rate reduced with early referral to regional burn center. *Plast Reconstr Surg*. 1998;102:1018-1022.
36. Yetin J, Bianchini JR, Owens JA. Etiological factors in Stevens–Johnson syndrome. *South Med J*. 1980;73:599-602.
37. Howland WW, Golitz LE, Weston WL, et al. Erythema multiforme: clinical histopathologic, and immunologic study. *J Am Acad Dermatol*. 1984;10:438-446.
38. Avakian R, Flowers FP, Araulo OE, et al. Toxic epidermal necrolysis: a review. *J Am Acad Dermatol*. 1991;25:69-79.
39. Kohanim S, Palioura S, Saeed HN, et al. Stevens-Johnson syndrome/toxic epidermal necrolysis – A comprehensive review and guide to therapy. I. systemic disease. *Ocul Surf*. 2016;14(1):2-19.
40. Dodiuk-Gad RP, Chung WH, Valeyrie-Allanore L, Shear NH. Stevens-Johnson and toxic epidermal necrolysis: an update. *Am J Clin Dermatol*. 2015;16(6):475-493.
41. Dodiuk-Gad RP, Olteanu C, Chung WH, Shear HN. The 9th International Congress on Cutaneous Adverse Drug Reactions at the 23rd World Congress of Dermatology in Vancouver, 2015. *Drug Saf*. 2016;39(3):271-276.
42. Chung WH, Chang WC, Lee YS, et al. Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. *JAMA*. 2014;312(5):525-534.
43. Kevsavan R, Narayan SK, Adithan C. Influence of CYP2C9 and CYP2C19 genetic polymorphisms on phenytoin-induced neurological toxicity in Indian epileptic patients. *Eur J Clin Pharmacol*. 2010;66(7):689-696.
44. Depondt C, Godard P, Espel RS, et al. A candidate gene study of antiepileptic druy tolerability and efficacy indentifies an association of CYP2C9 variants with phenytoin toxicity. *Eur J Neurol*. 2011;18(9):1159-1164.
45. Borgiani P, Di Fusco D, Erba F, et al. HCP5 genetic variant (RS3099844) contributes to nevirapine-induced Stevens Johnson syndrome/toxic epidermal necrolysis susceptibility in a population from Mozambique. *Eur J Clin Pharmacol*. 2014;70(3):275-278.
46. Ciccacci C, Di Fusco D, Marazzi MC, et al. Association between CYP2B6 polymorphisms and nevirapine-induced SJS/TEN: a pharmacogenetic study. *Eur J Clin Pharmacol*. 2013;69(1):1909-1916.
47. Pichler WJ, Beeler A, Keller M, et al. Pharmacological interaction of drugs with immune receptors: the p-I concept. *Allergol Int*. 2006;55(1):17-25.
48. Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Steven Johnson syndrome. *Nature*. 2004;428:486.
49. Tassaneeyakul W, Tiamkao S, Jantararoungtong T, et al. Association between HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population. *Epilepsia*. 2010;51:926-930.
50. Alfirevic A, Jorgensen AL, Williamson PR, et al. HLA-B locus in Caucasian patients with carbamazepine hypersensitivity. *Pharmacogenomics*. 2006;7:813-818.
51. Kaniwa N, Saito Y, Aihara M, et al. HLA-B locus in Japenese patients with anti-epileptics and allopurinol-related Steven Johnson

syndrome and toxic epidermal necrolysis. *Pharmacogenomics*. 2008; 9:1617-1622.
52. Lonjou C, Thomas L, Borot N, et al. A marker of Steven Johnson syndrome...ethnicity matters. *Pharmagenomics J*. 2006;6:265-268.
53. Lonjou C, Borot N, Sekula P, et al. A European study of HLA-B in Steven-Johnson syndrome and toxic epidermal necrolysis related to five high risk drugs. *Pharmacogenet Genomics*. 2008;18:99-107.
54. Hung SI, Chung WH, Liou LB, et al. HLA-b*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci USA*. 2005;102:4134-4139.
55. Chung WH, Hung SI. Recent advances in the genetics and immunology of Steven-Johnson syndrome and toxic epidermal necrolysis. *J Dermatol Sci*. 2012;66(3):190-196.
56. Miyauchi H, Hosokawa H, Akaeda T, et al. T-cell subsets in drug-induced toxic epidermal necrolysis. *Arch Dermatol*. 1991;127:851-855.
57. Heng MC, Allen SG. Efficiency of cyclophosphamides in toxic epidermal necrolysis: clinical and pathophysiologic aspects. *J Am Acad Dermatol*. 1991;25:778-786.
58. Leyva L, Torres MJ, Posadas S, et al. Anticonvulsant-induced toxic epidermal necrolysis: monitoring the immunologic response. *J Allergy Clin Immunol*. 2000;105:157-165.
59. Correia O, Delgado L, Roujeau JC, Le Cleach L, Fleming-Torrinha JA. Soluble interleukin 2 receptor and interleukin 1alpha in toxic epidermal necrolysis: a comparative analysis of serum and blister fluid samples. *Arch Dermatol*. 2002;138(1):29-32.
60. Le Cleach L, Delaire S, Boumsell L, et al. Blister fluid T lymphocytes during toxic epidermal necrolysis are functional cytotoxic cells which express human natural killer (NK) inhibitory receptors. *Clin Exp Immunol*. 2000;199(1):225-230.
61. Nassif A, Bensussan A, Dorothee G, et al. Drug specific cytotoxic T-cells in the skin lesions of a patient with toxic epidermal necrolysis. *J Invest Dermatol*. 2002;118(4):728-733.
62. Lerch M, Pichler WJ. The immunological and clinical spectrum of delayed drug-induced exanthems. *Curr Opin Allergy Clin Immunol*. 2004;4(5):411-419.
63. Merot Y, Gravallese E, Guillen FJ, et al. Lymphocyte subsets and Langerhans' cells in toxic epidermal necrolysis. *Arch Dermatol*. 1986;122:455-458.
64. Paquet P, Nikkels A, Arrese JE, Vanderkelen A, Pierard GE. Macrophages and tumor necrosis factor alpha in toxic epidermal necrolysis. *Arch Dermatol*. 1994;130(5):605-608.
65. Paquet P, Paquet F, Al Saleh W, et al. Immunoregulatory effector cells in drug- induced toxic epidermal necrolysis. *Am J Dermatopathol*. 2000;22(5):413-417.
66. Paul C, Wolkenstein P, Adle H, et al. Apoptosis as a mechanism of keratinocyte death in toxic epidermal necrolysis and Stevens–Johnson syndrome. *Br J Dermatol*. 1996;134:710-714.
67. Haake AR, Polaskowska RR. Cell death by apoptosis and epidermal biology. *J Invest Dermatol*. 1993;101:107-112.
68. Viard I, Wehrli P, Bullani R, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science*. 1998;282(6):490-493.
69. Inachi S, Muizutani H, Shimuzu M. Epidermal apoptotic cell death in erythema multiforme and Stevens–Johnson syndrome. Contribution of perforin positive cell infiltration. *Arch Dermatol*. 1997;133:845-849.
70. Revuz J, Penso D, Roujeau J, et al. Toxic epidermal necrolysis: clinical findings and prognosis factors in 87 patients. *Arch Dermatol*. 1987;123:1160-1165.
71. Rasmussen J. Toxic epidermal necrolysis. *Med Clin N Am*. 1980; 64:901-920.
72. Villada G, Roujeau JC, Clerici T, et al. Immunopathology of toxic epidermal necrolysis. Keratinocytes, HLA-DR expression, Langerhans cells and mononuclear cells: an immunopathologic study of five cases. *Arch Dermatol*. 1992;128:50-53.
73. Hertl M, Merk HF, Bohlen H. T-cell subsets in drug-induced toxic epidermal necrolysis. *Arch Dermatol*. 1992;128:272.
74. Roujeau JC, Huynh TN, Bracq C, et al. Genetic susceptibility to toxic epidermal necrolysis. *Arch Dermatol*. 1987;123:1171-1173.
75. Magina S, Lisboa C, Leal V, Palmares J, Mesquita-Guimaraes J. Dermatological and opthalmological sequels in toxic epidermal necrolysis. *Dermatology*. 2003;207:33-36.
76. Kohanim S, Palioura S, Saeed HN, et al. Acute and chronic ophthalmic involvement in Steven-Johnson syndrome/toxic epidermal necrolysis – A comprehensive review and guide to therapy. II. Ophthalmic disease. *Ocul Surf*. 2016;14(2):168-188.
77. Roujeau JC, Philippoteau C, Koso M, et al. Sjögren-like syndrome following toxic epidermal necrolysis. *Lancet*. 1985;1:609-611.
78. Wahle D, Beste D, Conley SF. Laryngeal involvement in toxic epidermal necrolysis. *Otolaryngol Head Neck Surg*. 1992;6:796-799.
79. Lebargy F, Wolkenstein P, Gisselbrecht M, et al. Pulmonary complications in toxic epidermal necrolysis: a prospective clinical study. *Intensive Care Med*. 1997;23:1237-1244.
80. Chosidow O, Delchier JC, Chaumette MT. Intestinal involvement in drug-induced toxic epidermal necrolysis. *Lancet*. 1991;337:928.
81. Lyell A. Toxic epidermal necrolysis (the scalded skin syndrome): a reappraisal. *Br J Dermatol*. 1979;100:69-86.
82. Meneux E, Paniel BJ, Pouget F, et al. Vulvovaginal sequelae in toxic epidermal necrolysis. *J Reprod Med*. 1997;42:153-156.
83. Meneux E, Wolkenstein P, Haddad B, et al. Vulvovaginal involvement in toxic epidermal necrolysis: a retrospective study of 40 cases. *Obstet Gynecol*. 1998;91:283-287.
84. El Daief SG, Das S, Ekekwe G, Nwosu EC. A successful pregnancy outcome after Stevens-Johnson Syndrome. *J Obstet Gynaecol*. 2014;34(5):445-446.
85. Rowan DM, Jones RW, Oakley A, De Silva H. Vaginal stenosis after toxic epidermal necrolysis. *J Low Genit Tract Dis*. 2010;14(4):390-392.
86. Niemeijer IC, van Praag MC, van Gemund N. Relevance and consequences of erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in gynecology. *Arch Gynecol Obstet*. 2009;280(5):851-854.
87. Krumlovsky F, Del Greco F, Herdson P, et al. Renal disease associated with toxic epidermal necrolysis (Lyell's disease). *Am J Med*. 1974;57:817-825.
88. Roujeau JC, Moritz S, Guillaume JC, et al. Lymphopenia and abnormal balance of T-lymphocyte subpopulation in toxic epidermal necrolysis. *Arch Dermatol Res*. 1985;277:24-27.
89. Adzick NS, Kim SH, Bondoc CC, et al. Management of toxic epidermal necrolysis in a pediatric burn center. *Am J Dis Child*. 1985;139:499-502.
90. Heimbach DM, Engrav LH, Marvin JA, et al. Toxic epidermal necrolysis: a step forward in treatment. *JAMA*. 1987;257:2171-2175.
91. Taylor JA, Grube B, Heimbach DM, et al. Toxic epidermal necrolysis: a comprehensive approach. *Clin Pediatr*. 1989;28:404-407.
92. Paller AS, Nelson A, Steffen L, et al. T-lymphocyte subset in the lesional skin of allogenic and autologous bone marrow transplant patients. *Arch Dermatol*. 1988;124:1795-1801.
93. Ginsburg CM. Stevens–Johnson syndrome in children. *Pediatr Infect Dis*. 1982;1:155-158.
94. Rasmussen JE. Cause, prognosis and management of toxic epidermal necrolysis. *Compr Ther*. 1990;16:3-6.
95. Guibal F, Bastuji-Garin S, Chosidow O, et al. Characteristics of toxic epidermal necrolysis in patients undergoing long-term glucocorticoid therapy. *Arch Dermatol*. 1995;131:669-672.
96. Rzany B, Schmitt H, Schoepf E. Toxic epidermal necrolysis in patients receiving glucocorticosteroids. *Acta Derm Venereol*. 1991;71:171-172.
97. Kardaun SH, Jonkman MF. Dexamethasone pulse therapy for Steven Johnson syndrome/toxic epidermal necrolysis. *Acta Derm Venereol*. 2007;87:144-148.
98. Schneck J, Fagot JP, Sekula P, et al. Effects of treatments on the mortality of Steven Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR Study. *J Am Acad Dermatol*. 2008;58:33-40.
99. Arevalo JM, Lorente JA, Gonazlez-Herrada C, et al. Treatment of toxic epidermal necrolysis with cyclosporin A. *J Trauma*. 2000;48(3):473-478.
100. Valleyrie-Allanore L, Wolkenstein P, Brochard L, et al. Open trail of ciclosporin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis. *Br J Dermatol*. 2010;163(4):847-853.
101. Chave TA, Mortimer NJ, Sladden MJ, et al. Toxic epidermal necrolysis: current evidence, practical management and future directions. *Br J Dermatol*. 2005;153(2):241-253.
102. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens–Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. *Arch Dermatol*. 2003;139(1):33-36.
103. Shortt R, Gomez M, Mittman N, et al. Intravenous immunoglobulin does not improve outcome in toxic epidermal necrolysis. *J Burn Care Rehabil*. 2004;25(3):246-255.

104. Stella M, Cassano P, Bollero D, et al. Toxic epidermal necrolysis treated with intravenous high-dose immunoglobulins: our experience. *Dermatology*. 2001;203(1):45-49.
105. Prins C, 2003, Effect of high-dose intravenous immunoglobulin therapy in Stevens-Johnson syndrome: a retrospective, multicenter study. REPEAT – Harr T, French LE. Toxic epidermal necrolysis and stevens-johnson syndrome. *Orphanet Journal of Rare Disease* 2010;5:39.
106. Huang YC, Li YC, Chen TJ. The efficacy of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis: a systemic review and meta-analysis. *Br J Dermatol*. 2012;167:424-432.
107. Wolkenstein P, Latarjet J, Roujeau JC, et al. Randomised comparison of thalidomide versus placebo in toxic epidermal necrolysis. *Lancet*. 1998;352(9140):1586-1589.
108. Sowder LL. Biobrane wound dressing used in the treatment of toxic epidermal necrolysis: a case report. *J Burn Care Rehabil*. 1990;11:237-239.
109. Roujeau JC. Treatment of severe drug eruptions. *J Dermatol*. 1999;26:718-722.
110. Halebian PH, Shires GT. Burn unit treatment of acute, severe exfoliating disorders. *Ann Rev Med*. 1989;40:137-147.
111. Fischer M, Fiedler E, Marsch WC, Wohlrab J. Antitumour necrosis factor-alpha-antibiodies(infliximab) in the treatment of a patient with toxic epidermal necrolysis. *Br J Dermatol*. 2002;146:707-709.
112. Marvin JA, Heimbach DM, Engrav LH, et al. Improved treatment of the Stevens–Johnson syndrome. *Arch Surg*. 1984;119:601-605.
113. Birchall N, Langdon R, Cuono C, et al. Toxic epidermal necrolysis: an approach to management using cryopreserved allograft skin. *J Am Acad Dermatol*. 1987;16:368-372.
114. Kaser DJ, Reichman DE, Laufer MR. Prevention of vulvovaginal sequelae in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Rev Obstr Gynecol*. 2011;4(2):81-85.
115. Tomlins P, Parulekar M, Rauz S. "Triple-TEN" in the Treatment of Acute Ocular Complications From Toxic Epidermal Necrolysis. *Cornea*. 2013;32(3):365-369.
116. Resnick SD. Staphylococcal toxin-mediated syndromes in childhood. *Semin Dermatol*. 1992;11:11-18.
117. Canoso JJ, Barza M. Soft tissue infections. *Rheum Dis Clin North Am*. 1993;15:235-239.
118. Elias PM, Fritsch P, Epstein EH. Staphylococcal scalded skin syndrome: clinical features, pathogenesis, and recent microbiological and biochemical developments. *Arch Dermatol*. 1977;113:207-219.
119. Dancer SJ, Garratt R, Sanhanha J, et al. The epidermolytic toxins are serine proteases. *FEBS Lett*. 1990;268:129-132.
120. Vath GM, Earhart CA, Rago JV, et al. The structure of the superantigen exfoliative toxin A suggests a novel regulation as a serine protease. *Biochemistry*. 1997;36:1559-1566.
121. Itani O, Crump R, Minouni F, et al. Ritter's disease (neonatal staphylococcal scalded skin syndrome). *Am J Dis Child*. 1992;146:425-426.
122. Patino JF, Castro D. Necrotizing lesions of soft tissue: a review. *World J Surg*. 1991;15:235-239.
123. Steven DL. Invasive group A streptococcal infections. *Clin Infect Dis*. 1992;14:2-13.
124. Francis KR, Lamaute HR, Davis JM, et al. Implications of risk factors in necrotizing fasciitis. *Am J Surg*. 1993;59:304-308.
125. Sharif HS, Clark DC, Aabed MY, et al. MR imaging of thoracic and abdominal wall infections: comparison with other imaging procedures. *AJR Am J Roentgenol*. 1990;154:989-995.
126. Stamenkovic I, Lew PD. Early recognition of potentially fatal necrotizing fasciitis: the use of frozen-section biopsy. *N Engl J Med*. 1984;310:1689-1693.
127. Freischlag JA, Ajalat G, Busuttil RW. Treatment of necrotizing soft tissue infection: the need for a new approach. *Am J Surg*. 1985;149:751-757.
128. Kaiser RE, Cerra FB. Progressive necrotizing surgical infections: a unified approach. *J Trauma*. 1981;24:349-352.
129. Green RJ, Dafoe DC, Raffin TA. Necrotizing fasciitis. *Chest*. 1996;110:219-229.
130. Risemann JA, Zamboni WA, Curtis A, et al. Hyperbaric oxygen therapy for necrotizing fasciitis reduces mortality and the need for debridement. *Surgery*. 1990;108:847-850.
131. Zamboni WA, Mazolewski PJ, Erdmann D, et al. Evaluation of penicillin and hyperbaric oxygen in the treatment of streptococcal myositis. *Ann Plast Surg*. 1997;39:131-136.
132. McHenry CR, Piotrowski JJ, Petrinic D, et al. Determinants of mortality for necrotizing soft-tissue infections. *Ann Surg*. 1995;221:558-565.
133. Adcock DM, Hicks MJ. Dermatopathology of skin necrosis associated with purpura fulminans. *Semin Thromb Hemost*. 1990;16:283-292.
134. Chasan PE, Hansbrough JF, Cooper ML. Management of cutaneous manifestations of extensive purpura fulminans in a burn unit. *J Burn Care Rehabil*. 1992;13:410-413.
135. Genoff MC, Hoffer MM, Achauer B, et al. Extremity amputation in meningococcemia induced purpura fulminans. *Plast Reconstr Surg*. 1992;89:878-881.
136. Nigwekar SU, Wolf M, Sterns RH, et al. Calciphylaxis from nonuremic causes: a systematic review. *Clin J Am Soc Nephrol*. 2008;3(4):1139-1143.
137. Gipstein RM, Coburn JW, Adams DA, et al. Calciphylaxis in man. A syndrome of tissue necrosis are in 11 patients with chronic renal failure. *Arch Intern Med*. 1976;136(11):1273-1280.
138. Selye H. *Calciphylaxis*. Chicago: University of Chicago Press; 1962.
139. Nigwekar SU, Kroshinksy D, Thadhani R. Calciphylaxis: risk factors, diagnosis, and treatment. *Am J Kidn Dis*. 2015;66(1):133-146.
140. Weenig RH, Sewell LD, Davis MD, et al. Calciphylaxis: natural history, risk factors, outcome. *J Am Acad Dermatol*. 2009;61(1):73-79.

43 Burn Injuries of the Eye

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ὁ λύχνος τοῦ σώματός ἐστιν ὁ ὀφθαλμός
ὅταν οὖν ὁ ὀφθαλμός σου ἁπλοῦς ᾖ, καὶ ὅλον τὸ σῶμά σου φωτεινόν ἐστιν.
ἐπὰν δὲ πονηρὸς ᾖ, καὶ τὸ σῶμά σου σκοτεινόν

Introduction

Both immediate and delayed presentations exist for eye problems in burned patients. Accordingly, in burns, the structure and function of a normal eye can be disrupted by concurrent blunt or penetrating injury, electrical current, thermal energy, or chemical agents. After the initial insult, foreign bodies, ongoing chemical injury, deterioration of the facial burn wound, infection, and environmental exposure can cause additional damage or progression of existing pathology. Although many providers may view comprehensive eye examination as an esoterica outside their skillset and purview, the frequency and acuity of sight-threatening complications necessitate the burn team learning the basics of eye evaluation.[1]

Selected Anatomy

The organ of sight arises through reciprocal interaction between the optic vesicle (neuroectoderm) and the lens placode (facial ectoderm). The full-thickness neuroectoderm protrudes toward the surface, inducing the primordial lens, and invaginating to form the optic cup. The lens vesicle, separating from the surface ectoderm, induces corneal development.[2] The upper and lower eyelids develop from primordial eyelid folds, fusing transversely from 8 weeks to 5 months, protecting the nascent ocular surface from initial environmental exposure as the fetal urinary system begins to contribute to the amniotic fluid composition.[3,4]

Eyelids are four-layered structures of skin, orbicularis muscle, tarsus with fibrous septae, and palpebral conjunctiva. The skin of the eyelids is thin and elastic in the normal state. Upper eyelid skin folds are formed from terminal skin attachments of underlying levator muscle, which functions with Müller's muscle to open the upper eyelid. The inferior rectus muscle provides analogous function via the capsulopalpebral fascia and inferior tarsus, retracting the lower lid with down-gaze.[5,6] The orbicularis muscle can be divided into pretarsal, preseptal, and orbital segments based on the structure they overlay: tarsus, orbital septum, or orbital rim. The pretarsal and preseptal parts are used in blinking and voluntary winking, while the orbital segments are used in forced closure. Motor innervation is via the zygomatic and temporal branches of the facial nerve. Epidermal appendages, including follicular sebaceous glands (of Zeiss), modified apocrine sweat glands (of Moll), and eyelashes, are located at the anterior margin of the mucocutaneous junction. Posteriorly, the fibrous tarsi harbor the Meibomian glands (about 50 in the upper lid and 25 in the lower lid) that secrete lipid-rich material into the tear film.

The tear film is a trilaminar structure; moving from the ocular surface externally, there is mucus on the cornea and conjunctiva, covered by an aqueous layer, with a lipid layer most externally. A healthy tear film remains stable for at least 10 s and maintains more than 300 μm of meniscus height.[7] The lacrimal gland, located laterally and superiorly in the orbit, produces the aqueous phase of the tear film, along with accessory lacrimal glands (of Krause and Wolfring) located in the superior and inferior fornices. The lipid layer is secreted by the Meibomian glands, stabilizing the tear film and reducing evaporative loss. A complex protein mixture within the tear film confers antimicrobial, inflammatory, and antiinflammatory properties and regulates corneal epithelial cell function.[8]

The conjunctiva covers the inner surface of the eyelids and the anterior sclera, reflecting between the two at the superior and inferior fornices. It is composed of stratified nonkeratinized squamous and columnar cells interspersed with goblet cells upon a continuous basement membrane and lamina propria. Other tissues include accessory lacrimal glands and immune surveillance cells; the lymphatic drainage of the conjunctiva is via the submandibular, parotid, and preauricular nodes. The limbus is the border between the conjunctiva and corneal epithelium. Circumscribing the limbus, the palisades of Vogt harbor the corneal epithelial stem cell niche.[9,10]

The corneal epithelium is approximately 6–7 cell layers (50 μm) tall and composed of stratified squamous epithelium with minimal keratinization. The basal layer is mitotically active and replenishes the more external layers as they are continuously sloughed. The corneal epithelial stem cell niche, at the limbus within the palisades of Vogt, allows reepithelialization when the entire basal layer is lost, as in severe burn injuries or toxic epidermal necrolysis. This mechanism requires cell proliferation and migration from the limbus to the center of the cornea and can take weeks to fully reepithelialize the cornea, compared with days when the basal corneal epithelial layer remains intact. The corneal epithelium produces and rests upon a basement membrane.[11] The layers deep to this basement membrane comprise the corneal stroma. The first 8–12 μm of stroma is called Bowman's membrane and is composed of randomly oriented collagen fibers. The stroma is approximately 500 μm (0.5 mm) thick. Precise arrangement of about 200 collagenous lamellae confers transmittance of visible

light.[12] Fibroblasts and immune surveillance cells populate the stroma. A deep layer, Descemet's membrane, about 10 μm in thickness, provides posterior structural integrity. Upon this membrane rests the corneal endothelium, rich in mitochondria and nonproliferative, which maintains corneal dehydration (and transparency) via active transport of solute into the aqueous. The cornea provides about two-thirds of the refractive power of a normal eye, approximately +40 diopters.

Examination

Eye examination in a burn ICU requires several modifications from the standard clinic setting. Clinicians must adapt to the overall patient condition and support machinery, which may include multiple intravenous and enteral access lines, ventilator and dialysis support, bulky wound dressings, difficult patient positioning, and, frequently, severe comorbid injuries and burns of the face. This is not the "comfort zone" for the ophthalmologist, but the frequency and acuity of comorbid eye involvement necessitate adaptation and innovation.[13] An assessment of visual function can be made with a near vision card, finger counting, or, at a minimum, light perception. Patients with endotracheal tubes can generate various responses, head nod or hand signal, to visual acuity testing under appropriate sedative/analgesic conditions. There are a variety of portable slit lamps that can be employed. Our preference is a handheld lens (20 diopter or equivalent) and penlight. With practice, the penlight may be axially directed through the lens or shone indirectly upon the ocular surface to section through the anterior segment, thereby providing fine detail of stromal and corneal epithelial problems. Loupes provide additive magnification when used with a handheld lens. Topical ocular surface anesthesia is usually employed.

If the injury was associated with an explosion, with flying debris or blunt/penetrating trauma to the eye and periorbita, an open globe injury may result. In this situation, examination must be performed without pressure on the globe until corneal or scleral perforation can be excluded. Pressure applied to an open globe could cause (further) herniation of intraocular contents and detract from potential recovery. If an open globe–suspect injury is identified, pupillary light response and visual acuity should be grossly documented (at least light perception/hand motion/finger counting), photographs obtained, and a shield placed over the eye sufficient to transmit any applied pressure to the osseous orbital rim rather than the orbital contents. Immediate ophthalmological consultation is indicated to evaluate a possible open globe.

Once an open globe injury is excluded, cotton swabs, Desmarres retractors, or an eyelid speculum are useful and often necessary due to facial burns and lid edema. "Swelling" is never an excuse to defer examination of the ocular surface because any delay in the recognition of significant injuries subjects a patient's visual recovery to avoidable jeopardy. Superficial foreign bodies can usually be removed by saline irrigation alone if identified quickly postburn. Fluorescein dye (strips or equivalent) should be available in the burn unit and used if there is any suspicion of corneal or conjunctival pathology.[14] The ocular surface should be irrigated to remove any discharge or ointment. A normal healthy cornea should appear clear and "glassy" with a sharp light reflex. A hazy light reflex can usually be appreciated in early-stage keratopathies. We generally apply dye in a balanced salt solution to the lateral canthus/inferior fornix and then have the patient blink a few times. Next the eye is opened and examined for epithelial irregularities and negative staining. Excess dye is then rinsed away with balanced salt solution. A normal healthy cornea will be devoid of stain; dye retention signifies pathology.[15–20] Areas of confluent, homogeneous stain signify epithelial defect (Fig. 43.1C). "Lacey" staining patterns usually signify epithelial keratopathy (Fig. 43.1B). Early-stage epithelial lesions of exposure and herpetic keratopathies are often difficult to appreciate without the assistance of dye. Adjustable-intensity pocket LED flashlights often have fairly cool light, which sufficiently highlights fluorescein; otherwise, a cobalt-blue filter or near-ultraviolet handheld light can be used. Photographs of findings often allow more comprehensive review while minimizing patient discomfort.

Indirect ophthalmoscopy via adilated pupil is occasionally useful and indicated in the burn unit. In cases of nonaccidental trauma, distinctive retinal lesions may be observed and should be documented with fundus photography for potential medicolegal review.[21] In the first 48–96 hours following carbon monoxide intoxication, cerebral swelling and herniation syndromes are frequently causes of death.[22–24] Funduscopy may show papilledema, which can be graded in severity.[25] In cases where persistently positive blood cultures raise clinical concern for hematogenous seeding, infectious microemboli can occasionally be visualized on thorough funduscopy.[26–29] Similarly there is a spectrum of retinal findings with disseminated candidiasis, defined as *Candida* isolated from three or more sites (urine, sputum, wound, blood, or eye).[30–32] Because choroidal blood flow is much higher than retinal blood flow,[33] these hematogenous lesions more frequently occur within the choroid and are initially observed underlying the retinal layers as gray-white round lesions, rather than occlusive lesions within the retinal vessels proper.[34–37] These lesions, termed chorioretinitis, enlarge as the infection progresses and may erupt into the vitreous.[38-40] This distinction is important because the stage/level of involvement determines treatment choices (ranging from intravenous antimicrobial therapy, intravitreal antimicrobial instillation, to vitrectomy for significant vitreitis).[39–47]

Applied Pathology

Thermal injuries to the eye concurrent with the burning event are, fortunately, rare. The typical presentation is decreased vision, eye pain/foreign body sensation, perilimbal hyperemia, and epithelial defect with fluorescein staining. If detected early, a corneal epithelial lesion, analogous to a blister, may be present and is usually translucent to opaque. Upon sloughing, an underlying epithelial defect of varying depth is apparent.[48] In the setting of closed-space (house) fires, it is difficult to determine whether a corneal injury is thermal or (gaseous) chemical in nature, and copious irrigation is recommended. In addition to tissue

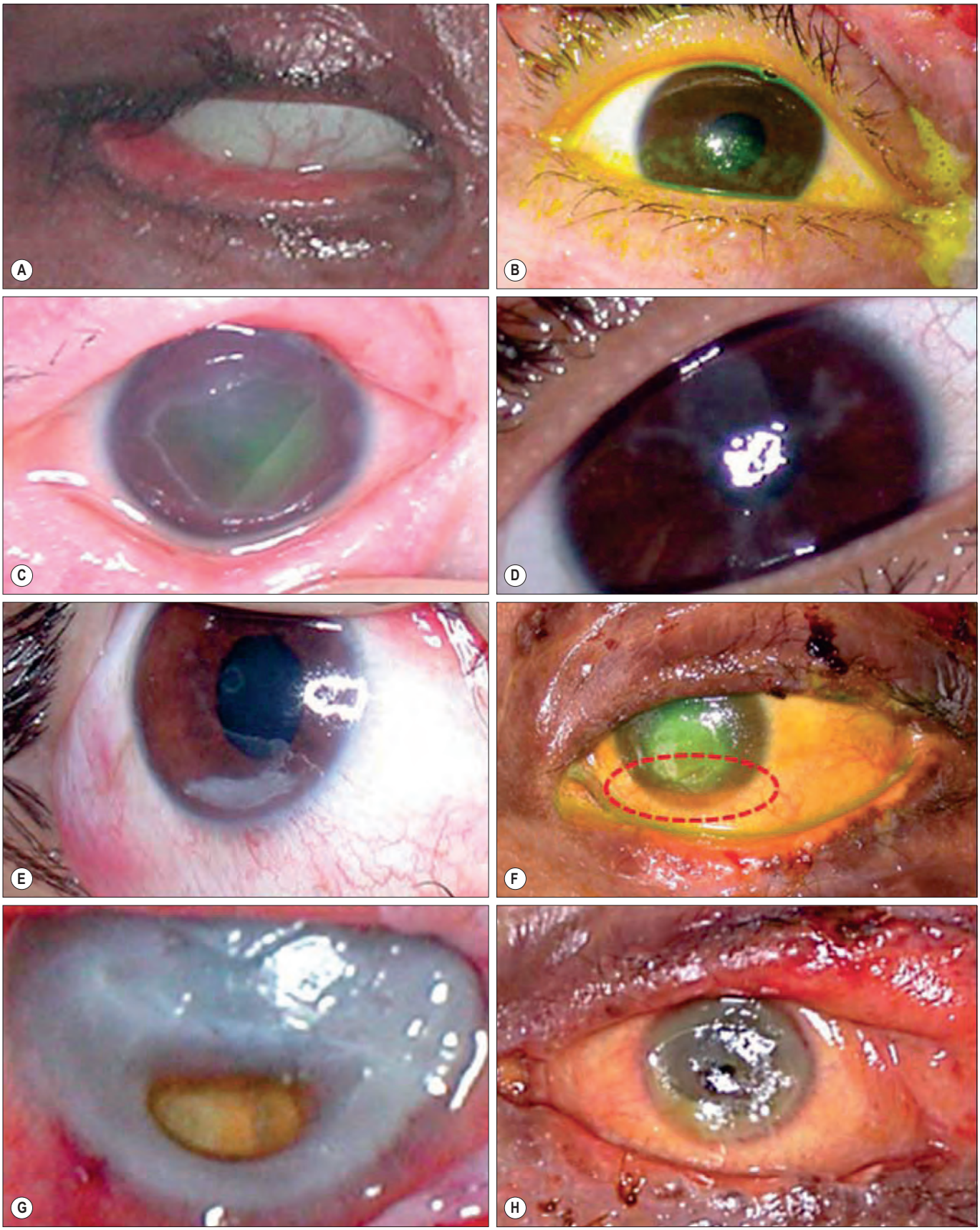

Fig. 43.1 Spectrum of exposure-related ocular surface disease encountered in the burn unit. A, Lagophthalmos. B, Exposure keratopathy. C, Epithelial defect. D, Herpetic keratitis. E, Corneal ulcer. F, Same, with hypopyon. G, Descemetocele. H, Corneal perforation.

destruction, eyelid burns compromise the skin barrier function and predispose to burn wound cellulitis and infection. Development of a preseptal inflammatory process (eyelid swelling, hyperemia, and pain) is frequent after eyelid burn injury, and microbiological cultures help in determining whether this process is sterile or infectious. If infected, it is termed preseptal cellulitis.[49–53] When observed, it is crucially important to evaluate extraocular muscle mobility and function. If the orbital septum is compromised, an orbital cellulitis or abscess may develop, which is an eye-threatening emergency.[54–62] Typical presentation of orbital cellulitis or abscess includes reduced extraocular movements and pain on extraocular muscle testing. Ophthalmological consultation, systemic antimicrobial therapy, and frequent reexamination are indicated. Surgical débridement may be needed for orbital abscess.

Chemical eye injuries are a true ophthalmological emergency.[63–65] Frequent and copious eye irrigation is generally indicated. Solid chemical particles should be removed by irrigation as rapidly as possible with upper and lower lid eversion and examination. Alkali injuries may need prolonged irrigation, up to several hours. Wound pH can be litmus tested, preferably 2–5 minutes after cessation of irrigation as early false-normal results may occur. Insertion of an irrigation aid, such as Morgan lenses, can provide continuous irrigation for several hours; these can also be useful for continuous antibiotic delivery in cases of refractory bacterial keratitis.[66–68]

Patients with Stevens–Johnson syndrome/toxic epidermal necrolysis (TEN) are treated in the burn unit, and eye involvement is seen in more than 60% of these cases. At worst, they present with complete corneal slough, membranous conjunctivitis, and lash auto-epilation (Fig. 43.1C). The natural history is scar formation at involved areas, symblepharon, forniceal shortening, corneal opacification/scarring, mucocutaneous junction loss/keratinization, entropion, and chronic, severe, dry-eye symptoms. Mounting evidence indicates that ocular surface recovery may be hastened, with improvement in vision, by prompt coverage of the ocular surface with amniotic membrane.[69–77] Patients with these conditions should receive definitive treatment at burn units where amniotic membrane transplantation is available and applied immediately when ocular surface involvement is apparent.[70,78]

ELECTRICAL INJURY

As with the systemic response, there are a number of unique ocular aspects of electrical burn injury. Cataract formation following electrical injury has been recognized for more than a half a century.[79–96] While the mechanism is not fully understood, within the lens (and other ocular tissues) there is substantial intercellular electrical coupling.[97–101] These reports note that electrical cataract tends to present within 12 months of the electrical burn event and that visual outcome following cataract extraction can be good in the absence of other eye pathology. Other findings, such as chorioretinal atrophy, are seen less frequently.[102,103] For both patient care and medicolegal reasons, electrical injury patients should be evaluated for cataract via dilated exam at admission, discharge, and 6 and 12 months postinjury.[104]

EXPOSURE KERATITIS AND EYELID BURNS

Eyelid burns and singed eyelashes identify a group of patients at high risk for ocular surface problems, with likelihood ratios (LR+), if present, for the development of corneal ulceration of 12 and 6.9, respectively.[105] Punctate epitheliopathy, or keratopathy, is usually the earliest stage of per se corneal injury, and, if present, it confers an LR+ for the development of corneal ulceration of 6.4. These subtle irregularities on the normally glassy corneal surface can be discerned with magnification and are accentuated by the application of fluorescein dye (Fig. 43.1B). The severity of epitheliopathy ranges from scattered, superficial submillimeter dots to a homogeneous area of abnormal epithelium, confluent keratopathy. The latter is essentially an epithelial defect prior to sloughing of the diseased epithelium. While keratopathy may be caused by direct thermal or chemical injury of the eye, it is much more frequently observed with corneal exposure resulting from the contraction of eyelid burn wounds/scars. It generally develops around 1 week postburn, and careful observation of the sleeping patient demonstrates incomplete resting eyelid closure, with scleral or corneal show (Fig. 43.1A). Any patient with incomplete lid closure, best observed while asleep, should undergo detailed examination of the ocular surface. Bell's phenomenon, up-gaze with lid closure, is absent in 25% of patients and does not reliably protect the ocular surface when present; however, an intact Bell's phenomenon may somewhat mitigate the severity of exposure keratopathy.

EPITHELIAL DEFECTS

An epithelial defect is present when an area of the cornea has lost epithelium (Fig. 43.1C). It is denoted by a subtle ridge where epithelium remains and by a solid area of fluorescein staining. This can be either full or partial thickness. Partial-thickness epithelial defects can heal rapidly from the remaining basal layers, whereas full-thickness injuries must heal from the periphery. Typically the epithelial defect seen from incomplete eyelid closure (exposure) is transverse, linear, and centered over the inferior third of the cornea. Careful daily examination of epithelial defects is required in burn patients, as is correction of underlying causes. If magnified examination reveals stromal opacification (i.e., any finding other than clear cornea at and around the epithelial defect), then a corneal ulcer is present and there is a high risk of vision loss. All indicated diagnostic and therapeutic maneuvers should be employed without delay.

CORNEAL ULCER

We define a corneal ulcer as an epithelial defect with any associated stromal infiltrate (Fig. 43.1E). Corneal transparency, or lack thereof, is an important finding with histopathological correlates. Transparency is lost when the stroma becomes hydrated. In burns, this is typically in response to injury or infection. This occurs when the keratinocyte basement membrane has been compromised, a process that can develop independent of phagocytic cells via production of active matrix metalloproteinase-9 (MMP-9) and then MMP-2 by corneal cells.[106] The active form of

these enzymes has also been observed in the tear fluid from ocular burn and infectious ulceration patients.[107] Altered capillary permeability and the evolving wound-healing response occur in a manner akin to skin wound healing. This includes phagocytic infiltration, tissue destruction and pathogen clearance, reepithelialization, and myofibroblast-mediated scar formation. The disorganized collagen formed as part of scar formation lacks the regular arrangement and spacing of a healthy, clear corneal stroma. As a result, it appears white/gray and reflects rather than transmits visible light, causing vision loss. Transparency can also be lost due to corneal endothelial dysfunction. Impaired function of the endothelial adenosine triphosphate (ATP)-dependent transport of solute from the stroma into the aqueous humor causes abnormally increased hydration of stromal proteins. The associated epithelial defect should be measured daily at a minimum on magnified exam because stability and reepithelialization indicate treatment response. Inhibition of serine proteases may slow epithelial migration, although inhibition of MMPs may actually facilitate reepithelialization.[108–112] The majority of corneal ulcers can be prevented in burned patients via early release and skin grafting of full-thickness eyelid burns.[113] Most corneal ulcers in burned patients are sterile, but the occurrence of bacterial superinfection is not uncommon.[114] For this reason, and because treatment of infectious corneal ulcers is aided by the provision of directed antibiotics, swab or scraping culture of corneal ulcers is a routine part of our diagnostic protocol. Corneal scraping is accomplished with ophthalmic tetracaine drops, sedation (usually intravenous ketamine), loupe magnification, adequate lighting, and either a #69 or the rounded belly of a #15 blade. Carefully, the margin of the corneal ulcer is scraped, maintaining the edge of the blade almost parallel to the corneal surface to avoid any penetrating injury. The specimen, often visible only with loupes, is plated on blood and chocolate agars (for the broadest spectrum of bacterial growth), Sabouraud's agar (for fungal organisms), and several glass slides, for Gram's stain (for bacteria), Giemsa stain (for cellular features and viral cytopathic effect), and potassium hydroxide stain (for fungal elements).[115] Rapid review of the slide specimens, if positive, enables immediate initiation of directed topical antimicrobial agents.[116–118] Initial response to treatment is nonprogression (stabilization) in the size of the epithelial defect and underlying stromal infiltrate. With continued healing, these gradually become smaller. Therefore every follow-up examination should scrupulously document the sizes of the epithelial defect and stromal infiltrate.

BACTERIAL KERATITIS

Bacterial corneal ulcers can occur in otherwise healthy patients, as with prolonged use of contact lenses, but burned patients are at particular risk because of lost eyelid function, ocular surface exposure, local contamination from colonized/infected skin wounds, and disruption of host immunity, among other factors.[119] *Acinetobacter* spp. have been reported, as well as *Staphylococcus* spp. and *Pseudomonas* spp.[120,121] Pathogen virulence factors play important roles in the outcome of these infections, and more virulent bacteria may be selected during the recovery of severely burned patients.[122] Bacterial keratitis typically follows a more fulminant course than sterile corneal ulcers caused by exposure (Fig. 43.1F).

FUNGAL KERATITIS

Burn patients are in jeopardy for developing secondary infections of persistent exposure-related epithelial lesions. Not infrequently, fungal organisms are isolated as colonizers or active pathogens from burn wounds of the face and eyelids; thus facial wound microbiology determines the risk of secondary infection at ocular surface lesions. We have seen secondary *Candida* keratitis (ulcer) arising in this manner. Fungal keratitis is typically more indolent and is unresponsive to antibacterial treatment. With magnification, satellite lesions may be observed around the primary lesion. Diagnosis can be made through scraping, potassium hydroxide prep, and fungal culture. Rarely a corneal biopsy is necessary to establish the diagnosis if a high clinical suspicion for fungal keratitis exists while cultures remain negative. In refractory cases, débridement and corneal transplant may be necessary.[123]

VIRAL (HERPETIC) KERATITIS

The systemic response to burn injury entails profound alterations in host immunity, including markedly reduced novel immunoglobin generation and adaptive cell-mediated immunity.[124–143] Type 1 T-helper (T_H1) cellular response, activated macrophage cell killing, is associated with clearance of systemic virus and survival in animal models. Elegant studies by Suzuki et al. demonstrated that, post-burn, chemokine CCL2 (a.k.a. monocyte chemoattractant protein-1) stimulates a subset of natural killer T cells to produce interleukin-4, an early signal in a cascade ultimately producing T_H2 cytokines and abolishing the beneficial T_H1 response.[144–159] This situation leads to increased susceptibility to Herpesviridae. Herpetic keratitis (reactivation) in burned patients is both a sight-threatening problem and a marker of profoundly altered immunity. Dendritic (branching) epithelial defects and stromal infiltrates are typical of herpetic keratopathy (Fig. 43.1D). Allowed to progress, these enlarge forming a "geographic" corneal ulcer with an irregular border. Real-time polymerase chain reaction testing of corneal swab specimens is invaluable for diagnosis, providing rapid (within hours) information about the presence and type of Herpesviridae infection.[160] Although tear specimens have also been studied, the diagnostic yield is substantially lower.

ORBITAL COMPARTMENT SYNDROME

Orbital compartment syndrome (OCS) presents when the globe is compressed by swelling of the orbital contents and is unable to decompress itself. The natural variation in eyelid laxity provides a variable individual susceptibility to this problem; if the globe is able to be moved anteriorly to accommodate the swelling, intraocular hypertension may not develop. Acute intraocular hypertension can lead to anterior ischemic optic neuropathy (AION), with loss of vision. In the setting of severe burns, it can rapidly cause complete loss of vision bilaterally.[161] Decreased arterial

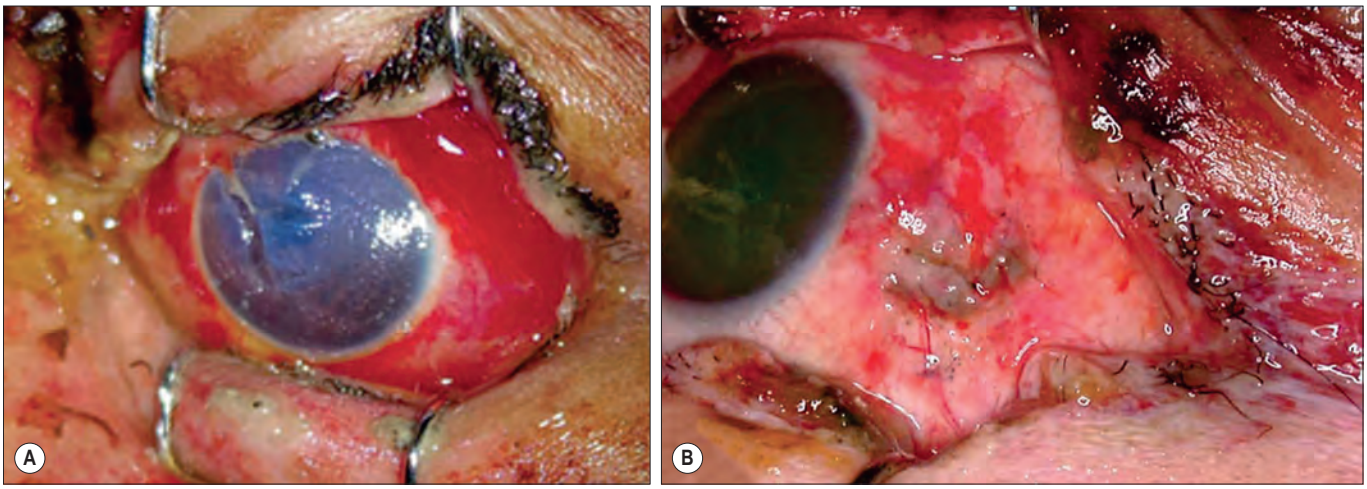

Fig. 43.2 A, Corneal laceration. B, Scleral laceration.

pressure further compounds the risk of AION infarction. Orbital compartment syndromes are occasionally observed in the first 24–96 hours after severe burn injury requiring large-volume resuscitation.[162] The development of compartment syndromes in unburned extremities or abdomen should prompt evaluation of the intraocular pressure; urgency is increased if there is concomitant arterial hypotension. Burns of the face and periorbita can lead to prodigious swelling and OCS in the absence of massive fluid resuscitation.[163] Full-thickness flame burns (charring) of the periorbital skin can prevent the normal swelling of the underlying tissues, thus facilitating OCS. Intraocular pressure can be evaluated grossly by direct palpation of the globe, by evaluating the mobility of the globe against the lower lid (the globe is tightly pressed against the conjunctival surface of the lower lid in OCS), or more exactly with a tonopen or Schioetz tonometer. Intraocular pressure is sensitive to extrinsic forces, so it is essential that the technique used to open the lids not compress the globe or a falsely elevated intraocular pressure reading may result. Measured at the cornea, intraocular pressures of 30 mm Hg or higher are cause for concern and frequent reevaluation. Avoiding excessive fluid/volume expansion and elevation of the head of the bed can help reduce intraocular pressure. If the globe is hard on palpation, the lower lid tightly apposed to the globe, or intraocular pressure remains at 30 mm Hg or higher, release of OCS is indicated to preserve vision and prevent AION. The intraocular pressure threshold for release should be somewhat lower when patients have ongoing arterial hypotension because tissue perfusion is a balance between arterial and tissue hydrostatic pressures.

AMBLYOPIA

Amblyopia is concerning in the burn unit primarily when prolonged eyelid closure or near-closure is requisite to treat ocular surface lesions in prepubertal children. Loss of visual stimuli leads to loss of capacity to perceive visual stimuli.[164–169] Amblyopia presents with decreased visual acuity in the absence of structural or refractive lesions. In practice, it is better to treat both eyes equally (e.g., tarsorrhaphy) if eyelid destruction and ocular surface exposure are present. In cases where vision is unilaterally affected, it is possible to intermittently patch, or treat with cycloplegics, the "good" eye, in an attempt to prevent amblyopia.[169] Involving an ophthalmology consultant is prudent when vision-preserving eyelid procedures raise concerns for iatrogenic amblyopia.

DESCEMETOCELE, CORNEAL PERFORATION, AND OPEN GLOBE

The posterior 50 μm of corneal stroma is Descemet's membrane. This posterior layer of corneal stroma, while thin, possesses a high degree of strength. When stromal destruction is near full thickness, the aqueous humor of the anterior chamber may be contained by this structure alone. Termed a descemetocele, it is a sign of an impending corneal perforation (Fig. 43.1G). Often an aqueous leak can be appreciated if fluorescein dye is applied over the area; the leaking aqueous humor dilutes and carries the dye into the tear lake (positive Seidel test). Corneal perforations (Fig. 43.1H) and lacerations (Figs. 43.2A and B) can be similarly recognized if the aqueous leak is not massive. With a massive loss of aqueous humor, the eye loses intraocular pressure, becoming "flat." Loss of intraocular pressure, or marked intraocular hypotension below 8 mm Hg, can result in choroidal detachment and loss of retinal function. Early application of tissue adhesive to descemetocele or acute perforation reduces the rate of eventual enucleation.[170,171]

Interventions

Topical lubricants provide protection to an at-risk ocular surface. We generally prefer petroleum-based or water-based ointments. The preservative present (a mild chemical toxin) in multidose artificial tear formulations can cause or exacerbate corneal injury if used more frequently than four times a day.

Topical antimicrobials are recommended if clinical findings or confirmatory microbiologic evidence exists of ocular

surface infection. For limited burns, erythromycin ointment provides antimicrobial coverage and lubrication. In major burns or with severe associated facial burns, high colony count, not infrequently Gram-negative, colonization often occurs of the eyelids and surrounding skin. In these patients, our first-line preference is bacitracin/polymyxin B ointment. We provide empiric coverage of corneal ulcers and significant epithelial defects with quinolone drops (moxifloxacin is preferred but more expensive) while culture data are pending. Fortified antibiotics (vancomycin, ceftazidime, or tobramycin) are used on a case-by-case basis, generally when positive culture data are available or pending, and clinical progression is observed while on empiric treatment. Fungal keratitis occurs infrequently, but, in severe burns, when culture data suggest yeast colonization of facial wounds near the eyes, we provide natamycin prophylaxis. Voriconazole eyedrops can similarly be compounded to fortified antibiotic drops and may be useful in the treatment of documented fungal keratitis. Herpetic keratitis in burned patients is treated with systemic antivirals; topical antivirals (ganciclovir or trifluridine) can be added to more quickly halt the progression of corneal injury. A direct comparison between systemic and topical treatments has not, to our knowledge, been performed in burn patients.[172] Due to altered host immunity discussed earlier, burn patients are in jeopardy of developing disseminated Herpesviridae, and topical monotherapy is not generally employed.

BANDAGE CONTACT LENS

Lenses useful as corneal bandages are characterized by low diopteric power, soft structure, and high gas permeability, and are often labeled "extended-wear" (e.g., Bausch and Lomb Night and Day or Acuvue Oasis). These are occasionally useful in facilitating reepithelialization and protecting corneas damaged by exposure. Once in place, these lenses should be evaluated frequently and discontinued or replaced when no longer effective. Due to risk of infection and other complications, it is prudent to involve an ophthalmology consultant when bandage contact lenses are employed.[173–177]

LATERAL CANTHOTOMY

Lateral canthotomy should be performed in cases of OCS, described earlier. Structure is provided to the lids by the canthal tendons, inserting on the upper and lower tarsi medially and laterally. The lateral origin is palpable as a bony prominence at the lateral orbital rim, called Whitnall's tubercle. Lateral canthotomy is performed by dividing the skin and lateral canthal tendon, freeing the lower lid from its bony attachment. Lidocaine 1% or 2% with epinephrine is infiltrated lateral to the lateral canthus and the skin is clamped parallel to the palpebral fissure, then divided with scissors anteroposteriorly. The lower lid is grasped and pulled away from the globe, placing the lateral canthal tendon on stretch, making it easier to locate and divide. The canthal tendon is divided with scissors anteriorly to Whitnall's tubercle on the orbital rim.[178,179] A successful lateral canthotomy leaves the lower lid freely mobile and no longer apposed to the globe. Afterward, the intraocular pressure should be reevaluated.

EYELID CLOSURE AND RECONSTRUCTION

Because the vast majority of burn-related eye disease results from exposure of the ocular surface, techniques facilitating eyelid closure are of central import. Temporary closure can be accomplished with Steri-Strips and cyanoacrylate skin adhesive; this closure may last 24–48 hours. Cyanoacrylate adhesive can also be used to temporarily close the lids by joining the lashes and eyelid margins of the lateral parts of lids;[180–186] in practice, this method of temporary eyelid closure lasts a few days. A temporary suture tarsorrhaphy can be constructed either with bedside sedation and local anesthesia or in the operating room. Tarsorrhaphy increases the rate of corneal epithelial wound healing.[174,187–189] Several techniques have been described; some permit facile reopening and reclosure if frequent eye examination is deemed necessary.[190–206] Chromic gut sutures often do not require removal and are occasionally used in our practice.[207] A tarsorrhaphy becomes progressively more "permanent" as deepithelialized surfaces of the eyelids are apposed. Several methods exist to create what we term "semi-permanent" tarsorrhaphy; these are indicated when large areas of full-thickness injury to the eyelids necessitate multiple reconstructive operations or after the failure of previous temporary suture tarsorrhaphy.[208] Less durable outcomes are associated with mattress sutures or bolster techniques than an internal fixation technique by which the gray line is split in the region of the planned tarsorrhaphy and the posterior and anterior laminae of the upper and lower lids are sutured to each other.[209] It is vitally important to avoid placing knots in contact with the corneal surface because these can cause abrasion injuries and corneal ulcers.

The forces of scar contraction powerfully influence eyelid function and, when tarsorrhaphy (including temporary) is indicated, often eyelid release and tissue interposition will also be required to preserve sight (Figs. 43.3A and B).[113] Essentially the procedure is a reverse blepharoplasty: the skin and scar of the lid is incised in the tarsal crease, and the upper lid mobilized inferiorly. Overcorrection is needed at the time of surgery because recurrent contraction in 2–3 weeks is the rule. The resulting defect can be covered with a split-thickness skin graft and secured with a combination of fibrin glue, sutures, or cyanoacrylate adhesive. If necessary, a secondary procedure is employed for the lower lids, although full-thickness skin autografts may be substituted to close the defect after release.[210] While release and skin graft interposition may protect a fresh tarsorrhaphy from disruption due to scar contraction at the eyelids, these grafts eventually contract despite all efforts at preservation.[211–215] Contraction and recurrence of cicatricial ectropion necessitate a series of repeated releases until both ocular surface and eyelid function stabilize. In cases of massive burns, when eyelid release is required and no sufficient donor site for sheet grafting of the upper lids can be spared, it is possible, despite burned skin, to mobilize the midportion of the brow and upper lid inferiorly from the medial and lateral brow in a myocutaneous V-Y inferior advancement flap, akin to this flap's utilization in oncological reconstruction.[216–218] This procedure may provide the release needed to allow formation of a stable tarsorrhaphy for ocular surface protection in critically injured patients.

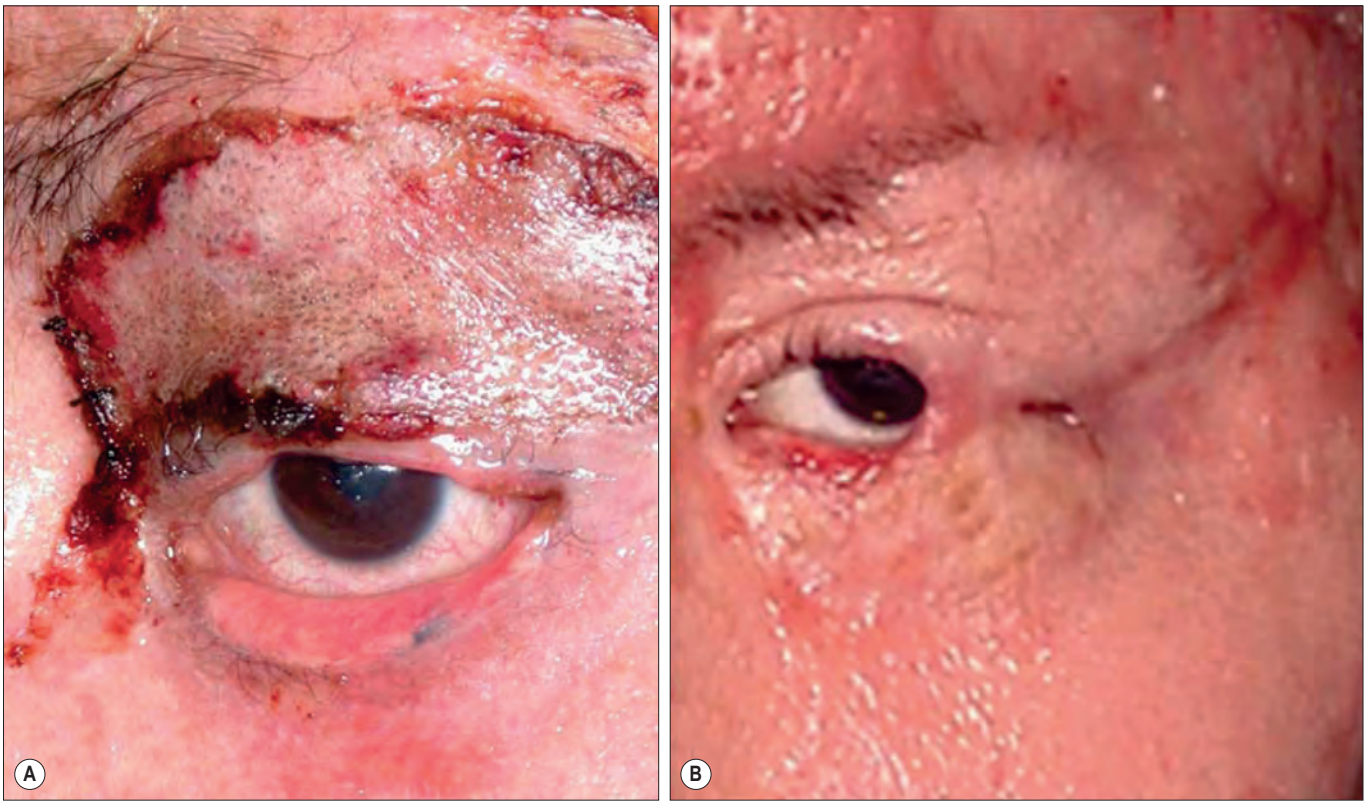

Fig. 43.3 A, Upper eyelid release, grafting, and lateral tarsorrhaphy. B, Follow-up.

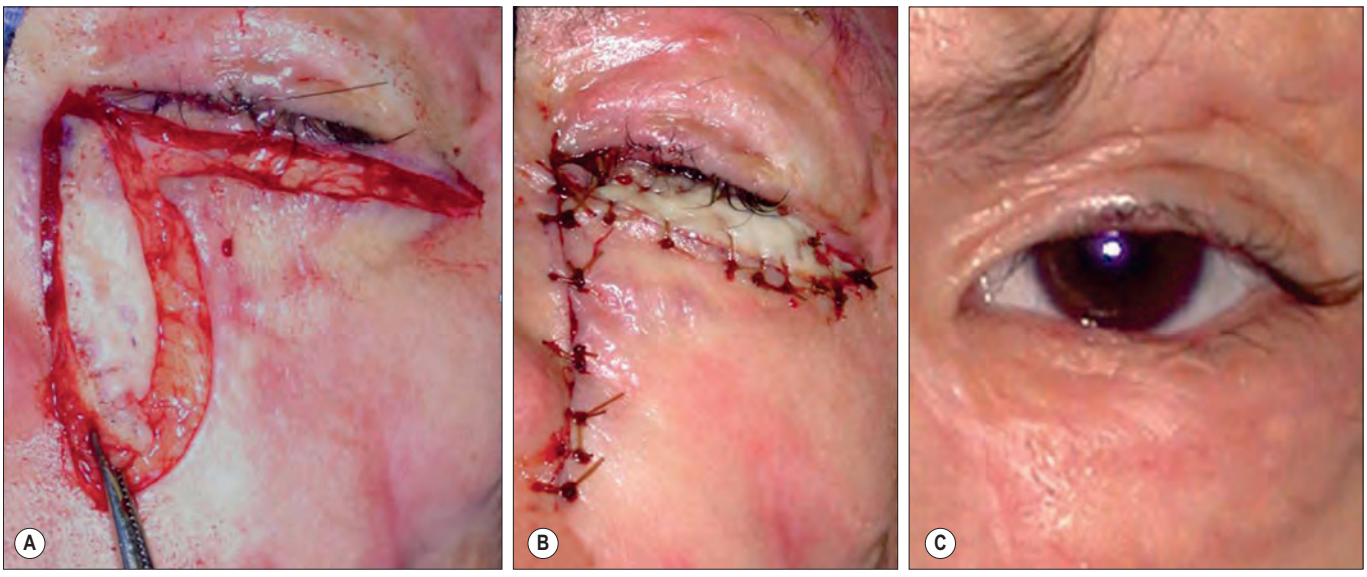

Fig. 43.4 Cicatricial ectropion of the lower lid; reconstruction with nasolabial island pedicle flap. A, Flap dissection. B, Flap inset. C, Follow-up.

Huang et al. suggest use of local skin flaps, when possible, to overcome the difficulty of autograft contraction and recurrent cicatricial ectropion. The lower lid may be treated with a superomedially based island pedicle flap from the nasolabial fold (Figs. 43.4A–C). This flap is quite durable, and the donor site heals with little morbidity.[219] If burn scar of the skin surrounding the donor site precludes closure, a split-thickness autograft can be used. Flaps available for the upper lid include paramedian forehead flap and orbicularis oculi myocutaneous flap from the lower lid with a laterally based pedicle (Fig. 43.5A–C).[220,221] The lower lid donor site defect of the latter may be closed with the previously discussed nasolabial fold island pedicle flap. Occasionally the tissue destruction resulting from burn injury is so severe that the structural integrity of the tarsal plate is compromised. This leads to lid dysfunction often recalcitrant to the preceding methods of treatment.[222] To address this, tarsal compromise must first be recognized. It can be replaced

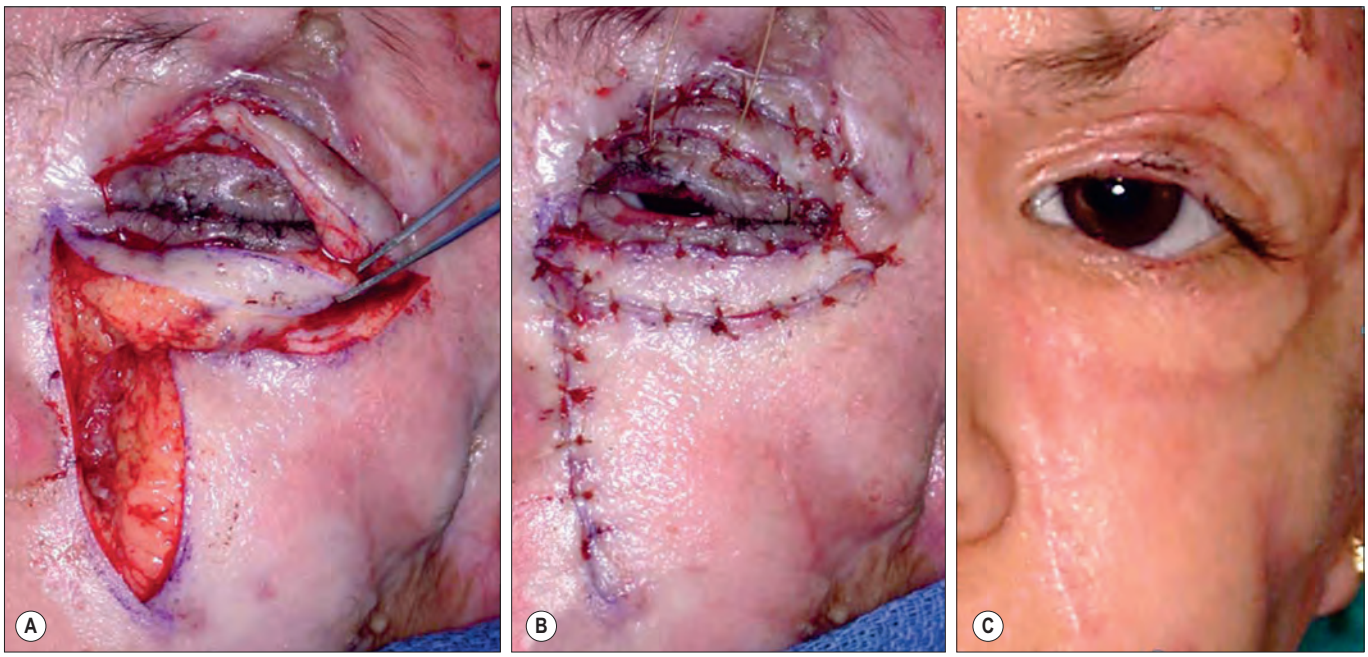

Fig. 43.5 Cicatricial ectropion; reconstruction with myocutaneous orbicularis flap and nasolabial flap. A, Flap dissection. B, Flaps inset. C, Follow-up.

using suitable cartilage, often harvested from the conchal bowl. Placed in a preseptal location[223] during eyelid contracture release and covered with a skin flap, this technique can be used in cases of subtotal eyelid loss so long as intact palpebral conjunctiva remains. Replacing lost conjunctival tissue is infrequently necessary postburn. This deformity can present with entropion and significant ocular surface injury and is frequently seen after Stevens–Johnson syndrome or TEN. We have successfully employed the technique of preseptal cartilage graft with skin resection (blepharoplasty) to rotate the lash line and scarred/keratinized mucocutaneous junction away from the corneal surface.[224] We have not yet had occasion to resort to conjunctival replacement procedures, such as buccal or nasal mucosal free grafts or nasal septal composite cartilage-mucosa grafts.[225,226]

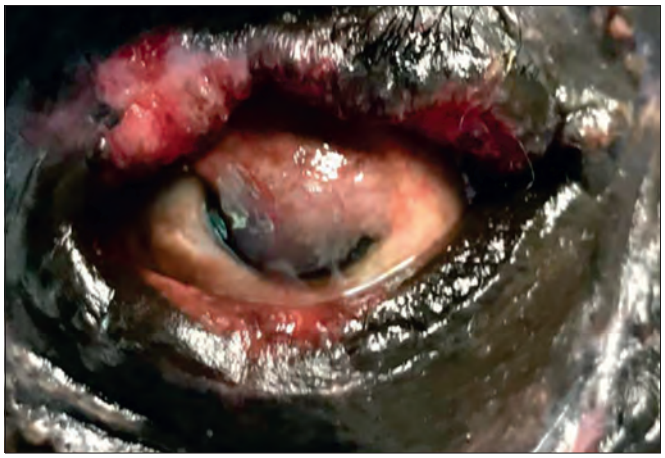

Fig. 43.6 Gundersen (conjunctival) flap.

CONJUNCTIVAL (GUNDERSEN) FLAPS

When corneal ulceration and epithelial loss are catastrophic and refractory to the previously described therapeutic measures, it is possible to mobilize the bulbar conjunctiva over the cornea (Fig. 43.6). These flaps provide a supply of vascularized tissue to create scar, deliver systemic antimicrobial therapy to the wound, and stabilize an impending perforation (e.g., descemetocele). A fornix flap is constructed by suture of the mobile conjunctiva in the inferior and superior fornices.[227] This flap may last 1–2 weeks before retracting and does not require any dissection. If small strips of apposing conjunctiva are excised, a more durable fornix flap may be held in place by adhesions similar to those formed via semipermanent tarsorrhaphy. Khodadoust described a microsurgical conjunctival flap, but its placement is more demanding than other options.[228] The classic Gundersen flap mobilizes the superior bulbar conjunctiva over the entire corneal surface, beginning through a transverse incision of the conjunctiva in the superior fornix. After the superior bulbar conjunctival flap is raised, a perilimbal peritomy is performed, the cornea deepithelialized, and the flap brought down over the cornea by securing its inferior edge between the 4 and 7 o'clock positions of the peritomy.[229,230] The superior aspect of the flap is sutured to Tenon's capsule between the 10 and 2 o'clock positions of the peritomy, and the entire superior surface of the globe is left denuded of conjunctiva, which rapidly reepithelializes. This flap is useful if performed with scrupulous avoidance of "buttonholing," as holes created in the flap invariably expand and allow corneal exposure. The goal of a Gundersen flap is to provide long-term corneal coverage, prevent perforation, and preserve an intact globe for later vision restoration.[231]

RECONSTRUCTION OF THE LACRIMAL APPARATUS

Rarely burn injury or resulting scarring compromises the normal flow of tears through the lacrimal system. Although a Jones tube or lacrimal stent may be useful in other settings, in the burned patient, scarring and markedly abnormal function of the eyelids combined with discharge due to chronic conjunctivitis render these tubes prone to clogging. The foreign body may also trigger local infectious complications.[232] Instead we employ a conjunctival mucosal flap to create a fistulous tract for tear drainage.[233] In cases where the punctum and upper lacrimal drainage apparatus are destroyed, this flap can be placed within the lacrimal sac, termed mucosal conjunctivodacryocystostomy. When the upper and lower lacrimal drainage structures are dysfunctional, the mucosal flap can be drained directly into the nasal or maxillary sinus cavities, mucosal conjunctivorhinostomy, and mucosal conjunctivoantrostomy, respectively. Refractory epiphora has been amenable to these treatments in 16 of 17 reported cases.[234]

CORNEAL TRANSPLANTATION

A stable ocular surface is generally requisite to achieve a successful corneal transplant.[235,236] Eyelid malposition must be corrected and epithelial defects and corneal ulcers closed and in a stable, if scarred, state. Corneal neovascularization frequently follows healing of corneal ulcers. If present, it will increase the risk of corneal allograft rejection, as does the presence of nonnative immune surveillance (Langerhans) cells.[237–239] Herpetic keratopathy is a further risk factor for rejection.[240] Thus a lamellar graft (partial-thickness corneal allograft) is preferred, because it preserves the patient's native endothelium from graft rejection.[241–245] Lamellar grafts are also more tolerant of elevated intraocular pressure, although they can undergo epithelial or stromal rejection.[246–249] As a salvage procedure, tectonic grafts can be used in the setting of frank perforation or descemetocele.[250–253] The purpose of these procedures is to maintain a closed globe and intraocular pressure. Amniotic membrane multilayer grafts may be useful as a temporizing measure and may play an antiinflammatory role in decreasing the rate of rejection of allografts placed in an emergent setting.[254–256] Rarely destruction of the eyelids, ocular surface, and/or ocular surface may lead to the situation in which the potential for vision exists, but no native reconstructive options exist. These cases may benefit from evaluation by centers experienced in the performance of and postoperative care for keratoprosthesis surgery.[257–300]

Complete references available online at www.expertconsult.inkling.com

References

1. Thach AB, United States. Department of the Army. Office of the Surgeon General. Ophthalmic care of the combat casualty. Falls Church, VA/Fort Sam Houston, TX/Bethesda, MD: Office of the Surgeon General, United States Army; Washington Borden Institute, United States Army Medical Dept. Center and School; Uniformed Services University of the Health Sciences; 2003. xvii, 495 pp.
2. Sevel D, Bothwell L, Hiss P, Isaacs R, Miller D. A re-appraisal of the development of the anterior chamber. *Ophthalmic Paediatr Genet*. 1985;6(1-2):257-263.
3. Sevel D. A reappraisal of the development of the eyelids. *Eye (Lond)*. 1988;2(Pt 2):123-129.
4. Findlater GS, McDougall RD, Kaufman MH. Eyelid development, fusion and subsequent reopening in the mouse. *J Anat*. 1993;183(Pt 1):121-129.
5. Sevel D. A reappraisal of the origin of human extraocular muscles. *Ophthalmology*. 1981;88(12):1330-1338.
6. Sevel D. The origins and insertions of the extraocular muscles: development, histologic features, and clinical significance. *Trans Am Ophthalmol Soc*. 1986;84:488-526.
7. Tung CI, Perin AF, Gumus K, Pflugfelder SC. Tear meniscus dimensions in tear dysfunction and their correlation with clinical parameters. *Am J Ophthalmol*. 2014;157(2):301-310 e1.
8. Pflugfelder SC. Tear dysfunction and the cornea: LXVIII Edward Jackson Memorial Lecture. *Am J Ophthalmol*. 2011;152(6):900-909 e1.
9. Stepp MA, Zieske JD. The corneal epithelial stem cell niche. *Ocul Surf*. 2005;3(1):15-26.
10. Li W, Hayashida Y, Chen YT, Tseng SC. Niche regulation of corneal epithelial stem cells at the limbus. *Cell Res*. 2007;17(1):26-36.
11. Kenyon KR. The synthesis of basement membrane by the corneal epithelium in bullous keratopathy. *Invest Ophthalmol*. 1969;8(2):156-168.
12. Meek KM, Knupp C. Corneal structure and transparency. *Prog Retin Eye Res*. 2015;49:1-16.
13. Scott R. The injured eye. *Philos Trans R Soc Lond B Biol Sci*. 2011;366(1562):251-260.
14. Eom Y, Lee JS, Keun Lee H, Myung Kim H, Suk Song J. Comparison of conjunctival staining between lissamine green and yellow filtered fluorescein sodium. *Can J Ophthalmol*. 2015;50(4):273-277.
15. Feenstra RP, Tseng SC. What is actually stained by rose bengal? *Arch Ophthalmol*. 1992;110(7):984-993.
16. Feenstra RP, Tseng SC. Comparison of fluorescein and rose bengal staining. *Ophthalmology*. 1992;99(4):605-617.
17. Machado LM, Castro RS, Fontes BM. Staining patterns in dry eye syndrome: rose bengal versus lissamine green. *Cornea*. 2009;28(7):732-734.
18. Maldonado-Codina C, Read ML, Efron N, Dobson CB, Morgan PB. Observation of solution-induced corneal staining with fluorescein, rose bengal and lissamine green. *Cont Lens Anterior Eye*. 2013;36(5):267-270.
19. Chodosh J, Dix RD, Howell RC, Stroop WG, Tseng SC. Staining characteristics and antiviral activity of sulforhodamine B and lissamine green B. *Invest Ophthalmol Vis Sci*. 1994;35(3):1046-1058.
20. Yoon KC, Im SK, Kim HG, You IC. Usefulness of double vital staining with 1% fluorescein and 1% lissamine green in patients with dry eye syndrome. *Cornea*. 2011;30(9):972-976.
21. Williams DF, Mieler WF, Williams GA. Posterior segment manifestations of ocular trauma. *Retina*. 1990;10(suppl 1):S35-S44.
22. Jiang J, Tyssebotn I. Cerebrospinal fluid pressure changes after acute carbon monoxide poisoning and therapeutic effects of normobaric and hyperbaric oxygen in conscious rats. *Undersea Hyperb Med*. 1997;24(4):245-254.
23. Hawkins M, Harrison J, Charters P. Severe carbon monoxide poisoning: outcome after hyperbaric oxygen therapy. *Br J Anaesth*. 2000;84(5):584-586.
24. Rose JJ, Wang L, Xu Q, et al. Carbon monoxide poisoning: pathogenesis, management and future directions of therapy. *Am J Respir Crit Care Med*. 2017;195(5):596-606.
25. Scott CJ, Kardon RH, Lee AG, Frisen L, Wall M. Diagnosis and grading of papilledema in patients with raised intracranial pressure using optical coherence tomography vs clinical expert assessment using a clinical staging scale. *Arch Ophthalmol*. 2010;128(6):705-711.
26. Herzlich AA, Yeh S, Shen D, et al. Identification of *Pseudomonas aeruginosa* DNA in a chorioretinal lesion associated with chronic granulomatous disease. *J Clin Pathol*. 2008;61(11):1229-1230.
27. Salminen L, Toivanen A. Bilateral uveitis during Serratia marcescens sepsis. *Am J Ophthalmol*. 1983;96(3):402-403.
28. Singalavanija A, Bedavanija A, Siripanthong S. Chorioretinal lesions in staphylococcal septicemia. *J Med Assoc Thai*. 1988;71(3):163-166.
29. Jung J, Lee J, Yu SN, et al. Incidence and risk factors of ocular infection caused by *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother*. 2016;60(4):2012-2017.
30. Geraymovych E, Conduff JH, Braich PS, Leffler CT, Brar VS. Prevalence and factors predictive of intraocular fungal infection in patients with fungemia at an academic urban tertiary care center. *Clin Ophthalmol*. 2015;9:1853-1858.
31. Adam MK, Vahedi S, Nichols MM, et al. Inpatient ophthalmology consultation for fungemia: prevalence of ocular involvement and necessity of funduscopic screening. *Am J Ophthalmol*. 2015;160(5):1078-1083 e2.
32. Brooks RG. Prospective study of Candida endophthalmitis in hospitalized patients with candidemia. *Arch Intern Med*. 1989;149(10):2226-2228.
33. Abdallah W, Fawzi A, Patel H, et al. Blood velocity measurement in the posterior segment of the rabbit eye using combined spectral Doppler and power Doppler ultrasound. *Graefes Arch Clin Exp Ophthalmol*. 2010;248(1):93-101.
34. Shah CP, McKey J, Spirn MJ, Maguire J. Ocular candidiasis: a review. *Br J Ophthalmol*. 2008;92(4):466-468.
35. Donahue SP, Greven CM, Zuravleff JJ, et al. Intraocular candidiasis in patients with candidemia. Clinical implications derived from a prospective multicenter study. *Ophthalmology*. 1994;101(7):1302-1309.
36. Donahue SP, Hein E, Sinatra RB. Ocular involvement in children with candidemia. *Am J Ophthalmol*. 2003;135(6):886-887.
37. Mehta S, Jiandani P, Desai M. Ocular lesions in disseminated candidiasis. *J Assoc Physicians India*. 2007;55:483-485.
38. Sanli E, Pandya VB, McDonald RJ, McCluskey PJ. Ocular candidiasis complicated by branch retinal vein occlusion. *Br J Ophthalmol*. 2013;97(3):375-376.
39. Oude Lashof AM, Rothova A, Sobel JD, et al. Ocular manifestations of candidemia. *Clin Infect Dis*. 2011;53(3):262-268.
40. Cohen M, Edwards JE Jr, Hensley TJ, Guze LB. Experimental hematogenous Candida albicans endophthalmitis: electron microscopy. *Invest Ophthalmol Vis Sci*. 1977;16(6):498-511.
41. Lavine JA, Mititelu M. Multimodal imaging of refractory Candida chorioretinitis progressing to endogenous endophthalmitis. *J Ophthalmic Inflamm Infect*. 2015;5(1):54.
42. Livermore JL, Felton TW, Abbott J, et al. Pharmacokinetics and pharmacodynamics of anidulafungin for experimental Candida endophthalmitis: insights into the utility of echinocandins for treatment of a potentially sight-threatening infection. *Antimicrob Agents Chemother*. 2013;57(1):281-288.
43. Blennow O, Tallstedt L, Hedquist B, Gardlund B. Duration of treatment for candidemia and risk for late-onset ocular candidiasis. *Infection*. 2013;41(1):129-134.
44. Mousselli HA, Norwood J. Failure of echinocandin therapy in the treatment of Candida glabrata chorioretinitis. *Am J Med Sci*. 2012;343(1):98-100.
45. Sallam A, Lynn W, McCluskey P, Lightman S. Endogenous Candida endophthalmitis. *Expert Rev Anti Infect Ther*. 2006;4(4):675-685.
46. Khan FA, Slain D, Khakoo RA. Candida endophthalmitis: focus on current and future antifungal treatment options. *Pharmacotherapy*. 2007;27(12):1711-1721.
47. Jang GJ, Kim KS, Shin WS, Lee WK. Treatment of candida chorioretinitis with voriconazole. *Korean J Ophthalmol*. 2005;19(1):73-76.
48. Capek KDTS, Merkley KH, Hawkins HK, et al Thermal injuries of the cornea: injury patterns and histopathology. ARVO. May 7–11; Baltimore, MD, 2017.
49. Jackson K, Baker SR. Clinical implications of orbital cellulitis. *Laryngoscope*. 1986;96(5):568-574.
50. Jackson K, Baker SR. Periorbital cellulitis. *Head Neck Surg*. 1987;9(4):227-234.
51. Wald ER. Periorbital and orbital infections. *Pediatr Rev*. 2004;25(9):312-320.
52. Chaudhry IA, Shamsi FA, Elzaridi E, et al. Inpatient preseptal cellulitis: experience from a tertiary eye care centre. *Br J Ophthalmol*. 2008;92(10):1337-1341.

53. Goncalves R, Menezes C, Machado R, Ribeiro I, Lemos JA. Periorbital cellulitis in children: analysis of outcome of intravenous antibiotic therapy. *Orbit*. 2016;35(4):175-180.
54. Hornblass A, Herschorn BJ, Stern K, Grimes C. Orbital abscess. *Surv Ophthalmol*. 1984;29(3):169-178.
55. Ferguson MP, McNab AA. Current treatment and outcome in orbital cellulitis. *Aust N Z J Ophthalmol*. 1999;27(6):375-379.
56. Reynolds DJ, Kodsi SR, Rubin SE, Rodgers IR. Intracranial infection associated with preseptal and orbital cellulitis in the pediatric patient. *J AAPOS*. 2003;7(6):413-417.
57. Nageswaran S, Woods CR, Benjamin DK Jr, Givner LB, Shetty AK. Orbital cellulitis in children. *Pediatr Infect Dis J*. 2006;25(8):695-699.
58. McKinley SH, Yen MT, Miller AM, Yen KG. Microbiology of pediatric orbital cellulitis. *Am J Ophthalmol*. 2007;144(4):497-501.
59. Yang M, Quah BL, Seah LL, Looi A. Orbital cellulitis in children-medical treatment versus surgical management. *Orbit*. 2009;28(2-3):124-136.
60. Kayhan FT, Sayin I, Yazici ZM, Erdur O. Management of orbital subperiosteal abscess. *J Craniofac Surg*. 2010;21(4):1114-1117.
61. Chaudhry IA, Al-Rashed W, Arat YO. The hot orbit: orbital cellulitis. *Middle East Afr J Ophthalmol*. 2012;19(1):34-42.
62. Kahloun R, Abroug N, Ben Abdessalem N, et al. Orbital infections: review of 28 cases. *Tunis Med*. 2015;93(11):673-677.
63. Deng FG. Clinical stages in alkali burn of the eye and its treatment]. *Zhonghua Yan Ke Za Zhi*. 1988;24(3):140-142.
64. White ML, Chodosh J, Jang J, Dohlman C. Incidence of Stevens-Johnson syndrome and chemical burns to the eye. *Cornea*. 2015;34(12):1527-1533.
65. Lo K, Kohanim S, Trief D, Chodosh J. Role of amniotic membrane transplantation in acute chemical injury. *Int Ophthalmol Clin*. 2013;53(4):33-41.
66. Morgan LB. A new drug delivery system for the eye. *IMS Ind Med Surg*. 1971;40(6):11-13.
67. Oppong MC. Experience with Morgan perfusion contact lens in treating eye infections and burns. *Ghana Med J*. 1975;14(3):201-205.
68. Wang M, Smith WA, Duncan JK, Miller JM. Treatment of Pseudomonas keratitis by continuous infusion of topical antibiotics with the Morgan lens. *Cornea*. 2017;36(5):617-620.
69. Jain R, Sharma N, Basu S, et al. Stevens-Johnson syndrome: the role of an ophthalmologist. *Surv Ophthalmol*. 2016;61(4):369-399.
70. Kohanim S, Palioura S, Saeed HN, et al. Acute and chronic ophthalmic involvement in Stevens-Johnson syndrome/toxic epidermal necrolysis. A comprehensive review and guide to therapy. II. Ophthalmic disease. *Ocul Surf*. 2016;14(2):168-188.
71. Sharma N, Thenarasun SA, Kaur M, et al. Adjuvant role of amniotic membrane transplantation in acute ocular Stevens-Johnson syndrome: a randomized control trial. *Ophthalmology*. 2016;123(3):484-491.
72. Ciralsky JB, Sippel KC, Gregory DG. Current ophthalmologic treatment strategies for acute and chronic Stevens-Johnson syndrome and toxic epidermal necrolysis. *Curr Opin Ophthalmol*. 2013;24(4):321-328.
73. Fu Y, Gregory DG, Sippel KC, Bouchard CS, Tseng SC. The ophthalmologist's role in the management of acute Stevens-Johnson syndrome and toxic epidermal necrolysis. *Ocul Surf*. 2010;8(4):193-203.
74. Gregory DG. The ophthalmologic management of acute Stevens-Johnson syndrome. *Ocul Surf*. 2008;6(2):87-95.
75. Gregory DG. Treatment of acute Stevens-Johnson syndrome and toxic epidermal necrolysis using amniotic membrane: a review of 10 consecutive cases. *Ophthalmology*. 2011;118(5):908-914.
76. Gregory DG. New Grading system and treatment guidelines for the acute ocular manifestations of Stevens-Johnson syndrome. *Ophthalmology*. 2016;123(8):1653-1658.
77. Shay E, Kheirkhah A, Liang L, et al. Amniotic membrane transplantation as a new therapy for the acute ocular manifestations of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Surv Ophthalmol*. 2009;54(6):686-696.
78. Capek KD, Marsh D, Stout SC, et al Total ocular surface coverage with amniotic membrane transplantion in pediatriac toxic epidermal necrolysis: a retrospective comparison with topical treatments. ARVO. Seattle WA, May 1, 2016.
79. Stankovic I, Kecmanovic Z. [Electric cataract as an occupational disease]. *Arh Hig Rada*. 1956;7(2):97-102.
80. Lock JA. Electrical cataract produced by a 240-volt current. *Br J Ophthalmol*. 1957;41(8):500-501.
81. Shimkhovich IS, Shiliaev VG. [Cataract of both eyes which developed as a result of brief exposures to an ultra-high-frequency electromagnetic field of high density]. *Vestn Oftalmol*. 1959;72:12-16.
82. Fatorelli A. [Cataract caused by electroshock. Study with presentation of cases]. *Arq Bras Oftalmol*. 1961;24:216-221.
83. Francois RC, Cabanes J. [Apropos of a case of cataract probably related to phototrauma due to an electric arc without direct passage of current]. *Arch Mal Prof*. 1963;24:539-541.
84. Oleszewski SC, Nyman JS. Electric cataract: a rare clinical entity. *Am J Optom Physiol Opt*. 1984;61(4):279-283.
85. Saffle JR, Crandall A, Warden GD. Cataracts: a long-term complication of electrical injury. *J Trauma*. 1985;25(1):17-21.
86. Al Rabiah SM, Archer DB, Millar R, Collins AD, Shepherd WF. Electrical injury of the eye. *Int Ophthalmol*. 1987;11(1):31-40.
87. Van Johnson E, Kline LB, Skalka HW. Electrical cataracts: a case report and review of the literature. *Ophthalmic Surg*. 1987;18(4):283-285.
88. Biro Z, Pamer Z. Electrical cataract and optic neuropathy. *Int Ophthalmol*. 1994;18(1):43-47.
89. Reddy SC. Electric cataract: a case report and review of the literature. *Eur J Ophthalmol*. 1999;9(2):134-138.
90. Chaudhuri Z, Pandey PK, Bhatia A. Electrical cataract: a case study. *Ophthalmic Surg Lasers*. 2002;33(2):166-168.
91. Caksen H, Yuca SA, Demirtas I, et al. Right thalamic hemorrhage resulting from high-voltage electrical injury: a case report. *Brain Dev*. 2004;26(2):134-136.
92. Seth RK, Abedi G, Daccache AJ, Tsai JC. Cataract secondary to electrical shock from a Taser gun. *J Cataract Refract Surg*. 2007;33(9):1664-1665.
93. Kuwabara T, Fukushima T, Makino K, Kondo H. Epileptic seizure, cataract, and tongue atrophy during the 8 years after electrical brain injury. *Intern Med*. 2009;48(13):1179-1182.
94. Flockerzi E, El-Husseiny M, Low U, Daas L, Seitz B. [Cataract development after electrical injury]. *Ophthalmologe*. 2016;113(11):950-951.
95. Khatib R, Koch KR, Heindl LM. [Electrical cataract after electrical injuries]. *Klin Monbl Augenheilkd*. 2016.
96. Flockerzi E, El-Husseiny M, Low U, Daas L, Seitz B. [Historical description of cataract development after electrical injury]. *Ophthalmologe*. 2017.
97. Eisenberg RS, Rae JL. Current-voltage relationships in the crystalline lens. *J Physiol*. 1976;262(2):285-300.
98. Taura T. [Experimental studies on mechanism of cataract formation. 4. Electrical changes in lens fiber membrane at experimental uveitis (author's transl)]. *Nippon Ganka Gakkai Zasshi*. 1980;84(3):247-251.
99. Bleicher JN, Hamiel SR, Gengler JS. Electrical cataract formation in the rabbit model. *Plast Reconstr Surg*. 1996;98(5):903.
100. DeRosa AM, Mese G, Li L, et al. The cataract causing Cx50-S50P mutant inhibits Cx43 and intercellular communication in the lens epithelium. *Exp Cell Res*. 2009;315(6):1063-1075.
101. Zhao M, Chalmers L, Cao L, et al. Electrical signaling in control of ocular cell behaviors. *Prog Retin Eye Res*. 2012;31(1):65-88.
102. Zablocki GJ, Hagedorn CL. Chorioretinal atrophy after electrical injury. *Digit J Ophthalmol*. 2011;17(3):40-42.
103. Duman R, Cevik SG, Tufekci A. Unilateral uveitis, cataract and retinal detachment following low-voltage electrical injury. *Burns Trauma*. 2015;3:19.
104. Moreschi C, Da Broi U, Lanzetta P. Medico-legal implications of traumatic cataract. *J Forensic Leg Med*. 2013;20(2):69-73.
105. Capek KD, Marsh D, Trocme SD, et al A child's eyes: epidemiology of sight-threatening problems in a pediatric burn unit. ASCRS New Orleans. May 8, 2016.
106. Matsubara M, Zieske JD, Fini ME. Mechanism of basement membrane dissolution preceding corneal ulceration. *Invest Ophthalmol Vis Sci*. 1991;32(13):3221-3237.
107. Sakimoto T, Shoji J, Sawa M. Active form of gelatinases in tear fluidin patients with corneal ulcer or ocular burn. *Jpn J Ophthalmol*. 2003;47(5):423-426.
108. Zieske JD, Bukusoglu G. Effect of protease inhibitors on corneal epithelial migration. *Invest Ophthalmol Vis Sci*. 1991;32(7):2073-2078.
109. Fini ME, Parks WC, Rinehart WB, et al. Role of matrix metalloproteinases in failure to re-epithelialize after corneal injury. *Am J Pathol*. 1996;149(4):1287-1302.
110. Sakimoto T, Ohnishi T, Ishimori A. Simultaneous study of matrix metalloproteinases, proinflammatory cytokines, and soluble cytokine receptors in the tears of noninfectious corneal ulcer patients. *Graefes Arch Clin Exp Ophthalmol*. 2014;252(9):1451-1456.

111. Horwitz V, Dachir S, Cohen M, et al. The beneficial effects of doxycycline, an inhibitor of matrix metalloproteinases, on sulfur mustard-induced ocular pathologies depend on the injury stage. *Curr Eye Res*. 2014;39(8):803-812.
112. Bian F, Pelegrino FS, Henriksson JT, et al. Differential effects of dexamethasone and doxycycline on inflammation and MMP production in murine alkali-burned corneas associated with dry eye. *Ocul Surf*. 2016;14(2):242-254.
113. Barrow RE, Jeschke MG, Herndon DN. Early release of third-degree eyelid burns prevents eye injury. *Plast Reconstr Surg*. 2000;105(3):860-863.
114. Yu MC, Hofling-Lima AL, Furtado GH. Microbiological and epidemiological study of infectious keratitis in children and adolescents. *Arq Bras Oftalmol*. 2016;79(5):289-293.
115. Adams GG, Dilly PN, Kirkness CM. Monitoring ocular disease by impression cytology. *Eye (Lond)*. 1988;2(Pt 5):506-516.
116. Gupta N, Tandon R. Investigative modalities in infectious keratitis. *Indian J Ophthalmol*. 2008;56(3):209-213.
117. Ly CN, Pham JN, Badenoch PR, et al. Bacteria commonly isolated from keratitis specimens retain antibiotic susceptibility to fluoroquinolones and gentamicin plus cephalothin. *Clin Exp Ophthalmol*. 2006;34(1):44-50.
118. Arora I, Singhvi S. Impression debridement of corneal lesions. *Ophthalmology*. 1994;101(12):1935-1940.
119. Alarcon I, Tam C, Mun JJ, et al. Factors impacting corneal epithelial barrier function against Pseudomonas aeruginosa traversal. *Invest Ophthalmol Vis Sci*. 2011;52(3):1368-1377.
120. Wang AG, Wu CC, Liu JH. Bacterial corneal ulcer: a multivariate study. *Ophthalmologica*. 1998;212(2):126-132.
121. Mitchell WH, Parson BJ, Weiner LJ. Pseudomonas ulceration of the cornea following major total body burn: a clinical study. *J Trauma*. 1976;16(4):317-319.
122. Lyczak JB, Cannon CL, Pier GB. Establishment of Pseudomonas aeruginosa infection: lessons from a versatile opportunist. *Microbes Infect*. 2000;2(9):1051-1060.
123. Wang T, Li S, Gao H, Shi W. Therapeutic dilemma in fungal keratitis: administration of steroids for immune rejection early after keratoplasty. *Graefes Arch Clin Exp Ophthalmol*. 2016.
124. Cuthbertson D, Tilstone WJ, Green JA. Immunoglobulins in injured patients. *Lancet*. 1969;1(7602):987-988.
125. Balikov B, Artz CP. Solometo DF. Serum gamma globulin in the burned patient; with special reference to septicemia. *U S Armed Forces Med J*. 1957;8(3):321-331.
126. Munster AM. New horizons in surgical immunobiology. Host defence mechanisms in burns. *Ann R Coll Surg Engl*. 1972;51(2):69-80.
127. Munster AM, Hoagland HC, Pruitt BA Jr. The effect of thermal injury on serum immunoglobulins. *Ann Surg*. 1970;172(6):965-969.
128. Munster AM, Artz CP. A neglected aspect of trauma pathophysiology: the immunologic response to injury. *South Med J*. 1974;67(8):935-940.
129. Bjornson AB, Altemeier WA, Bjornson HS. Changes in humoral components of host defense following burn trauma. *Ann Surg*. 1977;186(1):88-96.
130. Alexander JW, Ogle CK, Stinnett JD, Macmillan BG. A sequential, prospective analysis of immunologic abnormalities and infection following severe thermal injury. *Ann Surg*. 1978;188(6):809-816.
131. Alexander JW. Immunological responses in the burned patient. *J Trauma*. 1979;19(11 suppl):887-889.
132. Alexander JW, MacMillan BG, Stinnett JD, et al. Beneficial effects of aggressive protein feeding in severely burned children. *Ann Surg*. 1980;192(4):505-517.
133. Deitch EA, Dobke M, Baxter CR. Failure of local immunity. A potential cause of burn wound sepsis. *Arch Surg*. 1985;120(1):78-84.
134. Blazar BA, Rodrick ML, O'Mahony JB, et al. Suppression of natural killer-cell function in humans following thermal and traumatic injury. *J Clin Immunol*. 1986;6(1):26-36.
135. Stein MD, Gamble DN, Klimpel KD, Herndon DN, Klimpel GR. Natural killer cell defects resulting from thermal injury. *Cell Immunol*. 1984;86(2):551-556.
136. Klimpel GR, Herndon DN, Fons M, et al. Defective NK cell activity following thermal injury. *Clin Exp Immunol*. 1986;66(2):384-392.
137. Klimpel GR, Herndon DH, Stein MD. Peripheral blood lymphocytes from thermal injury patients are defective in their ability to generate lymphokine-activated killer (LAK) cell activity. *J Clin Immunol*. 1988;8(1):14-22.
138. Munster AM, Eurenius K, Katz RM, et al. Cell-mediated immunity after thermal injury. *Ann Surg*. 1973;177(2):139-143.
139. Hansbrough J, Peterson V, Zapata-Sirvent R, Claman HN. Postburn immunosuppression in an animal model. II. Restoration of cell-mediated immunity by immunomodulating drugs. *Surgery*. 1984;95(3):290-296.
140. Deitch EA, Landry KN, McDonald JC. Postburn impaired cell-mediated immunity may not be due to lazy lymphocytes but to overwork. *Ann Surg*. 1985;201(6):793-802.
141. Hansbrough JF, Zapata-Sirvent R, Bender EM, Peterson V. Prevention of suppressed cell-mediated immunity in burned mice with histamine-2 receptor antagonist drugs. *J Surg Res*. 1985;39(2):150-156.
142. Deitch EA, Winterton J, Berg R. Thermal injury promotes bacterial translocation from the gastrointestinal tract in mice with impaired T-cell-mediated immunity. *Arch Surg*. 1986;121(1):97-101.
143. Zapata-Sirvent RL, Hansbrough JF, Bender EM, et al. Postburn immunosuppression in an animal model. IV. Improved resistance to septic challenge with immunomodulating drugs. *Surgery*. 1986;99(1):53-59.
144. Fujita K, Sandford AP, Kobayashi M, et al. Role of natural killer T (NKT) cells lacking interleukin (IL)-4 producing abilities on the CC-chemokine ligand 2-associated herpes simplex virus type 1 infection in human severe combined immunodeficiency (SCID) mouse chimeras. *Burns*. 2005;31(2):145-152.
145. Katakura T, Kobayashi M, Herndon DN, Suzuki F. Effect of IL-12 and soluble IL-4 receptor on the herpesvirus infection in human SCID chimeras whose Th2 cells predominate. *Immunol Cell Biol*. 2004;82(4):421-426.
146. Kobayashi M, Takahashi H, Herndon DN, Pollard RB, Suzuki F. Therapeutic effects of IL-12 combined with benzoylmesaconine, a non-toxic aconitine-hydrolysate, against herpes simplex virus type 1 infection in mice following thermal injury. *Burns*. 2003;29(1):37-42.
147. Kobayashi M, Takahashi H, Herndon DN, Pollard RB, Suzuki F. Effect of a combination therapy between IL-12 and soluble IL-4 receptor (sIL-4R) on Candida albicans and herpes simplex virus type I infections in thermally injured mice. *Can J Microbiol*. 2002;48(10):886-894.
148. Katakura T, Kobayashi M, Fujita K, et al. A combination therapy using IL-12 and soluble IL-4 receptor on herpes simplex virus Type 1 infection in a human-SCID chimera model of thermal injury. *Clin Immunol*. 2002;105(3):363-370.
149. Furukawa K, Kobayashi M, Herndon DN, Pollard RB, Suzuki F. Appearance of monocyte chemoattractant protein 1 (MCP-1) early after thermal injury: role in the subsequent development of burn-associated type 2 T-cell responses. *Ann Surg*. 2002;236(1):112-119.
150. Kobayashi H, Kobayashi M, Utsunomiya T, et al. Therapeutic protective effects of IL-12 combined with soluble IL-4 receptor against established infections of herpes simplex virus type 1 in thermally injured mice. *J Immunol*. 1999;162(12):7148-7154.
151. Takagi K, Suzuki F, Barrow RE, et al. Growth hormone improves the resistance of thermally injured mice infected with herpes simplex virus type 1. *J Trauma*. 1998;44(3):517-522.
152. Takagi K, Suzuki F, Barrow RE, Wolf SE, Herndon DN. Recombinant human growth hormone modulates Th1 and Th2 cytokine response in burned mice. *Ann Surg*. 1998;228(1):106-111.
153. Utsunomiya T, Kobayashi M, Herndon DN, Pollard RB, Suzuki F. A relationship between the generation of burn-associated type 2 T cells and their antagonistic cells in thermally injured mice. *Burns*. 1997;23(4):281-287.
154. Takagi K, Suzuki F, Barrow RE, et al. Growth hormone improves immune function and survival in burned mice infected with herpes simplex virus type 1. *J Surg Res*. 1997;69(1):166-170.
155. Matsuo R, Kobayashi M, Herndon DN, Pollard RB, Suzuki F. Interleukin-12 protects thermally injured mice from herpes simplex virus type 1 infection. *J Leukoc Biol*. 1996;59(5):623-630.
156. Utsunomiya T, Kobayashi M, Herndon DN, Pollard RB, Suzuki F. Glycyrrhizin (20 beta-carboxy-11-oxo-30-norolean-12-en-3 beta-yl-2-O-beta-D-glucopyranuronosyl-alpha-D-glucopyranosiduronic acid) improves the resistance of thermally injured mice to opportunistic infection of herpes simplex virus type 1. *Immunol Lett*. 1995;44(1):59-66.
157. Kobayashi M, Herndon DN, Pollard RB, Suzuki F. CD4+ contrasuppressor T cells improve the resistance of thermally injured mice infected with HSV. *J Leukoc Biol*. 1995;58(2):159-167.
158. Matsuo R, Ball MA, Kobayashi M, et al. Effects of a traditional Chinese herbal medicine, Kanzo-bushi-to, on the resistance of

thermally injured mice infected with herpes simplex virus type 1. *Int J Immunopharmacol*. 1994;16(10):855-863.
159. Kobayashi M, Herndon DN, Pollard RB, Suzuki F. Z-100, a lipid-arabinomannan extracted from Mycobacterium tuberculosis, improves the resistance of thermally injured mice to herpes virus infections. *Immunol Lett*. 1994;40(3):199-205.
160. Ma JX, Wang LN, Zhou RX, Yu Y, Du TX. Real-time polymerase chain reaction for the diagnosis of necrotizing herpes stromal keratitis. *Int J Ophthalmol*. 2016;9(5):682-686.
161. Vallejo A, Lorente JA, Bas ML, Gonzalez Y. Blindness due to anterior ischemic optic neuropathy in a burn patient. *J Trauma*. 2002; 53(1):139-141.
162. Sullivan SR, Ahmadi AJ, Singh CN, et al. Elevated orbital pressure: another untoward effect of massive resuscitation after burn injury. *J Trauma*. 2006;60(1):72-76.
163. Hurst J, Johnson D, Campbell R, Baxter S, Kratky V. Orbital compartment syndrome in a burn patient without aggressive fluid resuscitation. *Orbit*. 2014;33(5):375-377.
164. Lessell S. Nutritional amblyopia. *J Neuroophthalmol*. 1998;18(2): 106-111.
165. Mills MD. The eye in childhood. *Am Fam Physician*. 1999;60(3):907-916, 918.
166. Hoyt CS. Amblyopia: a neuro-ophthalmic view. *J Neuroophthalmol*. 2005;25(3):227-231.
167. Anderson SJ, Swettenham JB. Neuroimaging in human amblyopia. *Strabismus*. 2006;14(1):21-35.
168. Polat U. Restoration of underdeveloped cortical functions: evidence from treatment of adult amblyopia. *Restor Neurol Neurosci*. 2008;26(4-5):413-424.
169. West S, Williams C. Amblyopia in children (aged 7 years or less). *BMJ Clin Evid*. 2016;2016. pii: 0709.
170. Hirst LW, Smiddy WE, Stark WJ. Corneal perforations. Changing methods of treatment, 1960: 1980. *Ophthalmology*. 1982;89(6): 630-635.
171. Hirst LW, Smiddy WE, De Juan E. Tissue adhesive therapy for corneal perforations. *Aust J Ophthalmol*. 1983;11(2):113-118.
172. Sahin A, Hamrah P. Acute herpetic keratitis: what is the role for ganciclovir ophthalmic gel? *Ophthalmol Eye Dis*. 2012;4:23-34.
173. Hovding G. Conjunctival and contact lens bacterial flora during continuous 'bandage' lens wear. *Acta Ophthalmol (Copenh)*. 1982;60(3):439-448.
174. Ali Z, Insler MS. A comparison of therapeutic bandage lenses, tarsorrhaphy, and antibiotic and hypertonic saline on corneal epithelial wound healing. *Ann Ophthalmol*. 1986;18(1):22-24.
175. Gruber E. The Acuvue disposable contact lens as a therapeutic bandage lens. *Ann Ophthalmol*. 1991;23(12):446-447.
176. Hugkulstone CE. Use of a bandage contact lens in perforating injuries of the cornea. *J R Soc Med*. 1992;85(6):322-323.
177. Donnenfeld ED, Selkin BA, Perry HD, et al. Controlled evaluation of a bandage contact lens and a topical nonsteroidal anti-inflammatory drug in treating traumatic corneal abrasions. *Ophthalmology*. 1995;102(6):979-984.
178. Hill C, Reid C, Tzannes A, Burns B, Bartlett M. Prehospital lateral canthotomy. *Emerg Med J*. 2013;30(2):155-156.
179. Ferguson IM, Shareef MZ, Burns B, Reid C. A human cadaveric workshop: one solution to competence in the face of rarity. *Emerg Med Australas*. 2016;28(6):752-754.
180. Margo CE, Trobe JD. Tarsorrhaphy from accidental instillation of cyanoacrylate adhesive in the eye. *JAMA*. 1982;247(5):660-661.
181. Raynor LA. Treatment for inadvertent cyanoacrylate tarsorrhaphy: case report. *Arch Ophthalmol*. 1988;106(8):1033.
182. Donnenfeld ED, Perry HD, Nelson DB. Cyanoacrylate temporary tarsorrhaphy in the management of corneal epithelial defects. *Ophthalmic Surg*. 1991;22(10):591-593.
183. Ehrenhaus M, D'Arienzo P. Improved technique for temporary tarsorrhaphy with a new cyanoacrylate gel. *Arch Ophthalmol*. 2003;121(9):1336-1337.
184. Voon LW, Chua CN, Hanson R. The use of N-butyl cyanoacrylate (indermil) in lateral tarsorrhaphy. *Arch Ophthalmol*. 2004;122(2):279-281.
185. Trivedi D, McCalla M, Squires Z, Parulekar M. Use of cyanoacrylate glue for temporary tarsorrhaphy in children. *Ophthal Plast Reconstr Surg*. 2014;30(1):60-63.
186. Kirkham TH. Temporary tarsorrhaphy. *Am J Ophthalmol*. 1977;83(1): 137.
187. Wagoner MD, Steinert RF. Temporary tarsorrhaphy enhances reepithelialization after epikeratoplasty. *Arch Ophthalmol*. 1988;106(1): 13-14.
188. Panda A, Pushker N, Bageshwar LM. Lateral tarsorrhaphy: is it preferable to patching? *Cornea*. 1999;18(3):299-301.
189. Cosar CB, Cohen EJ, Rapuano CJ, et al. Tarsorrhaphy: clinical experience from a cornea practice. *Cornea*. 2001;20(8):787-791.
190. Fox SA. A new tarsorrhaphy suture. *Arch Ophthalmol*. 1961;66: 833-834.
191. Bodian M. A simple operation for lateral tarsorrhaphy. *Arch Ophthalmol*. 1965;74:74-76.
192. Jackson WE. Tarsorrhaphy. *Surg Clin North Am*. 1969;49(6): 1469-1473.
193. Grove AS Jr. Marginal tarsorrhaphy: a technique to minimize premature eyelid separation. *Ophthalmic Surg*. 1977;8(1):56-59.
194. Kapoor S, Agarwal DP, Gupta AK, Sood M. A new technique of tarsorrhaphy for children. *J Pediatr Ophthalmol*. 1977;14(1):56-57.
195. Missotten L. Lasting temporary tarsorrhaphy. *Bull Soc Belge Ophtalmol*. 1979;185:27.
196. Putterman AM. Suture tarsorrhaphy system to control keratopathy after ptosis surgery. *Ophthalmic Surg*. 1980;11(9):577-580.
197. Gossman MD, Bowe BE, Tanenbaum M. Reversible suture tarsorrhaphy for eyelid malposition and keratopathy. *Ophthalmic Surg*. 1991;22(4):237-239.
198. Hallock GG. Temporary tarsorrhaphy "zipper. *Ann Plast Surg*. 1992;28(5):488-490.
199. Quist LH. A simple and effective tarsorrhaphy technique without the use of external bolsters. *Ophthal Plast Reconstr Surg*. 1993;9(2): 148-149.
200. Rapoza PA, Harrison DA, Bussa JJ, Prestowitz WF, Dortzbach RK. Temporary sutured tube-tarsorrhaphy: reversible eyelid closure technique. *Ophthalmic Surg*. 1993;24(5):328-330.
201. Steiner GC, Gossman MD, Tanenbaum M. Modified tarsal pillar tarsorrhaphy. *Am J Ophthalmol*. 1993;116(1):103-104.
202. Rosenberg GJ. Temporary tarsorrhaphy suture to prevent or treat scleral show and ectropion secondary to laser resurfacing or laser blepharoplasty. *Plast Reconstr Surg*. 2000;106(3):721-725, discussion 726-727.
203. Shoham A, Lifshitz T. A new method of temporary tarsorrhaphy. *Eye (Lond)*. 2000;14(Pt 5):786-787.
204. Castillo GD, Remigio D. Temporary tarsorrhaphy during facial resurfacing surgery. *Arch Facial Plast Surg*. 2001;3(4):280-281.
205. Kitchens J, Kinder J, Oetting T. The drawstring temporary tarsorrhaphy technique. *Arch Ophthalmol*. 2002;120(2):187-190.
206. McInnes AW, Burroughs JR, Anderson RL, McCann JD. Temporary suture tarsorrhaphy. *Am J Ophthalmol*. 2006;142(2):344-346.
207. Raju VK, Mathalone B. Tarsorrhaphy with catgut. *Ophthalmic Surg*. 1980;11(9):625-626.
208. Klein MB, Ahmadi AJ, Sires BS Marginal tarsorrhaphy for corneal protection following severe eyelid burns: a salvage procedure. 37th American Burn Association. Chicago, IL, 2005.
209. Mocan MC, Erdogan-Poyraz C, Erdener U, Orhan M, Irkec M. Comparison of the outcomes of internal-fixation versus bolster-suture tarsorrhaphy. *Ophthal Plast Reconstr Surg*. 2007;23(3): 222-224.
210. Huang TT, Blackwell SJ, Lewis SR. Burn injuries of the eyelids. *Clin Plast Surg*. 1978;5(4):571-581.
211. Murphy MT, Bradrick JP. Technique for fixation of the Frost suture. *J Oral Maxillofac Surg*. 1995;53(11):1360-1361.
212. Desciak EB, Eliezri YD. Surgical pearl: temporary suspension suture (Frost suture) to help prevent ectropion after infraorbital reconstruction. *J Am Acad Dermatol*. 2003;49(6):1107-1108.
213. Jothi S, Moe KS. Lower eyelid splinting: an alternative to the Frost suture. *Laryngoscope*. 2007;117(1):63-66.
214. Sharabi SE, Hatef DA, Hollier LH Jr, Izaddoost S. Opening eyes to the Frost suture. *J Oral Maxillofac Surg*. 2010;68(6):1430-1431.
215. Connolly KL, Albertini JG, Miller CJ, Ozog DM. The suspension (Frost) suture: experience and applications. *Dermatol Surg*. 2015;41(3):406-410.
216. Kakudo N, Ogawa Y, Kusumoto K. Success of the orbicularis oculi myocutaneous vertical v-y advancement flap for upper eyelid reconstruction. *Plast Reconstr Surg*. 2009;123(1):423-424.
217. Demir Z, Yuce S, Karamursel S, Celebioglu S. Orbicularis oculi myocutaneous advancement flap for upper eyelid reconstruction. *Plast Reconstr Surg*. 2008;121(2):443-450.

218. Andrades PR, Calderon W, Leniz P, et al. Geometric analysis of the V-Y advancement flap and its clinical applications. *Plast Reconstr Surg*. 2005;115(6):1582-1590.
219. Huang TT, Capek KD 10 years of experience in using a nasolabial axial skin flap to manage cicatricial lower eyelid deformity in burn children. 48th American Burn Association. Las Vegas, NV. May 5, 2016.
220. Huang TT, Herndon DN Use of the nasolabial skin flap and/or orbicularis oculi musculocutaneous flap to reconstruct lower eyelid ectropion in burn patients. 38th American Burn Association. Las Vegas, NV. 2006.
221. Li XQ, Wang JQ. Orbicularis oculi myocutaneous flap for upper cicatricial ectropion. *J Craniofac Surg*. 2016;27(1):70-73.
222. Huang TT, Branski LK, Herndon DN, Dibildox M. Reconstruction of lower burn eyelid deformity recalcitrant to conventional treatment. 43rd American Burn Association. Chicago, IL, 2011.
223. Huang TT, Amayo E, Lewis SR. A histological study of the lower tarsus and the significance in the surgical management of a involutional (senile) entropion. *Plast Reconstr Surg*. 1981;67(5):585-590.
224. Capek K, Trocme SD, Huang TT, Herndon DN Surgical management of eyelid entropion in pediatric toxic epidermal necrolysis. 18th Congress of the International Society for Burn Injuries. Miami, FL, August 30, 2016.
225. Callahan A. Correction of entropion from Stevens-Johnson syndrome: use of nasal septum and mucosa for severely cicatrized eyelid entropion. *Arch Ophthalmol*. 1976;94(7):1154-1155.
226. Inchingolo F, Tatullo M, Abenavoli FM, et al. Upper eyelid reconstruction: a short report of an eyelid defect following a thermal burn. *Head Face Med*. 2009;5:26.
227. Haik GM. A fornix conjunctival flap as a substitute for the dissected conjunctival flap: a clinical and experimental study. *Trans Am Ophthalmol Soc*. 1954;52:497-524.
228. Khodadoust A, Quinter AP. Microsurgical approach to the conjunctival flap. *Arch Ophthalmol*. 2003;121(8):1189-1193.
229. Gundersen T. Conjunctival flaps in the treatment of corneal disease with reference to a new technique of application. *AMA Arch Ophthalmol*. 1958;60(5):880-888.
230. Wiedman MS, Gundersen T. Conjunctival flaps and cautery. *Int Ophthalmol Clin*. 1968;8(3):637-653.
231. Gundersen T, Pearlson HR. Conjunctival flaps for corneal disease: their usefulness and complications. *Trans Am Ophthalmol Soc*. 1969;67:78-95.
232. Kikkawa DO, Heinz GW, Martin RT, Nunery WN, Eiseman AS. Orbital cellulitis and abscess secondary to dacryocystitis. *Arch Ophthalmol*. 2002;120(8):1096-1099.
233. Sloan DF, Huang TT, Larson DL, Lewis SR. Reconstruction of eyelids and eyebrows in burned patients. *Plast Reconstr Surg*. 1976;58(3):340-346.
234. Huang TT, Sasaki K, Nozaki M. Reconstruction of the lacrimal excretory system. *Plast Reconstr Surg*. 1992;90(3):399-404.
235. Vanathi M, Panda A, Vengayil S, Chaudhuri Z, Dada T. Pediatric keratoplasty. *Surv Ophthalmol*. 2009;54(2):245-271.
236. Shi W, Wang T, Gao H, Xie L. Management of severe ocular burns with symblepharon. *Graefes Arch Clin Exp Ophthalmol*. 2009;247(1):101-106.
237. Kuffova L, Knickelbein JE, Yu T, et al. High-risk corneal graft rejection in the setting of previous corneal herpes simplex virus (HSV)-1 infection. *Invest Ophthalmol Vis Sci*. 2016;57(4):1578-1587.
238. Kumar V, Kumar A. Immunological aspects of corneal transplant. *Immunol Invest*. 2014;43(8):888-901.
239. Philipp W, Gottinger W. T6-positive Langerhans cells in diseased corneas. *Invest Ophthalmol Vis Sci*. 1991;32(9):2492-2497.
240. Serna-Ojeda JC, Loya-Garcia D, Navas A, et al. Long-term outcomes of pediatric penetrating keratoplasty for herpes simplex virus keratitis. *Am J Ophthalmol*. 2017;173:139-144.
241. Liu J, Shi W, Li S, Gao H, Wang T. Modified lamellar keratoplasty and immunosuppressive therapy guided by in vivo confocal microscopy for perforated Mooren's ulcer. *Br J Ophthalmol*. 2015;99(6):778-783.
242. Venkataratnam S, Ganekal S, Dorairaj S, Kolhatkar T, Jhanji V. Big-bubble deep anterior lamellar keratoplasty for post-keratitis and post-traumatic corneal stromal scars. *Clin Exp Ophthalmol*. 2012;40(6):537-541.
243. Wang J, Zhao G, Xie L, Chen M, Zhao J. Therapeutic effect of deep anterior lamellar keratoplasty for active or quiescent herpetic stromal keratitis. *Graefes Arch Clin Exp Ophthalmol*. 2012;250(8):1187-1194.
244. Sedghipour MR, Sorkhabi R, Shenasi A, Dehghan H. Outcome of penetrating keratoplasty in corneal ulcer: a single-center experience. *Clin Ophthalmol*. 2011;5:1265-1268.
245. Li J, Yu L, Deng Z, et al. Deep anterior lamellar keratoplasty using acellular corneal tissue for prevention of allograft rejection in high-risk corneas. *Am J Ophthalmol*. 2011;152(5):762-770 e3.
246. Liu H, Chen Y, Wang P, et al. Efficacy and safety of deep anterior lamellar keratoplasty vs. penetrating keratoplasty for keratoconus: a meta-analysis. *PLoS ONE*. 2015;10(1):e0113332.
247. Huang D, Qiu WY, Zhang B, Wang BH, Yao YF. Peripheral deep anterior lamellar keratoplasty using a cryopreserved donor cornea for Terrien's marginal degeneration. *J Zhejiang Univ Sci B*. 2014;15(12):1055-1063.
248. Gao H, Wang X, Echegaray JJ, et al. Partial lamellar keratoplasty for peripheral corneal disease using a graft from the glycerin-preserved corneoscleral rim. *Graefes Arch Clin Exp Ophthalmol*. 2014;252(6):963-968.
249. Huang T, Zhang X, Wang Y, et al. Outcomes of deep anterior lamellar keratoplasty using the big-bubble technique in various corneal diseases. *Am J Ophthalmol*. 2012;154(2):282-289 e1.
250. Iyer G, Srinivasan B, Rishi E, et al. Large lamellar corneoscleral grafts: tectonic role in initial management of severe ocular chemical injuries. *Eur J Ophthalmol*. 2016;26(1):12-17.
251. Li N, Wang X, Wan P, et al. Tectonic lamellar keratoplasty with acellular corneal stroma in high-risk corneal transplantation. *Mol Vis*. 2011;17:1909-1917.
252. Shi W, Liu M, Gao H, et al. Penetrating keratoplasty with small-diameter and glycerin-cryopreserved grafts for eccentric corneal perforations. *Cornea*. 2009;28(6):631-637.
253. Older JJ, Allansmith MR. Penetrating keratoplasty in a patient with 75% third degree burns. *Ann Ophthalmol*. 1975;7(2):309-311.
254. Hoffmann S, Szentmary N, Seitz B. Amniotic membrane transplantation for the treatment of infectious ulcerative keratitis before elective penetrating keratoplasty. *Cornea*. 2013;32(10):1321-1325.
255. Wee SW, Choi SU, Kim JC. Deep anterior lamellar keratoplasty using irradiated acellular cornea with amniotic membrane transplantation for intractable ocular surface diseases. *Korean J Ophthalmol*. 2015;29(2):79-85.
256. Ramamurthy S, Reddy JC, Vaddavalli PK, Ali MH, Garg P. Outcomes of repeat keratoplasty for failed therapeutic keratoplasty. *Am J Ophthalmol*. 2016;162:83-88 e2.
257. Robert MC, Arafat SN, Spurr-Michaud S, et al. Tear matrix metalloproteinases and myeloperoxidase levels in patients with Boston keratoprosthesis type I. *Cornea*. 2016;35(7):1008-1014.
258. Choi CJ, Stagner AM, Jakobiec FA, Chodosh J, Yoon MK. Eyelid mass in Boston keratoprosthesis type 2. *Ophthal Plast Reconstr Surg*. 2016.
259. Salvador-Culla B, Jeong KJ, Kolovou PE, et al. Titanium coating of the Boston keratoprosthesis. *Transl Vis Sci Technol*. 2016;5(2):17.
260. Davies E, Chodosh J. Infections after keratoprosthesis. *Curr Opin Ophthalmol*. 2016;27(4):373-377.
261. Wang L, Jeong KJ, Chiang HH, et al. Hydroxyapatite for keratoprosthesis biointegration. *Invest Ophthalmol Vis Sci*. 2011;52(10):7392-7399.
262. Kumar R, Dohlman CH, Chodosh J. Oral acetazolamide after Boston keratoprosthesis in Stevens-Johnson syndrome. *BMC Res Notes*. 2012;5:205.
263. Palioura S, Kim B, Dohlman CH, Chodosh J. The Boston keratoprosthesis type I in mucous membrane pemphigoid. *Cornea*. 2013;32(7):956-961.
264. Paschalis EI, Chodosh J, Spurr-Michaud S, et al. In vitro and in vivo assessment of titanium surface modification for coloring the backplate of the Boston keratoprosthesis. *Invest Ophthalmol Vis Sci*. 2013;54(6):3863-3873.
265. Gonzalez-Saldivar G, Lee NG, Chodosh J, Freitag SK, Stacy RC. Dacryops in the setting of a Boston type II keratoprosthesis. *Ophthal Plast Reconstr Surg*. 2014;30(3):e73-e75.
266. Chang HY, Luo ZK, Chodosh J, Dohlman CH, Colby KA. Primary implantation of type I Boston keratoprosthesis in nonautoimmune corneal diseases. *Cornea*. 2015;34(3):264-270.
267. Grassi CM, Crnej A, Paschalis EI, et al. Idiopathic vitritis in the setting of Boston keratoprosthesis. *Cornea*. 2015;34(2):165-170.
268. Grassi CM, Cruzat A, Taniguchi EV, et al. Periprosthetic tissue loss in patients with idiopathic vitreous inflammation after the Boston keratoprosthesis. *Cornea*. 2015;34(11):1378-1382.
269. Jardeleza MS, Rheaume MA, Chodosh J, Lane AM, Dohlman CH. Retinal detachments after Boston keratoprosthesis: incidence,

predisposing factors, and visual outcomes. *Digit J Ophthalmol*. 2015;21(4):1-15.
270. Homayounfar G, Grassi CM, Al-Moujahed A, et al. Boston keratoprosthesis type I in the elderly. *Br J Ophthalmol*. 2017;101(4):514-518.
271. Kammerdiener LL, Speiser JL, Aquavella JV, et al. Protective effect of soft contact lenses after Boston keratoprosthesis. *Br J Ophthalmol*. 2016;100(4):549-552.
272. Robert MC, Crnej A, Shen LQ, et al. Infliximab after Boston keratoprosthesis in Stevens-Johnson syndrome: an update. *Ocul Immunol Inflamm*. 2016;1–5.
273. Lee R, Khoueir Z, Tsikata E, et al. Long-term visual outcomes and complications of Boston keratoprosthesis type II implantation. *Ophthalmology*. 2017;124(1):27-35.
274. Poon LY, Chodosh J, Vavvas DG, Dohlman CH, Chen TC. Endoscopic cyclophotocoagulation for the treatment of glaucoma in Boston keratoprosthesis type II patient. *J Glaucoma*. 2017;26(4):e146-e149.
275. Langan EA, Liu C, Ogden S, Griffiths CE. A tooth for an eye: cicatricial pemphigoid and the osteo-odonto-keratoprosthesis. *Arch Dermatol*. 2010;146(10):1188-1189.
276. Michael R, Charoenrook V, de la Paz MF, et al. Long-term functional and anatomical results of osteo- and osteoodonto-keratoprosthesis. *Graefes Arch Clin Exp Ophthalmol*. 2008;246(8):1133-1137.
277. Liu C, Hille K, Tan D, Hicks C, Herold J. Keratoprosthesis surgery. *Dev Ophthalmol*. 2008;41:171-186.
278. Tan DT, Tay AB, Theng JT, et al. Keratoprosthesis surgery for end-stage corneal blindness in asian eyes. *Ophthalmology*. 2008;115(3):503-510 e3.
279. Iyer G, Pillai VS, Srinivasan B, et al. Modified osteo-odonto keratoprosthesis: the Indian experience: results of the first 50 cases. *Cornea*. 2010;29(7):771-776.
280. De La Paz MF, De Toledo JA, Charoenrook V, et al. Impact of clinical factors on the long-term functional and anatomic outcomes of osteo-odonto-keratoprosthesis and tibial bone keratoprosthesis. *Am J Ophthalmol*. 2011;151(5):829-839 e1.
281. Garg R, Khanna P, Sinha R. Perioperative management of patients for osteo-odonto-kreatoprosthesis under general anaesthesia: a retrospective study. *Indian J Anaesth*. 2011;55(3):271-273.
282. Narayanan V, Nirvikalpa N, Rao SK. Osteo-odonto-keratoprosthesis – a maxillofacial perspective. *J Craniomaxillofac Surg*. 2012;40(8):e426-e431.
283. Tan A, Tan DT, Tan XW, Mehta JS. Osteo-odonto keratoprosthesis: systematic review of surgical outcomes and complication rates. *Ocul Surf*. 2012;10(1):15-25.
284. Yu JF, Huang YF. Glaucoma with modified osteo-odonto keratoprosthesis. *Cornea*. 2012;31(10):1214, author reply 1215.
285. Basu S, Pillai VS, Sangwan VS. Mucosal complications of modified osteo-odonto keratoprosthesis in chronic Stevens-Johnson syndrome. *Am J Ophthalmol*. 2013;156(5):867-873 e2.
286. Klufas MA, Yannuzzi NA, D'Amico DJ, Kiss S. Vitreoretinal aspects of permanent keratoprosthesis. *Surv Ophthalmol*. 2015;60(3):216-228.
287. Charoenrook V, Michael R, de la Paz MF, et al. Osteokeratoprosthesis using tibial bone: surgical technique and outcomes. *Ocul Surf*. 2016;14(4):495-506.
288. Iyer G, Srinivasan B, Agarwal S. Rachapalle SR. Laminar resorption in modified osteo-odonto-keratoprosthesis procedure: a cause for concern. *Am J Ophthalmol*. 2014;158(2):263-269 e2.
289. Lee RM, Ong GL, Lam FC, et al. Optical functional performance of the osteo-odonto-keratoprosthesis. *Cornea*. 2014;33(10):1038-1045.
290. Lim LS, Ang CL, Wong E, Wong DW, Tan DT. Vitreoretinal complications and vitreoretinal surgery in osteo-odonto-keratoprosthesis surgery. *Am J Ophthalmol*. 2014;157(2):349-354.
291. Weisshuhn K, Berg I, Tinner D, et al. Osteo-odonto-keratoprosthesis (OOKP) and the testing of three different adhesives for bonding bovine teeth with optical poly-(methyl methacrylate) (PMMA) cylinder. *Br J Ophthalmol*. 2014;98(7):980-983.
292. Avadhanam VS, Liu CS. A brief review of Boston type-1 and osteo-odonto keratoprostheses. *Br J Ophthalmol*. 2015;99(7):878-887.
293. Berg BI, Dagassan-Berndt D, Goldblum D, Kunz C. Cone-beam computed tomography for planning and assessing surgical outcomes of osteo-odonto-keratoprosthesis. *Cornea*. 2015;34(4):482-485.
294. Iyer G, Srinivasan B, Agarwal S, et al. Bone augmentation of the osteo-odonto alveolar lamina in MOOKP: will it delay laminar resorption? *Graefes Arch Clin Exp Ophthalmol*. 2015;253(7):1137-1141.
295. Iyer G, Srinivasan B, Agarwal S, et al. Glaucoma in modified osteo-odonto-keratoprosthesis eyes: role of additional stage 1A and Ahmed glaucoma drainage device-technique and timing. *Am J Ophthalmol*. 2015;159(3):482-489 e2.
296. Basu S, Sureka S, Shukla R, Sangwan V. Boston type 1 based keratoprosthesis (Auro Kpro) and its modification (LVP Kpro) in chronic Stevens Johnson syndrome. *BMJ Case Rep*. 2014;2014.
297. Iyer G, Srinivasan B, Agarwal S, Shanmugasundaram S, Rajan G. Structural and functional rehabilitation in eyes with lamina resorption following MOOKP: can the lamina be salvaged? *Graefes Arch Clin Exp Ophthalmol*. 2014;252(5):781-790.
298. Sawatari Y, Marx RE, Perez VL, Parel JM. Biointegration of the osteo-odonto lamina in the modified osteo-odonto keratoprosthesis: engineering of tissue to restore lost vision. *Int J Oral Maxillofac Implants*. 2013;28(5):e304-e309.
299. Iyer G, Srinivasan B, Agarwal S, Barbhaya R. Visual rehabilitation with keratoprosthesis after tenonplasty as the primary globe-saving procedure for severe ocular chemical injuries. *Graefes Arch Clin Exp Ophthalmol*. 2012;250(12):1787-1793.
300. Sawatari Y, Perez VL, Parel JM, et al. Oral and maxillofacial surgeons' role in the first successful modified osteo-odonto-keratoprosthesis performed in the United States. *J Oral Maxillofac Surg*. 2011;69(6):1750-1756.

44 The Burn Problem: A Pathologist's Perspective

HAL K. HAWKINS

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Introduction

A large burn is not a simple injury but a very complicated disease. This statement, restated from its publication in 1840, holds true with additional force in 2016.[1] Massive destruction of skin tissue by burns stimulates many complex reactions that are still only partly understood. Malfunction of every organ system complicates the responses of patients to large burns. These malfunctions can be clarified by examination of the body after death. Postmortem examination also may reveal unsuspected infections or adverse effects of therapy. In addition, postmortem examination leads to review of the circumstances of injury and of the causal sequence in which complications occurred. Analysis of an entire case from the point of view of pathogenesis often clarifies the nature of the patient's most significant problems. The manner of death is accident in most cases, but collection of additional information on the circumstances of the initial injury sometimes reveals evidence of homicide. After presentation of the major systemic problems that occur in burn patients, this chapter reviews some of the observations made at autopsy organized by organ system. It also surveys experimental evidence that bears on pathogenic mechanisms relevant to disease processes seen at autopsy. The observations reviewed here are drawn from the experience of more than 300 autopsies performed on burned children who died at the Shriners Burns Hospital in Galveston, Texas, from 1971 to the present.

Systemic Reactions to Burns

HYPOXIA AND ISCHEMIA

Immediately after burn injury, massive loss of intravascular fluid into the burned tissue begins to occur.[2,3] Unless this fluid loss is replaced very promptly and carefully, serious hypovolemia develops.[4–6] *Hypovolemia* and the resulting reduction of tissue perfusion to levels less than that necessary for cellular survival, which is defined as *ischemia*, causes necrosis of certain cells. Typically, the cells first affected by ischemia are those with the greatest oxygen demand, including neurons in the brain, cardiac myocytes, intestinal epithelial cells, and proximal tubular epithelial cells in the kidney. After the death of selected cell types or whole segments of organs (infarcts), responses are generated that often lead to further injury of remote organs. Cellular necrosis stimulates an intense acute inflammatory reaction. In the skin, the tissues at the base of the zone of necrosis become acutely inflamed. Cytokines released by inflammatory cells and surviving cells in the tissue have effects throughout the body. In addition, in endothelial cells injured by hypoxia, the enzyme xanthine dehydrogenase is converted to xanthine oxidase, which releases superoxide during degradation of adenosine, which in turn is released by necrotic cells.[7,8] Superoxide, released into the circulation by this metabolic process and by neutrophils, can injure the lung by damaging both endothelial and epithelial cells and allowing protein-rich fluid to exude into alveoli. In experimental models of burn injury, as well as in models of ischemia–reperfusion injury, the lungs have been shown to be injured by these processes.[9,10] Ischemia caused by reduced perfusion may lead to necrosis of pancreatic acinar epithelium and acute pancreatitis. Thermal injury to skeletal muscle, or lack of perfusion of muscle, may lead to local exudation of fluid and development of such high pressures in fascial compartments that arterial perfusion is prevented. This "compartment syndrome," unless relieved by prompt surgical intervention, leads to necrosis of muscle throughout the entire compartment.[11] The consequences of massive necrosis of muscle often include secondary injury to the lungs, owing to release of reactive oxygen species, and myoglobinuria with secondary renal damage.[12] At the time of injury, patients frequently inhale carbon monoxide, which compromises the oxygen-carrying capacity of the blood. The resultant tissue hypoxia can cause death at the scene, and if the patient survives, it can be sufficient to lead to irreversible neuronal injury, cerebral edema, and brain death days later. *Hypoxemia*, sometimes related to carbon monoxide intoxication, also contributes to cardiac and renal injury. In addition, when fires occur in closed spaces, the "flashover" process consumes all available oxygen so that the patient's environment may contain too little oxygen to sustain life. Occasionally, a burn victim is found without pulse or respiratory effort, probably as a consequence of hypoxia, and is revived by cardiopulmonary resuscitation (CPR). In such cases, ischemic and hypoxic injury may be profound in multiple organs.

INFECTION

Necrotic skin provides an excellent environment for proliferation of bacteria and fungi, and as long as necrotic tissue remains, the risk of infection remains high. Immunosuppression contributes to this risk, and burn patients develop serious infections with agents usually encountered only in patients treated with immunosuppressive drugs. The mechanisms of this immunosuppression are still under investigation but include excessive secretion of glucocorticoids,

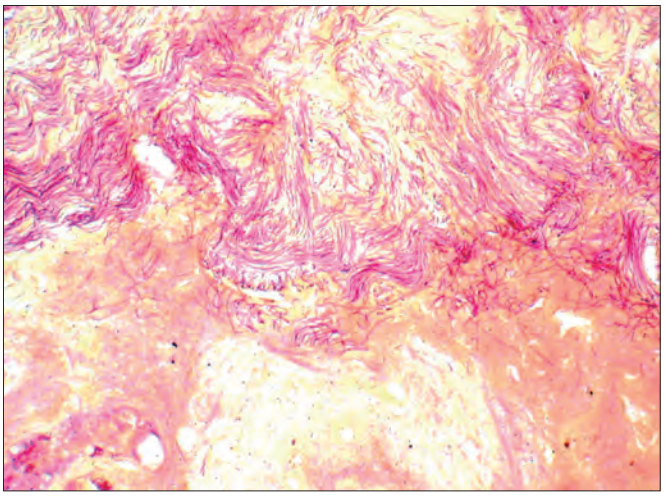

Fig. 44.1 Micrograph showing a dense cluster of filamentous Gram-negative rods within necrotic skin in a patient with severe wound infection from whom *Pseudomonas aeruginosa* was recovered in culture. Tissue Gram stain.

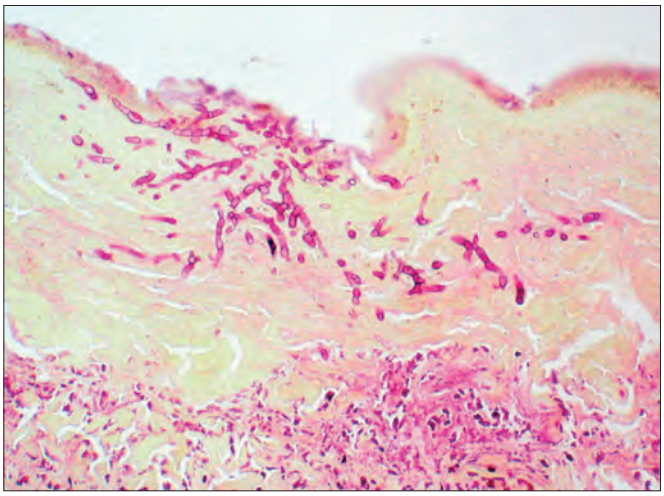

Fig. 44.2 Micrograph showing fungal hyphae within necrotic tissue extending close to the boundary with intact, viable dermal tissue. Periodic acid–Schiff stain.

abnormal cytokine signaling, and altered maturation of neutrophils and macrophages. When burn wounds become infected and large numbers of bacteria accumulate, those with high pathogenic capacity invade the adjacent viable tissue, produce further necrosis, and gain access to the circulation. This is the condition of burn wound sepsis, which historically has been the leading cause of death in burn patients. In Linares' series of 115 autopsies, sepsis was present in 73%, as documented by positive blood culture and demonstration of invasive infection of viable tissue.[13] When pneumonia was found at autopsy in such a case, the cause of death was classified as burn wound sepsis, with pneumonia as a contributing cause. In more recent cases, pneumonia has been considered the primary cause of death. In 80% of these fatal cases of sepsis, the burn wound was the source of the infection. The most important pathogens were *Pseudomonas aeruginosa, Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli, Enterobacter* spp., and *Candida* spp. More recently, antibiotic-resistant *Acinetobacter* has emerged as a frequent cause of fatal sepsis. Burn wound sepsis is recognized clinically when a burn wound is the site of proliferating microorganisms exceeding 10^5/g of tissue and there is histologic evidence of active invasion of subjacent unburned tissue.[14]

It is important to assess the presence and extent of infection within the burn wound, both by careful clinical examination of wounds and by biopsy of suspicious areas. A high index of suspicion serves burn patients well. All biopsy and excision specimens in our institution are sampled and studied histologically using special stain, a tissue Gram stain for bacteria, and methenamine silver for fungi. In large excision specimens, samples are taken from sites of especially deep tissue injury and sites that show abnormal discoloration of dermal or subcutaneous tissue. When infectious microorganisms are found, it is important to determine their location with respect to the boundary between living and necrotic tissue. This boundary may be irregular but is generally distinct and marked by inflammation in wounds that are several days old, and it may be indistinct in very fresh specimens because karyolysis takes some time to develop in burn wounds.

Wound infections generally begin with colonization of the skin surface and proliferation of organisms on the surface, often with extension into hair follicles followed by growth within the necrotic tissue. Growth within necrotic tissue is considered evidence of tissue infection, however, and is potentially more dangerous than growth on the surface of necrotic skin. Even when quantitative cultures show more than 10^5 bacteria per gram of tissue, when careful histologic study shows that the organisms are limited to the skin surface or the superficial necrotic tissue, the risk of sepsis appears to be low. Such growth on or in necrotic tissue, however, sets the stage for invasion of viable tissue. The finding of clusters of bacteria or fungi within viable tissue implies a serious risk of sepsis and further tissue invasion. Bacterial invasion of viable tissue is readily apparent by histologic study of appropriate tissue samples (Fig. 44.1). Invasive fungal infection presents a somewhat different pattern in that there is often a wavefront of necrosis that accompanies fungal invasion (Fig. 44.2). Thus, the presence of fungal hyphae extending to a boundary between necrotic and viable tissue is considered evidence of fungal invasion of viable tissue. On this basis, infections identified within burn wounds are reported as surface colonization; invasion of necrotic tissue, which may be superficial or deep; and invasion of viable tissue. The responsible surgeon is called immediately when invasion of viable tissue is found. If the level of clinical suspicion is high, cryosectioning techniques can be useful. We use a tape transfer device to facilitate handling of these specimens, since cryosections of adipose tissue and necrotic tissue adhere poorly to slides. The results are confirmed with routine sections on the following day. Diagnosis of viral infection of the skin is achieved most efficiently by sampling freshly opened vesicular lesions or the bases of recently ruptured vesicles and molecular testing by polymerase chain reaction (PCR).

When septicemia occurs, there is a generalized reaction, which often includes hypotension, tachycardia, increased

hyperthermia or hypothermia, and poor perfusion of the intestines and other viscera.[15] Coagulopathy is also an important complication of sepsis.[16] In addition, after bacteria have gained entrance to the general circulation, tissue infection may develop at distant sites. This is most likely to occur in the lungs. One recent case demonstrated clearly the route of dissemination of fatal burn wound sepsis. The patient was admitted in a clinically septic condition 2 weeks after sustaining a large burn and died despite aggressive therapy. At the time of autopsy, there were many areas of bacterial proliferation within the burn wound, invasion of viable tissue deep to the burn eschar, and thrombosis of blood vessels invaded by bacteria at the margin of the necrotic zone. Bacteria were especially numerous within the smooth muscle of veins in the dermis, suggestive of biofilm formation. Septic emboli with fibrous organization were seen in pulmonary artery branches in all lobes of the lungs. There were foci of necrosis throughout the lungs in which bacterial proliferation was visible within the walls of arteries, and these necrotic areas were surrounded by massive pulmonary hemorrhage and edema. Very little acute inflammatory reaction was seen around the many foci of bland necrosis in the lungs. A direct hematogenous route of spread of infection from the skin to the lungs seemed clear in this case. This pattern is similar to that of ecthyma gangrenosum of the skin, which is also characterized by bland necrosis thought to be caused by ischemia.[17,18] A similar angioinvasive pattern of pulmonary infection can be seen with generalized infection caused by *Aspergillus* spp. or similar filamentous fungi. On the other hand, airway obstruction is known to predispose to pneumonia acquired through the airways by preventing normal clearance of bacteria from the airways and by providing a favorable medium for bacterial growth. Multiple foci of airway obstruction are almost always seen at autopsy in burn patients.[19] In another recent case, although pneumonia was not present, there was invasion of antibiotic-resistant *Pseudomonas* spp. directly into the wall of a bronchus (Fig. 44.3). Although many serious infections in burn patients are caused by endogenous flora and many derive from wound infections present at the time of admission, nosocomial infection is a constant hazard.[20,21] The problem of burn wound sepsis is amenable to therapy. The strategy of excision of the potentially infected burn wound as early as possible, together with judicious administration of effective antibiotics, can reduce the number of deaths caused by infection. After the institution of early excision and grafting of burn patients in our institution, the incidence of burn wound sepsis as a cause of death declined dramatically, but the problem of sepsis persists. Organisms resistant to all available antibiotics are seen in burn patients with increasing frequency, and development of new antibiotics has not kept pace.[22] Patients who are referred for therapy more than 1 week after burn injury often have extensive invasive wound infection and sepsis caused by antibiotic-resistant organisms. Other microorganisms also can cause life-threatening infections in burn patients. *Fungal infection* is a continuing problem in patients with large burns.[23] Diagnosis of specific fungal infections by histopathology is difficult because important morphologic features that allow identification in culture do not occur in tissues, and fungi may display unexpected structural features in injured tissues. Pigmented fungal species generally do not show invasive behavior, and saprophytic species can mimic Zygomycetes. In one recent case of apparent systemic fungal infection, invasive and systemic dissemination of a pseudofungus of the genus *Oomycetes* was demonstrated.[24] Molecular methods (reverse transcriptase PCR) were used to identify the organism in this case. Zygomycetes have recently been recognized as dangerous burn wound pathogens.[25] It seems likely that the increased availability of molecular diagnostic testing of infectious agents may lead to recognition of additional previously unrecognized causes of invasive infection in burn patients as well as allowing more precise and rapid diagnosis of infection. Viral infections may also complicate burns. We have also experienced cases in which acquisition or reactivation of herpes virus infections led to major tissue injury. The risks of infection of a victim of a large burn are somewhat similar to those of an immunosuppressed transplant patient. Recent studies have illustrated the usefulness of the study of autopsy tissue in generating hypotheses to be tested in the laboratory.[26,27]

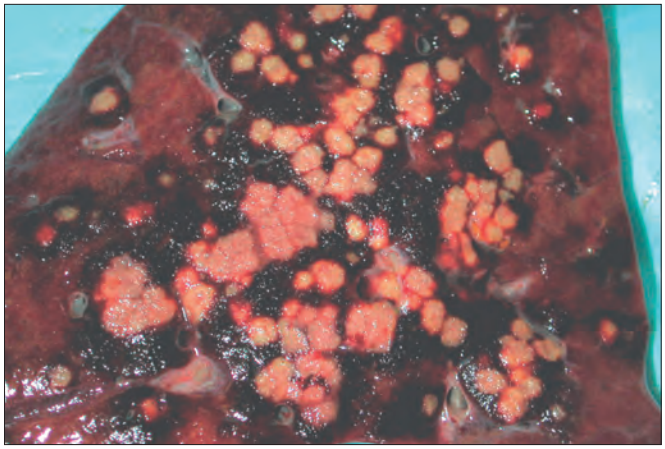

Fig. 44.3 Photograph showing a slice of the upper lobe of the lung taken at autopsy from a patient who showed clinical signs of sepsis when he developed disseminated infection after multiple wound cultures of open wounds yielded multiple antibiotic-resistant *Pseudomonas* spp.

COAGULOPATHY

The burn wound has procoagulant effects and may induce coagulation throughout the circulation (disseminated intravascular coagulation [DIC]).[28,29] Tissue necrosis can lead to coagulopathy. Generation of thrombin within the circulation leads to generation of fibrin peptides and stimulates acute inflammatory reactions, including increased vascular permeability and upregulation of adhesion molecules on neutrophils and endothelial cells (Fig. 44.4).[30] Generation of fibrin degradation products may interfere with normal thrombosis, and thrombocytopenia can develop.[31] Activation of the kinin system can stimulate further abnormal vascular permeability and hypotension.[32] Consumption of coagulation factors can lead to abnormal bleeding, which can cause extensive tissue injury secondarily. It is important to note that the acute-phase response to burn injury includes increased synthesis of fibrinogen

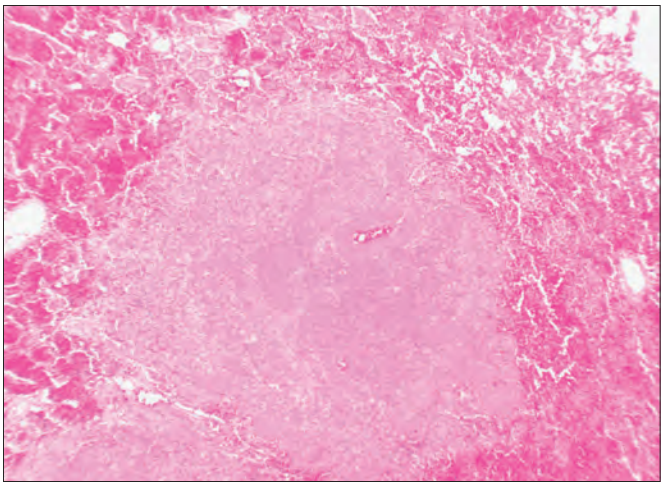

Fig. 44.4 Micrograph, taken at low magnification, showing a small round pale area of necrotic lung tissue in which no nuclei are staining, surrounded by a zone of congestion and hemorrhage, with very little acute inflammatory reaction. Hematoxylin and eosin stain.

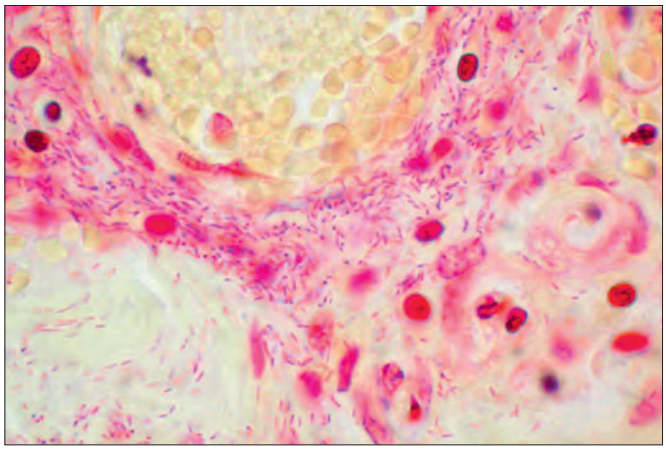

Fig. 44.5 High-magnification micrograph showing short Gram-negative rods growing profusely within the wall of a small pulmonary artery branch. Brown–Hopps tissue Gram stain.

and factor VIII. During the first 3–10 days after burn injury, patients often have greater than normal clotting activity. When DIC occurs, coagulation factors, including antithrombin, are depleted.[33,34] When DIC occurs in the patient's terminal course, microscopic fibrin thrombi are seen in many organs at the time of autopsy, most commonly in the lungs, the skin, the kidneys, and the gastrointestinal (GI) tract.[13,35]

Review of Organ Systems Affected by Burns

INTEGUMENTARY SYSTEM

The skin is the site of initial injury in burn patients, and many of the events that lead to dysfunction or failure of other organs begin in the skin. Thermal injury rapidly produces irreversible injury and cell death in all tissues in the skin. In many cases, a burn wound excised within 48 hours of injury shows that the entire dermis and all of the hair follicles are necrotic, but much of the subcutaneous adipose tissue remains viable. It appears that the greater insulating capacity of adipose tissue protects it. In some cases, however, necrosis extends deep into the subcutaneous tissue. Frequently a bandlike infiltrate of degenerating polymorphonuclear neutrophils is seen in histologic sections in the midst of a totally necrotic dermis. This suggests that the boundary between necrotic and viable tissue may have extended deeper after the initial burn injury and its inflammatory response. There is experimental evidence that burn wounds often evolve from an initial level of necrosis to a deeper level, even from second to third degree, as a result of poor perfusion of the tissue immediately deep to the initial burn injury.[36] This process of vascular stasis deep to the burn is undoubtedly due in part to the rapid loss of intravascular fluid from the damaged capillaries and venules just below the necrotic burn wound. In addition, there is evidence that neutrophils contribute to this process of burn wound extension (Fig. 44.5).[37]

A fortunately rare complication involving the skin of patients with large burns is the development of squamous cell carcinoma during the late phase of recovery. This so-called "Marjolin ulcer" shows extensive local invasion but generally can be controlled with adequate local excision.[38–40]

RESPIRATORY SYSTEM

Respiratory failure, defined as the inability to maintain adequate oxygen saturation while 100% oxygen is given via ventilator, is the immediate cause of death in some burn patients. The causes and mechanisms of respiratory failure are multiple and will be addressed separately, although often more than one mechanism operates. Direct thermal injury to the trachea and bronchi probably does not occur, except in patients exposed to large amounts of steam. In addition to the problems listed below, patients may develop problems related to the airways such as pneumothorax or interstitial emphysema, aspiration of gastric contents, pulmonary embolism, and nonspecific pulmonary edema related to increased venous pressure. Lesions of the lungs, which may be multiple, are often found at autopsy in burn patients.[41]

Diffuse alveolar damage, the histopathologic correlate of acute respiratory distress syndrome, affects the pulmonary parenchyma in all lobes, although it is often patchy in distribution, and begins with exudation of protein-rich fluid into alveolar spaces. This exudate is a consequence of damage to or increased permeability of both capillary endothelial cells and the epithelial type I cells of the alveolar lining. Within hours, the exudates form hyaline membranes, which are a histologic hallmark of this disease process (Fig. 44.6). Within a few days, the exudate begins to undergo organization by spindle-shaped fibroblasts within alveolar spaces (Fig. 44.7), and collagenous fibrosis develops, which obliterates alveoli and greatly thickens the septa between alveoli and extends between capillaries and the alveolar surface. Macrophages accumulate within alveoli, and alveolar epithelial type II cells multiply. In the

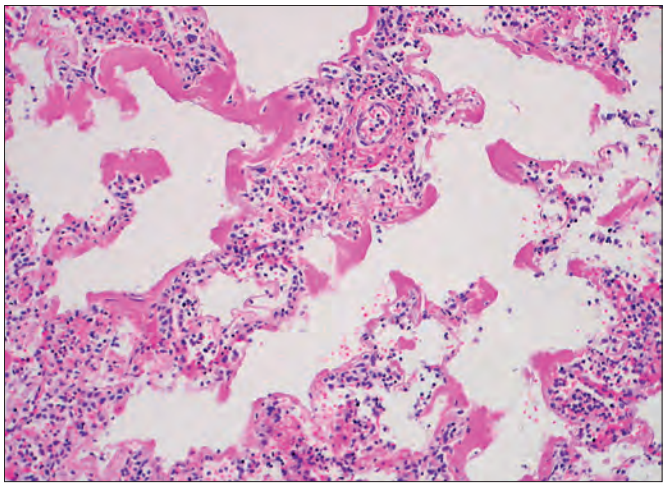

Fig. 44.6 Section of lung tissue showing bright pink, homogeneous hyaline membranes attached to alveolar walls and septa of alveolar ducts. This is from a 2-year-old patient who died 8 days after a large scald burn. This represents the exudative phase of diffuse alveolar damage, which may be seen in the absence of smoke inhalation injury. Hematoxylin and eosin stain.

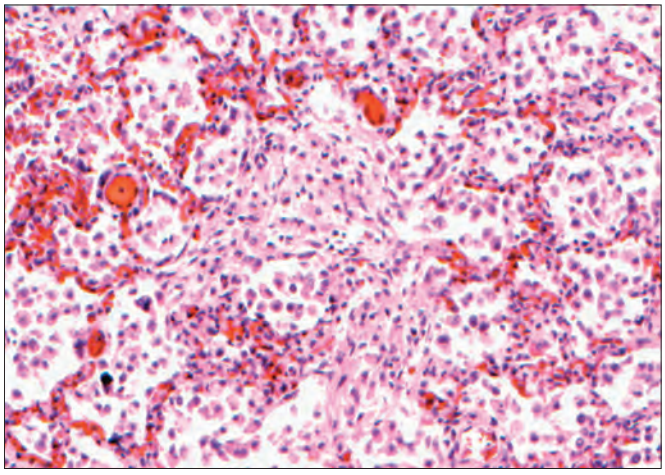

Fig. 44.7 Micrograph showing numerous elongated cells resembling fibroblasts occupying alveolar spaces and secreting connective tissue matrix. This abnormality represents the proliferative phase of diffuse alveolar damage. This patient died 1 month after a large flame burn and had clinical evidence of smoke inhalation injury and acute respiratory distress syndrome. Hematoxylin and eosin stain.

late stages, there is severe interstitial fibrosis. Multiple pathogenetic mechanisms are involved for this process, and it is not yet clear which of these are most significant in patients with burn injury.[42,43] The burn injury stimulates activation of complement, which could stimulate vascular leakage in the pulmonary bed. These and many other peptides are thought to activate circulating neutrophils, which produce secondary injury to the vascular and epithelial membranes in the lung.[44,45] Conversion of xanthine dehydrogenase to xanthine oxidase in the burn wound can cause release of superoxide into the venous circulation, stimulating endothelial injury and oxidative stress in the lung.[7] The neutrophils reacting to the burn wound undergo an oxidative burst, with release of superoxide into the circulation. This process is greatly enhanced if the patient's course is complicated by ischemic injury to muscle compartments, limbs, or other organs. Lipid peroxidation is a recognized consequence of burn injury. Superoxide can also react with nitric oxide, produced in the wound or the lung, to form peroxynitrite, a highly toxic substance.[46] Thrombin peptides, released during thrombosis of blood vessels in the wound, can also activate neutrophils and stimulate endothelial cells to express adhesion molecules.[47] The kinin system can be activated during thermal injury, with its systemic consequences. When patients develop sepsis, additional pulmonary damage may be produced by release of proinflammatory cytokines and augmentation of the processes that lead to inflammatory injury of the lung.[13,48] Neuropeptides, including substance P and calcitonin gene-related peptide (CGRP), may have a role in increasing vascular leakage in the airways.[49,50] Finally, the presence of oxygen in high concentration can itself lead to injury manifest as diffuse alveolar damage.[51–53] Despite this plethora of mechanisms that can lead to pulmonary injury in burn patients, many patients with massive burn injury do not develop clinically apparent respiratory difficulty. The conditions that seem to be most strongly associated with this form of pulmonary injury are delayed fluid resuscitation, limb ischemia, and sepsis. A recent publication noted that although diffuse alveolar damage has been found less frequently than infection as a cause of death at autopsy in recent years, the histologic changes of diffuse alveolar damage are frequently identified at the time of autopsy.[54]

Smoke inhalation injury commonly complicates burns that occur in burning buildings. The toxic effects of products of combustion directly injure tissues in the airways and lead to lung injury after a phase characterized by airway inflammation and exudation. These patients are recognized during bronchoscopy by observing hyperemia of the tracheobronchial mucosa and small particles of carbonaceous soot within the airways. Associated findings include facial burns and singed nasal hairs. These patients usually do not require ventilator therapy for several days but are at high risk of developing respiratory failure, which responds poorly to ventilator therapy and may prove fatal even when the burn injury is small. The mortality rate of burn injury has been found to be greatly increased when inhalation injury also is present.[55–59] Experimental studies in sheep and dogs have partially clarified the mechanisms of smoke inhalation injury.[60–63] In animals, the immediate reactions to inhalation of toxic smoke include detachment of numerous ciliated columnar cells from the tracheobronchial epithelium, massive secretion of mucus by secretory cells, and a more than 10-fold increase in tracheobronchial blood flow.[64–66] Within a few hours, an intense acute inflammatory reaction develops in the airways, with exudation of numerous neutrophils and release of protein-rich fluid that may coagulate within airways, forming occlusive "casts" (Fig. 44.8). After 48 hours, the exudate of neutrophils fills many terminal bronchioles and begins to extend into the lung parenchyma (Fig. 44.9). Studies using markers of upper airway mucus, including Alcian blue staining and immunostaining for Muc5B, demonstrate the presence of this material in small peripheral airways and alveoli, showing that the obstructive material moves from larger to smaller, more

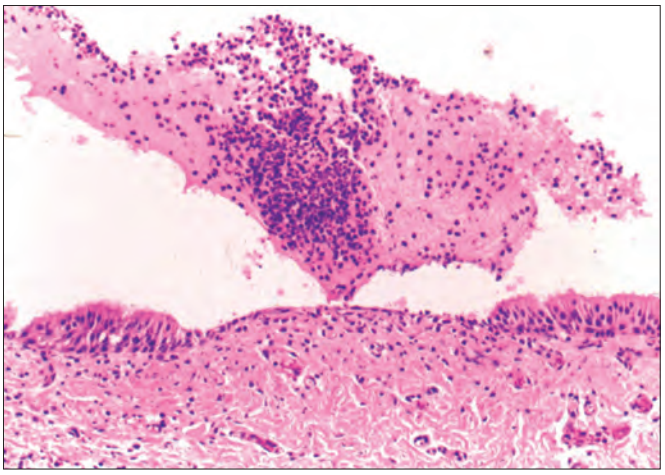

Fig. 44.8 Micrograph of a sheep trachea sampled 3 hours after experimental smoke inhalation injury by insufflation of cooled cotton smoke under anesthesia. Numerous polymorphonuclear neutrophils appear to be flowing into the tracheal lumen from a gap in the epithelial lining. Hematoxylin and eosin stain.

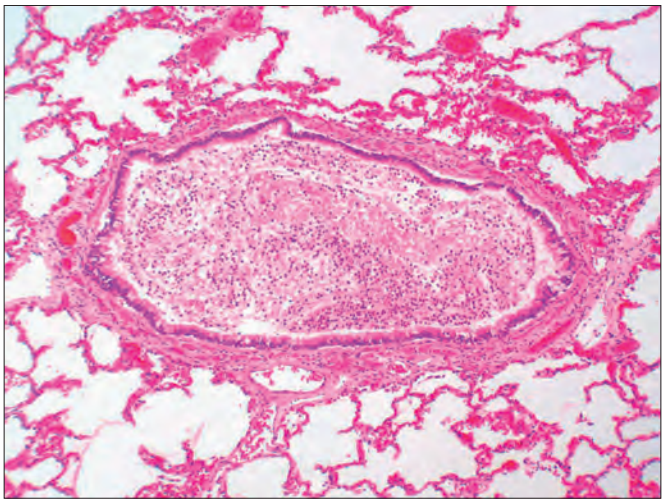

Fig. 44.10 Micrograph showing a bronchiole in human lung tissue obtained at autopsy 7 days after a large flame burn. The lumen is almost completely obstructed by a mixture of fibrin, mucus, and neutrophils. Hematoxylin and eosin stain.

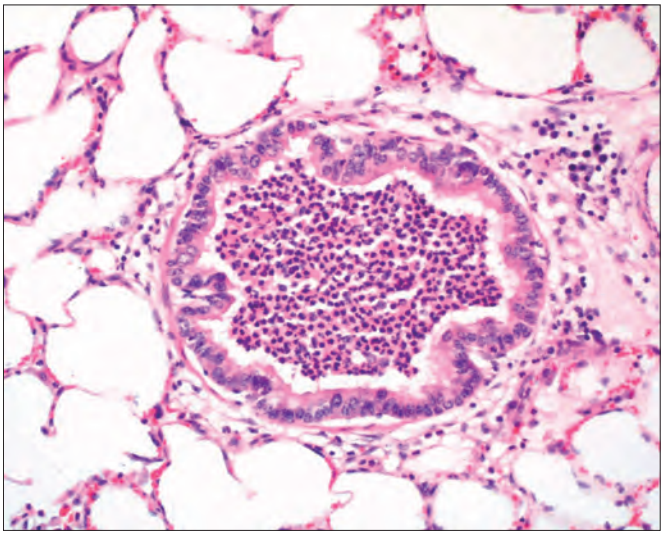

Fig. 44.9 Micrograph showing polymorphonuclear neutrophils filling the lumen of a small bronchiole in a sheep 48 hours after experimental smoke inhalation injury. Hematoxylin and eosin stain.

peripheral airways.[26] This inflammatory reaction resolves in the experimental animal, and the epithelium slowly regenerates. However, autopsy evidence suggests that exudation of neutrophils and protein into the airways resolves poorly in humans and may persist for weeks (Fig. 44.10). The loss of airway epithelium, which may be extensive, does not regenerate for long periods. Perhaps because of failure of the mucociliary escalator, mucus can be seen to accumulate around terminal bronchioles focally.[19] Failure of mucociliary clearance would be expected to increase the risk of pneumonia in burn patients. Multiple mechanisms may be responsible for the respiratory disease evoked by inhalation of toxic smoke.[67] Factors that may be likely to lead to selective damage to the airways include local release of neuropeptides by afferent C-fibers in the airways and activation of vagal reflexes and activation of proinflammatory processes in reaction to injury to the airway mucosa, particularly local production of interleukin (IL)-8.[68–71] Local production of nitric oxide and other reactive nitrogen species has significant deleterious effects in this form of acute lung injury, according to large animal experiments.[72,73] Local activation of thrombin during the formation of fibrin clots and local production of endothelin-1 may further enhance the inflammatory reaction in the airways.[74,75] Experimental studies in sheep have demonstrated that activation of poly-adenosyl-ribose polymerase (PARP) contributes to lung injury after burn and smoke inhalation injury.[76] Obstruction of small bronchi and bronchioles is thought to lead to failure of ventilation of multiple small segments of lung tissue, and inappropriate vasodilation in these poorly ventilated segments caused by the vascular effects of nitric oxide may well contribute to the failure of adequate oxygenation.[26] Treatment with nebulized heparin or tissue plasminogen activator has been found to reduce the degree of airway injury in the ovine model, demonstrating the importance of fibrin polymerization in this model.[77,78] Segmental atelectasis and prominent vasodilation in focal areas are features of smoke inhalation injury seen in experimental animals and in patients examined at autopsy after burn injury and smoke inhalation injury. Obstruction of bronchi and bronchioles by mucus, fibrin, and cell debris contributes to respiratory malfunction in experimental animals, and similar obstructive material is seen in human lung tissue at autopsy.[19,26,62,67,79] A recent review of more than 40 years' experience at the Shriners Burns Hospital in Galveston found that although clinical evidence of smoke inhalation injury was present in only 14% of patients admitted for recent burns, such evidence was recorded in 66% of the patients who died. Although autopsy cases in which death is attributable to smoke inhalation injury without infection have become uncommon, histologic evidence of diffuse alveolar damage is still commonly seen in lung tissue sampled at autopsy.[54]

CARDIOVASCULAR SYSTEM

Despite the tachycardia and increased output common to patients with burn injury, structural lesions of the heart have been uncommon in our autopsy series, which represents a pediatric population. However, cardiac hypertrophy is a consistent finding.[80] Cardiac dilation and clinical evidence of poor myocardial contractility develop in some patients after burn injury. Bacterial endocarditis occurs in occasional patients with sepsis complicating burn injury. Nonbacterial thrombotic endocarditis (marantic endocarditis) has also been seen and may also give rise to embolic complications (Fig. 44.11). When the endocardial region of the left ventricle is examined at autopsy, small foci of necrosis associated with local hemorrhage are often observed (Fig. 44.12). Contraction band necrosis in these foci is sometimes the only evidence of myocardial injury. These lesions may represent poor perfusion of a tissue with high metabolic demands during terminal episodes of hypotension. In some cases, they may represent the effects of endogenous or exogenous adrenergic agents.[81,82] This mode of injury is potentially preventable in burn patients.

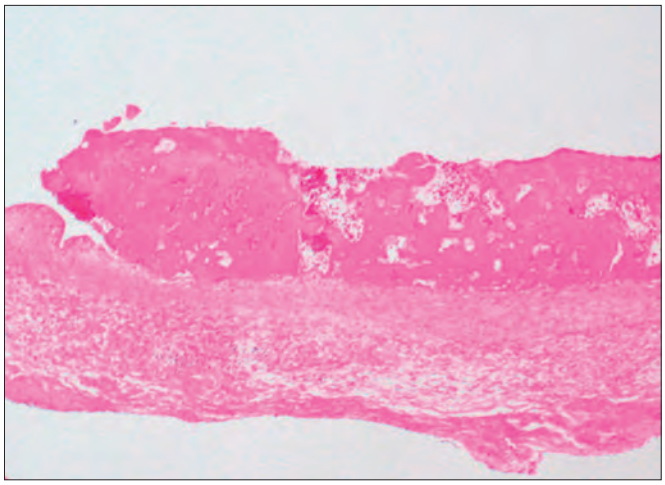

Fig. 44.11 Micrograph of a hematoxylin and eosin-stained cardiac valve showing a deposit of fibrin on the tricuspid valve of a patient who died of sepsis and had nonbacterial thrombotic (marantic) endocarditis diagnosed at autopsy. Gram stains did not reveal any bacteria.

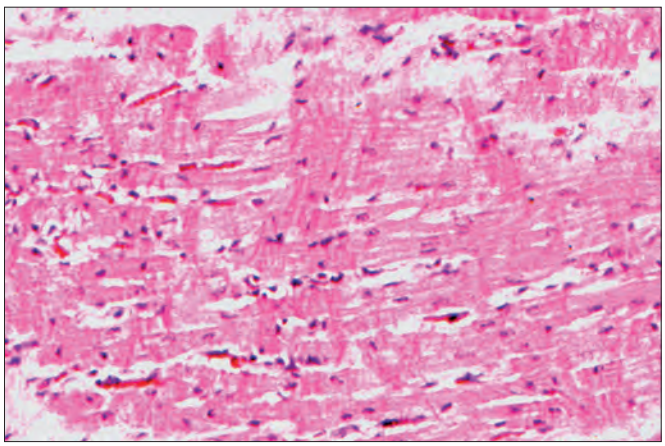

Fig. 44.12 High-magnification micrograph of heart tissue showing the presence of multiple contraction bands in cardiac myocytes, seen as refractile dark red bands running across muscle fibers. This is an early irreversible change that is seen early after ischemic injury causes lethal cell injury, especially when the tissue is reperfused with blood. It can also be seen in the setting of β-adrenergic toxicity. Hematoxylin and eosin stain.

URINARY SYSTEM

Patients with extensive burn injury, if resuscitated adequately during the first few hours, may have normal renal function throughout their hospital courses. However, when the initial fluid resuscitation was not optimal or when patients develop episodes of sepsis, acute renal failure may develop. In such cases the autopsy may reveal acute tubular necrosis.[41,83] Clinical renal failure was an independent factor associated with increased mortality rate in the analysis of prognostic factors in patients with greater than 80% total body surface burns in our institution.[84] Patients with renal failure seem to be at especially high risk for the infectious complications of burn injury.

DIGESTIVE SYSTEM AND HEPATOBILIARY TRACT

The association of duodenal ulcers with burn injury, described by Curling, is a classic lesion that still occurs in patients with burn injury, although its incidence is low, probably as a result of routine treatment of burn patients with inhibitors of gastric acid secretion.[85] Local mucosal necrosis and hemorrhage or erosion, an early manifestation of this process, are seen in some cases.

The intestinal tract is especially susceptible to ischemic and hypoxic injury, and lesions related to poor perfusion are often found at the time of autopsy. Decreased blood flow in the splanchnic circulation is a well-established physiologic consequence of endotoxemia.[14,86] Thus, sepsis is associated with an increased risk of intestinal injury. Hypoxic or ischemic injury of the intestinal epithelium can lead to translocation of intestinal flora into the mesenteric lymphatic circulation and into the portal venous circulation.[87,88] Alterations in the bacterial ecology of the gut can favor the escape of bacteria from the intestine.[89] Thus, hypotension and hypoxia can also be causes of sepsis. In our autopsy experience, abscesses or foci of tissue infection in the intestinal tract were uncommon. The intestinal lesion most commonly seen at autopsy is transverse streaks of hemorrhage in the small intestine in a "ladder" pattern, associated with focal necrosis of folds of mucosa. This is called superficial hemorrhagic necrosis (Fig. 44.13).[90] Perforation of the intestinal tract is an uncommon occurrence in patients with burn injury. Occasional patients develop pseudomembranous colitis or "typhlitis," typically a consequence of infection by toxin-producing *Clostridium difficile* (Fig. 44.14). This complication can be minimized by screening for the toxin in the stool. Rarely, ischemic injury in the intestinal tract is sufficient to yield zones of transmural necrosis.

The liver is enlarged in most autopsies of children who succumb to burn injury, often to double or triple its normal weight. Such massive hepatomegaly can compromise ventilation.[91] Steatosis is often found at autopsy (Fig. 44.15).

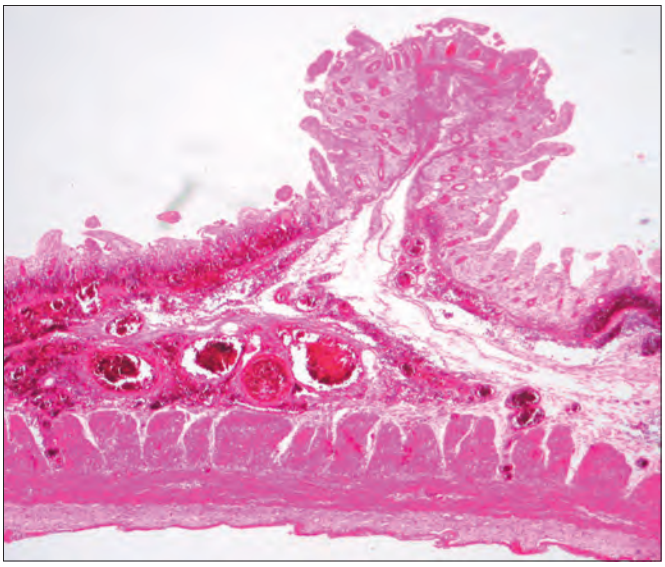

Fig. 44.13 Low-power micrograph showing a transverse mucosal fold in the jejunum of a patient who was septic and hypotensive for several days before death. Whereas the mucosal fold at the top is necrotic and shows no nuclear staining, the remainder of the intestinal mucosa and wall are intact but show submucosal hemorrhage. Hematoxylin and eosin stain.

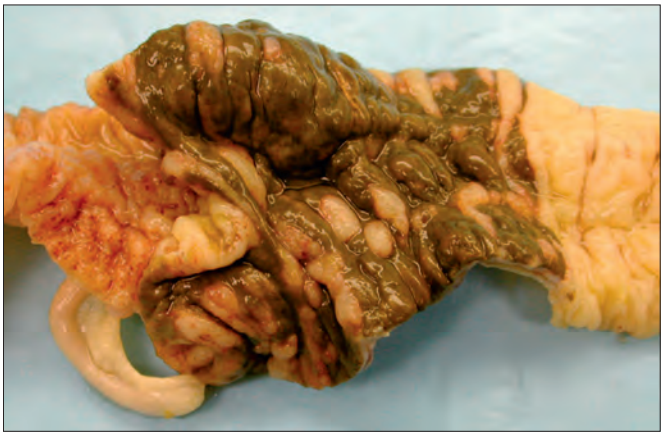

Fig. 44.14 Photograph showing dark green to black discoloration of patches elevated above the surrounding mucosa in the cecum of a patient who had intestinal distension and occult blood in the stools. This is a typical appearance of pseudomembranous colitis. Hematoxylin and eosin stain.

The degree of steatosis is often mild, however, even in the presence of massive hepatomegaly. Analysis of the lipid content of liver obtained at autopsy documented the presence of excess lipid but showed that its quantity was far too small to account for the increase in weight of the liver.[92] Congestion of the liver is also frequently seen at autopsy, often with centrilobular necrosis, which may be a consequence of reduced splanchnic blood flow in patients with sepsis and elevated venous pressure. Intracellular cholestasis is commonly observed in patients with burn injury. The basis for this abnormality is not clear, although multiple physiologic derangements could be expected to lead to cholestasis.[93,94]

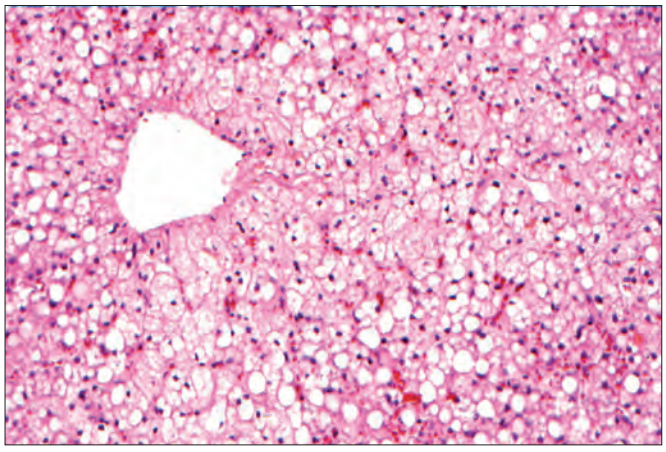

Fig. 44.15 Micrograph showing liver tissue in which almost every cell contains one or several large pale vacuoles that are the sites where lipid was stored within hepatocytes. Steatosis or fatty metamorphosis is consistently seen in the liver at autopsy but may not account for the increase in size and mass of the liver. This patient was 6 years old and lived for 1 month after injury. His liver was 2.2 times the normal weight. Hematoxylin and eosin stain.

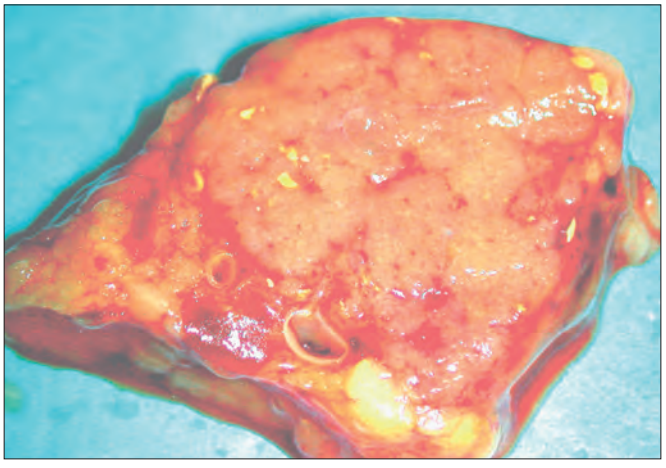

Fig. 44.16 A cross-section of the pancreas obtained at autopsy. The patient died after a long course of sepsis. The bright yellow flecks represent fat necrosis with saponification of fatty acids liberated by pancreatic lipases, and patchy hemorrhage is visible within and around the gland.

Acute pancreatitis is found at autopsy in a sizable minority of cases of fatal burns. Often necrosis and hemorrhage appear out of proportion to the extent of acute inflammation. The pancreas is particularly vulnerable to the reduced splanchnic blood flow that accompanies sepsis (Fig. 44.16). Increased clinical suspicion of pancreatitis has led to assessment of circulating amylase and lipase. On this basis, clinical pancreatitis is not rare in our patient population but is often transient.

LYMPHOID SYSTEM

Depletion of lymphocytes from lymphoid tissues throughout the body is a consistent feature seen at autopsy in patients with burn injuries. The abnormalities were well described by Linares in 1978.[95] The thymus is consistently

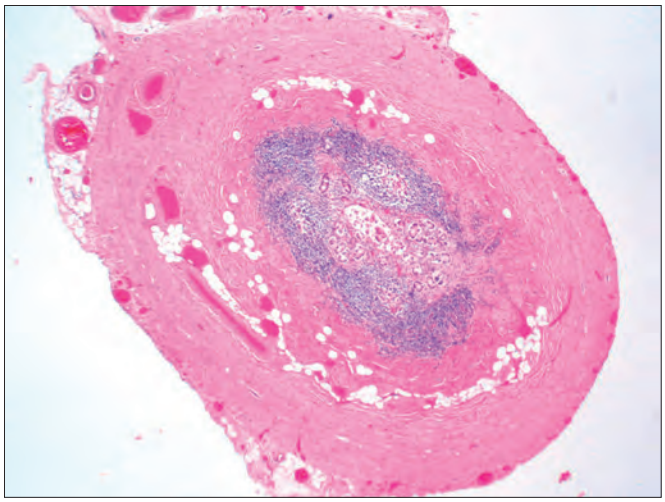

Fig. 44.17 Low-magnification micrograph showing a cross-section of the appendix. There is striking depletion of the amount of blue-staining lymphoid tissue that normally makes up the bulk of the surface of a section of the appendix. Hematoxylin and eosin stain.

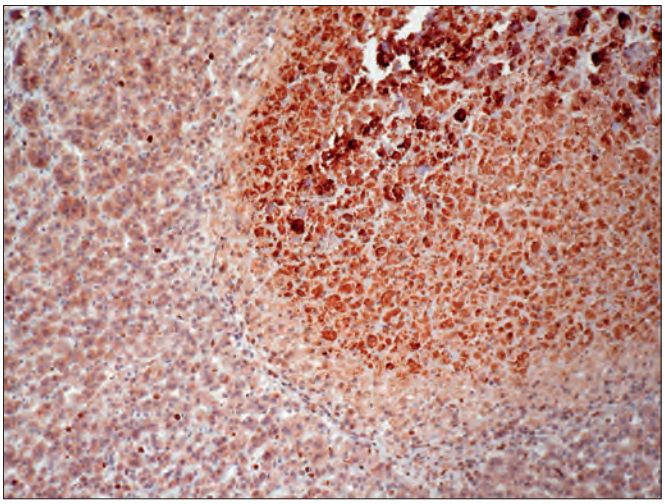

Fig. 44.18 Micrograph that is an immunohistochemical stain for herpes simplex virus type II of the adrenal cortex of a child who had extensive skin infection and injury caused by reactivation of a neonatal herpes infection. The dark brown material is reaction product that was not seen when the antibody was omitted. Multiple small necrotic lesions were seen in the liver and adrenal glands.

very small, even in young children. The lymph nodes often lack germinal centers and may be strikingly depleted of lymphocytes. Sinus histiocytosis is often present, and pyroninophilic cells resembling plasma cells are often prominent in the portions of the node normally occupied by B cells. The splenic white pulp is deficient, sometimes strikingly so. The GI lymphoid tissue of the terminal ileum is generally atrophic, despite its normal prominence in children, and the appendix often shows a striking lack of normal lymphoid tissue in its wall (Fig. 44.17). These abnormalities of lymphoid tissue correlate with the deficient immune response typical of patients with extensive burn injury. To some extent, they may represent the effects of high levels of endogenous glucocorticoids in burn patients.

ENDOCRINE SYSTEM

Excessive secretion of glucocorticoids and of epinephrine by the adrenal gland is characteristic of the prolonged hypermetabolic response to burns. Morphologic evidence of lipid depletion of the adrenal cortex has not been seen in our experience. In one interesting case, reactivation of neonatal infection with herpes simplex virus type II occurred in a young child with a large burn, leading to extensive skin injury and graft loss. Focal necrotic lesions were found in the adrenal cortex that were labeled by an immunostain for herpes simplex, indicating that dissemination of the infection had occurred (Fig. 44.18).

MUSCULOSKELETAL SYSTEM

Lesions of skeletal muscle are uncommon in burn patients but are ominous when they occur. Occasionally, direct thermal or electrical injury extends into deep muscle, and at times, this injury can be so severe that adequate debridement is not practical. When invasive bacterial or fungal infection extends into muscle, again, it may not be feasible to treat adequately by excision of the infected tissue, and the infection may be resistant to antibiotic therapy and likely to disseminate. Atrophy of skeletal muscle occurs as part of the catabolic state of burn patients and represents a challenge for those involved in rehabilitative efforts.

CENTRAL NERVOUS SYSTEM

When the brain and spinal cord are examined carefully at autopsy, abnormalities can be found in the great majority of patients who die after burn injury. The commonest lesion is degeneration or loss of neurons in the portions of the cortex most susceptible to hypoxic and ischemic injury. These lesions can be a result of hypovolemia during resuscitation, shock developing as part of the syndrome of sepsis, or as a consequence of respiratory failure. Of course, extensive hypoxic brain injury may occur in patients who are asphyxiated during the initial burn injury. Some patients, especially those who require CPR at the scene of injury, develop massive cerebral edema and brain death several days after the initial injury, reflecting development of massive cerebral edema in response to extensive hypoxic–ischemic injury in the brain. Severe hypoxic brain injury also can occur in burn patients who are deprived of oxygen during the progress of a house fire or who are poisoned by carbon monoxide at the scene of the burn. Direct thermal injury to the brain occurs occasionally in young children; can be detected by radiologic imaging studies; and is represented at autopsy by small foci of tissue necrosis on the cortical surface, surrounded by hyperemia.

The Burn Autopsy

As long as patients develop complications of burn injury that are difficult to manage, especially when the pathogenesis of these complications remains uncertain, careful postmortem examination of patients who do not survive will continue to contribute to patient care. The major medical

problems that complicate burn injury are summarized in the next few paragraphs. There is no disease with more complex clinical and physiopathologic derangements than an extensive burn. Observations made at the time of autopsy often clarify the nature of the problems that have led to the patient's demise. Sometimes the findings lead to suggestions for changes in procedure that may lead to improved patient safety. Very often a review of recent deaths effectively reminds the staff of the importance of measures to prevent wound infection. Often a causal sequence of events can be reconstructed by including the clinical evidence, including cultures with sensitivity testing and metabolic profiling, and the autopsy findings. Infectious processes, for example, often can be traced from their sites of origin, in the skin or elsewhere, to the fatal conclusion. Dangers caused by the emergence of highly resistant bacterial strains can be traced. The autopsy should always be approached from the point of view of using both clinical and autopsy evidence to better understand the reactions of the patient to the burn injury and to the treatments provided. In other words, the burn autopsy can provide not only an appropriate morphologic analysis but also a dynamic interpretation of the pathogenesis of the disease processes of importance in an individual patient. When approached in this way, investigation of patient deaths becomes a valuable learning experience for all those who participate.[96] Often, unexpected lesions are found that were likely to have been significant in the patient's course. Of course, the circumstances of burn injury may have legal implications.[97] Documentation of the patient's injuries and careful interpretation of the hospital course can provide factual evidence when only supposition would be available otherwise. Several recent publications have confirmed the continuing usefulness of autopsies, especially in the setting of burn trauma.[98–102] We advocate a policy of carrying out complete autopsies on all patients who die after burn injury whenever possible in collaboration with the local medical examiner or coroner.

Complete references available online at
www.expertconsult.inkling.com

Further Reading

Barrow RE, Hawkins HK, Aarsland A, et al. Identification of factors contributing to hepatomegaly in severely burned children. *Shock*. 2005;24(6):523-528.

Cox RA, Mlcak RP, Chinkes DL, et al. Upper airway mucus deposition in lung tissue of burn trauma victims. *Shock*. 2008;29(3):356-361.

Kallinen O, Partanen TA, Maisniemi K, et al. Comparison of premortem clinical diagnosis and autopsy findings in patients with burns. *Burns*. 2008;34(5):595-602.

Linares HA. A report of 115 consecutive autopsies in burned children: 1966–80. *Burns*. 1981;8:263-270.

Pereira CT, Barrow RE, Sterns AM, et al. Age-dependent differences in survival after severe burns: a unicentric review of 1,674 patients and 179 autopsies over 15 years. *J Am Coll Surg*. 2006;202(3):536-548.

References

1. Long J. Post-mortem appearances found after burns. *Lond Med Gaz*. 1840;25:743-750.
2. Harkins HN. Experimental burns. I. The rate of fluid shift and its relation to the onset of shock in severe burns. *Arch Surg*. 1935;31:71-85.
3. Underhill FP, Kapsinow R, Fisk M. Studies on the mechanism of water exchange in the animal organism. *Am J Physiol*. 1930;95:302-314.
4. Cope O, Moore FD. The redistribution of body water and the fluid therapy of the burned patient. *Ann Surg*. 1947;126:1010-1045.
5. Evans EI, Purnell OJ, Robinett PW, Batchelor A, Martin M. Fluid and electrolyte requirements in severe burns. *Ann Surg*. 1952;135:804-817.
6. Demling RH. Fluid replacement in burned patients. *Surg Clin North Am*. 1987;67:15-30.
7. Horton JW. Free radicals and lipid peroxidation mediated injury in burn trauma: the role of antioxidant therapy. *Toxicology*. 2003;189(1-2):75-88.
8. Meneshian A, Bulkley GB. The physiology of endothelial xanthine oxidase: from urate catabolism to reperfusion injury to inflammatory signal transduction. *Microcirculation*. 2002;9(3):161-175.
9. Sakano T, Okerberg CV, Shippee RL, et al. A rabbit model of inhalation injury. *J Trauma*. 1993;34:411-416.
10. Clements NC Jr, Habib MP. The early pattern of conjugated dienes in liver and lung after endotoxin exposure. *Am J Respir Crit Care Med*. 1995;151(3 Pt 1):780-784.
11. Justis DL, Law EJ, MacMillan BG. Tibial compartment syndromes in burn patients. A report of four cases. *Arch Surg*. 1976;111(9):1004-1008.
12. Rosen CL, Adler JN, Rabban JT, et al. Early predictors of myoglobinuria and acute renal failure following electrical injury. *J Emerg Med*. 1999;17(5):783-789.
13. Linares HA. A report of 115 consecutive autopsies in burned children: 1966-80. *Burns Incl Therm Inj*. 1982;8(4):263-270.
    This classic paper describes many features of severe burn injury that are still found when autopsies are done on young patients who die after burns.
14. Teplitz C. The pathology of burns and the fundamentals of burn wound sepsis. In: Atrz CL, Moncrief JA, Pruitt BA, eds. *Burns*. Philadelphia: WB Saunders;1979:45.
15. Bone RC, Sibbald WJ, Sprung CL. The ACCP-SCCM consensus conference on sepsis and organ failure. *Chest*. 1992;101:1481-1482.
16. Effeney DJ, Blaisdell FW, McIntyre KE, Graziano CJ. The relationship between sepsis and disseminated intravascular coagulation. *J Trauma*. 1978;18(10):689-695.
17. Eldridge JP, Baldridge ED, MacMillan BG. Ecthyma gangrenosum in a burned child. *Burns Incl Therm Inj*. 1986;12(8):578-585.
18. Jones SG, Olver WJ, Boswell TC, Russell NH. Ecthyma gangrenosum. *Eur J Haematol*. 2002;69(5-6):324.
19. Cox RA, Mlcak RP, Chinkes DL, et al. Upper airway mucus deposition in lung tissue of burn trauma victims. *Shock*. 2008;29(3):356-361.
    This paper reports study of human autopsy tissue from the viewpoint gained from extensive experience analyzing tissues from sheep after experimental smoke inhalation injury. Airway obstruction was found to be frequent and focally severe.
20. Wisplinghoff H, Perbix W, Seifert H. Risk factors for nosocomial bloodstream infections due to Acinetobacter baumannii: a case-control study of adult burn patients. *Clin Infect Dis*. 1999;28(1):59-66.
21. Wurtz R, Karajovic M, Dacumos E, Jovanovic B, Hanumadass M. Nosocomial infections in a burn intensive care unit. *Burns*. 1995;21(3):181-184.
22. Depuydt PO, Blot SI, Benoit DD, et al. Antimicrobial resistance in nosocomial bloodstream infection associated with pneumonia and the value of systematic surveillance cultures in an adult intensive care unit. *Crit Care Med*. 2006;34(3):653-659.
23. Murray CK, Loo FL, Hospenthal DR, et al. Incidence of systemic fungal infection and related mortality following severe burns. *Burns*. 2008;34(8):1108-1112.
24. Franco DM, Aronson JF, Hawkins HK, et al. Systemic Pythium insidiosum in a pediatric burn patient. *Burns*. 2010;36(5):e68-e71.
25. Mitchell TA, Hardin MO, Murray CK, et al. Mucormycosis attributed mortality: a seven-year review of surgical and medical management. *Burns*. 2014;40(8):1689-1695. PubMed PMID: 24881507.
26. Cox RA, Burke AS, Soejima K, et al. Airway obstruction in sheep with burn and smoke inhalation injuries. *Am J Respir Cell Mol Biol*. 2003;29(3 Pt 1):295-302.
27. Cox RA, Jacob S, Andersen CR, et al. Integrity of airway epithelium in pediatric burn autopsies: association with age and extent of burn injury. *Burns*. 2015;41(7):1435-1441. PubMed PMID: 26093952, Pubmed Central PMCID: 4618191.
28. Curreri PW, Katz AJ, Dotin LN, Pruitt BA. Coagulation abnormalities in the thermally injured patient. *Current Topics in Surgical Research*. 1970;2:401-411.
29. McManus WF, Eurenius K, Pruitt BA. Disseminated intravascular coagulation in burned patients. *J Trauma*. 1973;13:416-422.
30. Alkjaersig N, Fletcher AP, Peden JC, Monafo WW. Fibrinogen catabolism in burned patients. *J Trauma*. 1980;20:154-159.
31. Bick R. Disseminated intravascular coagulation and related syndromes: a clinical review. *Semin Thromb Hemost*. 1988;14:299-337.
32. Olsson P. Clinical views on the kinin system. *Scand J Clin Lab Invest*. 1969;24:123-124.
33. Niedermayr M, Schramm W, Kamolz L, et al. Antithrombin deficiency and its relationship to severe burns. *Burns*. 2007;33(2):173-178.
34. Lavrentieva A, Kontakiotis T, Bitzani M, et al. The efficacy of antithrombin administration in the acute phase of burn injury. *Thromb Haemost*. 2008;100(2):286-290.
35. Watanabe T, Imamura T, Nakagaki K, Tanaka K. Diseminated intravascular coagulation in autopsy cases: its incidence and clinicopathologic significance. *Pathol Res Pract*. 1979;165:311-322.
36. Papp A, Kiraly K, Harma M, et al. The progression of burn depth in experimental burns: a histological and methodological study. *Burns*. 2004;30(7):684-690.
37. Mileski WJ, Borgstrom D, Lightfoot E, et al. Inhibition of leukocyte-endothelial adherence following thermal injury. *J Surg Res*. 1992;52:334-339.
38. Schnell LG, Danks RR. Massive Marjolin's ulcer in a burn graft site 46 years later. *J Burn Care Res*. 2009;30(3):533-535.
39. Kowal-Vern A, Criswell BK. Burn scar neoplasms: a literature review and statistical analysis. *Burns*. 2005;31(4):403-413.
40. Theopold C, Hoeller D, Velander P, Demling R, Eriksson E. Graft site malignancy following treatment of full-thickness burn with cultured epidermal autograft. *Plast Reconstr Surg*. 2004;114(5):1215-1219.
41. Linares HA. Autopsy findings in burned children. In: Carvajal HF, Parks DH, eds. *Burns in Children*. Chicago: Year Book Medical Publishers; 1988.
42. Demling RH, Wong C, Jin LJ, et al. Early lung dysfunction after major burns: role of edema and vasoactive mediators. *J Trauma*. 1985;25:959-966.
43. Clowes GHA, Zuschneid W, Dragacevic S, Turner M. The nonspecific pulmonary inflammatory reactions leading to respiratory failure after shock, gangrene and sepsis. *J Trauma*. 1968;8:899-914.
44. Swank DW, Moore SB. Roles of the neutrophil and other mediators in adult respiratory distress syndrome. *Mayo Clin Proc*. 1989;64(9):1118-1132.
45. Mulligan MS, Smith CW, Anderson DC, et al. Role of leukocyte adhesion molecules in complement-induced lung injury. *J Immunol*. 1993;150:2401-2406.
46. Huie RE, Padmaja S. The reaction of NO with superoxide. *Free Rad R*. 1993;18:195-199.
47. Cooper JA, Solano SJ, Bizios R, Kaplan JE, Malik AB. Pulmonary neutrophil kinetics after thrombin-induced intravascular coagulation. *J Appl Physiol: Respirat Environ Exercise Physiol*. 1984;57:826-832.
48. Lentz LA, Ziegler ST, Cox CS, et al. Cytokine response to thermal injury, shock sepsis and organ failure. In: Schlag G, Redl H, Siegel JH, Traber DL, eds. *The second Wiggers Bernard Conference*. New York: Springer-Verlag; 1993:245-264.
49. Lin YS, Kou YR. Acute neurogenic airway plasma exudation and edema induced by inhaled wood smoke in guinea pigs: role of tachykinins and hydroxyl radical. *Eur J Pharmacol*. 2000;394(1):139-148.
50. Siney L, Brain SD. Involvement of sensory neuropeptides in the development of plasma extravasation in rat dorsal skin following thermal injury. *Br J Pharmacol*. 1996;117(6):1065-1070.
51. Fukushima M, King LS, Kang KH, Banerjee M, Newman JH. Lung mechanics and airway reactivity in sheep during development of oxygen toxicity. *J Appl Physiol*. 1990;69(5):1779-1785.
52. Moran JF, Robinson LA, Lowe JE, Wolfe WG. Effects of oxygen toxicity on regional ventilation and perfusion in the primate lung. *Surgery*. 1981;89(5):575-581.
53. Barazzone C, Horowitz S, Donati YR, Rodriguez I, Piguet PF. Oxygen toxicity in mouse lung: pathways to cell death. *Am J Respir Cell Mol Biol*. 1998;19(4):573-581.

54. Sousse LE, Herndon DN, Andersen CR, et al. Pulmonary histopathologic abnormalities and predictor variables in autopsies of burned pediatric patients. *Burns*. 2015;41(3):519-527. PubMed PMID: 25445004, Pubmed Central PMCID: 4380749.
55. Barrow RE, Spies M, Barrow LN, Herndon DN. Influence of demographics and inhalation injury on burn mortality in children. *Burns*. 2004;30(1):72-77.
56. Kobayashi K, Ikeda H, Higuchi R, et al. Epidemiological and outcome characteristics of major burns in Tokyo. *Burns*. 2005;31(suppl 1):S3-S11.
57. Muller MJ, Pegg SP, Rule MR. Determinants of death following burn injury. *Br J Surg*. 2001;88(4):583-587.
58. Suzuki M, Aikawa N, Kobayashi K, Higuchi R. Prognostic implications of inhalation injury in burn patients in Tokyo. *Burns*. 2005;31(3):331-336.
59. Tredget EE, Shankowsky HA, Taerum TV, Moysa GL, Alton JD. The role of inhalation injury in burn trauma. A Canadian experience. *Ann Surg*. 1990;212(6):720-727.
60. Linares HA, Herndon DN, Traber DL. Sequence of morphologic events in experimental smoke inhalation. *J Burn Care Rehab*. 1989;10:27-37.
61. Herndon DN, Traber DL, Niehaus GD, Linares HA, Traber LD. The pathophysiology of smoke inhalation injury in a sheep model. *J Trauma*. 1984;24(12):1044-1051.
62. Murakami K, Traber DL. Pathophysiological basis of smoke inhalation injury. *News Physiol Sci*. 2003;18:125-129.
63. Soejima K, Schmalstieg FC, Sakurai H, Traber LD, Traber DL. Pathophysiological analysis of combined burn and smoke inhalation injuries in sheep. *Am J Physiol Lung Cell Mol Physiol*. 2001;280(6):L1233-L1241.
64. Abdi S, Evans MJ, Cox RA, et al. Inhalation injury to tracheal epithelium in an ovine model of cotton smoke exposure. Early phase (30 minutes). *Am Rev Respir Dis*. 1990;142:1436-1439.
65. Abdi S, Herndon D, McGuire J, Traber L, Traber DL. Time course of alterations in lung lymph and bronchial blood flows after inhalation injury. *J Burn Care Rehabil*. 1990;11(6):510-515.
66. Stothert JC Jr, Ashley KD, Kramer GC, et al. Intrapulmonary distribution of bronchial blood flow after moderate smoke inhalation. *J Appl Physiol*. 1990;69(5):1734-1739.
67. Enkhbaatar P, Traber DL. Pathophysiology of acute lung injury in combined burn and smoke inhalation injury. *Clin Sci*. 2004;107(2):137-143.
68. Veronesi B, Carter JD, Devlin RB, Simon SA, Oortgiesen M. Neuropeptides and capsaicin stimulate the release of inflammatory cytokines in a human bronchial epithelial cell line. *Neuropeptides*. 1999;33(6):447-456.
69. Zimmerman BJ, Anderson DC, Granger DN. Neuropeptides promote neutrophil adherence to endothelial cell monolayers. *Am J Physiol*. 1992;263:G678-G682.
70. Lentz CW, Abdi S, Traber LD. The role of sensory neuropeptides in inhalation injury. *Pro Amer Burn Assoc*. 1992;10:27-37.
71. Kunkel SL, Standiford TJ, Kasahara K, Strieter RM. Interleukin-8 (IL-8): the major neutrophil chemotactic factor in the lung. *Exp Lung Res*. 1991;17:17-23.
72. Enkhbaatar P, Murakami K, Shimoda K, et al. Inhibition of neuronal nitric oxide synthase by 7-nitroindazole attenuates acute lung injury in an ovine model. *Am J Physiol Regul Integr Comp Physiol*. 2003;285(2):R366-R372.
73. Enkhbaatar P, Murakami K, Shimoda K, et al. The inducible nitric oxide synthase inhibitor BBS-2 prevents acute lung injury in sheep after burn and smoke inhalation injury. *Am J Respir Crit Care Med*. 2003;167(7):1021-1026.
74. Cox RA, Soejima K, Burke AS, et al. Enhanced pulmonary expression of endothelin-1 in an ovine model of smoke inhalation injury. *J Burn Care Rehabil*. 2001;22(6):375-383.
75. Cox RA, Enkhabaatar P, Burke AS, et al. Effects of a dual endothelin-1 receptor antagonist on airway obstruction and acute lung injury in sheep following smoke inhalation and burn injury. *Clin Sci*. 2005;108(3):265-272. PubMed PMID: 15554871.
76. Shimoda K, Murakami K, Enkhbaatar P, et al. Effect of poly(ADP ribose) synthetase inhibition on burn and smoke inhalation injury in sheep. *Am J Physiol Lung Cell Mol Physiol*. 2003;285(1):L240-L249.
77. Murakami K, McGuire R, Cox RA, et al. Recombinant antithrombin attenuates pulmonary inflammation following smoke inhalation and pneumonia in sheep. *Crit Care Med*. 2003;31(2):577-583.
78. Murakami K, McGuire R, Cox RA, et al. Heparin nebulization attenuates acute lung injury in sepsis following smoke inhalation in sheep. *Shock*. 2002;18(3):236-241.
79. Fracasso T, Schmeling A. Delayed asphyxia due to inhalation injury. *Int J Legal Med*. 2010;125(2):289-292.
80. Pereira CT, Barrow RE, Sterns AM, et al. Age-dependent differences in survival after severe burns: a unicentric review of 1,674 patients and 179 autopsies over 15 years. *J Am Coll Surg*. 2006;202(3):536-548.

    This paper thoroughly surveys the findings in autopsies of children who died after burns and highlights some unexpected observations.
81. Rona G, Boutet M, Huttner I, Peters H. Pathogenesis of isoproterenol-induced myocardial alterations: functional and morphological correlates. *Recent Adv Stud Cardiac Struct Metab*. 1973;3:507-525.
82. Kahn DS, Rona G, Chappel CI. Isoproterenol-induced cardiac necrosis. *Ann NYAcad Sci*. 1969;156(1):285-293.
83. Martineau PP, Hartman FW. The renal lesions in extensive cutaneous burns. *JAMA*. 1947;134:429-436.
84. Wolf SE, Rose JK, Desai MH, et al. Mortality determinants in massive pediatric burns. An analysis of 103 children with > or = 80% TBSA burns (> or = 70% full-thickness). *Ann Surg*. 1997;225(5):554-565.
85. Curling TB. On acute ulceration of duodenum in cases of burn. *Trans R Med Chir Soc Lond*. 1842;25:260-281.
86. Fronek K, Zweifach BW. Changes of splanchnic hemodynamics in hemorrhagic hypotension and endotoxemia. *J Surg Res*. 1971;11(5):232-237.
87. Deitch EA, Berg R. Bacterial translocation from the gut: a mechanism of infection. *J Burn Care Rehab*. 1987;8:475-482.
88. Baker JW, Deitch EA, Berg RD, Specian RD. Hemorrhagic shock induces bacterial translocation from the gut. *J Trauma*. 1988;28:896-906.
89. Berg RD, Wommack E, Deitch EA. Immunosuppression and intestinal bacterial overgrowth synegistically promote bacterial translocation. *Arch Surg*. 1988;123:1359-1364.
90. Ahrén C, Haglund V. Mucosal lesions in the small intestine of the cat durning low flow. *Acta Physiol Scand*. 1973;88:541-550.
91. Barrow RE, Mlcak R, Barrow LN, Hawkins HK. Increased liver weights in severely burned children: comparison of ultrasound and autopsy measurements. *Burns*. 2004;30(6):565-568.
92. Barrow RE, Hawkins HK, Aarsland A, et al. Identification of factors contributing to hepatomegaly in severely burned children. *Shock*. 2005;24(6):523-528.

    The massive hepatomegaly that is consistently found at autopsy in patients who die weeks after their initial burn is a biological problem still seeking an explanation.
93. Hurd T, Lysz T, Dikdan G, et al. Hepatic cellular dysfunction in sepsis: an ischemic phenomenon? *Curr Surg*. 1988;45:114-119.
94. Cano N, Gerolami A. Intrahepatic cholestatsis during total parenteral nutrition. *Lancet*. 1983;1:985.
95. Linares HA, Beathard GA, Larson DL. Morphological changes of lymph nodes of children following acute thermal burns. *Burns*. 1978;4:165-170.
96. Miller SF. Response to: cause of death and correlation with autopsy findings in burns patient. *Burns*. 2013;39(8):1649. PubMed PMID: 24041513.
97. Romolo FS, Aromatario M, Bottoni E, et al. Accidental death involving professional fireworks. *Forensic Sci Int*. 2014;234:e5-e9. PubMed PMID: 24279979.
98. D'Avignon LC, Hogan BK, Murray CK, et al. Contribution of bacterial and viral infections to attributable mortality in patients with severe burns: an autopsy series. *Burns*. 2010;36(6):773-779.
99. Gomez R, Murray CK, Hospenthal DR, et al. Causes of mortality by autopsy findings of combat casualties and civilian patients admitted to a burn unit. *J Am Coll Surg*. 2009;208(3):348-354.
100. Kallinen O, Partanen TA, Maisniemi K, et al. Comparison of premortem clinical diagnosis and autopsy findings in patients with burns. *Burns*. 2008;34(5):595-602.

    This paper from Finland compares clinical diagnoses with autopsy findings in burn patients and emphasizes the value of a high autopsy rate in these cases.
101. Silfvast T, Takkunen O, Kolho E, Andersson LC, Rosenberg P. Characteristics of discrepancies between clinical and autopsy diagnoses in the intensive care unit: a 5-year review. *Intensive Care Med*. 2003;29(2):321-324.
102. Bloemsma GC, Dokter J, Boxma H, Oen IM. Mortality and causes of death in a burn centre. *Burns*. 2008;34(8):1103-1107.

45 Molecular and Cellular Basis of Hypertrophic Scarring

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Introduction

Clinically postburn hypertrophic scars (HTS) are elevated, erythematous, pruritic, and inelastic.[1] In addition to poor cosmesis, these scars typically form contractures resulting in dysfunction and discomfort, leading to significant morbidity for burn patients (Fig. 45.1). HTS is fundamentally different from normal skin and mature scar in several key ways: (1) the extracellular matrix (ECM) of HTS is significantly altered in both composition and architecture, (2) the behavior of keratinocytes and fibroblasts present in HTS is profibrotic compared to mature scar, and (3) many profibrotic cytokines are upregulated and their expression prolonged. Generally, HTS undergoes some remodeling and maturation over time, and this may account for the variability in descriptions of HTS. Many features of HTS are shared by other fibroproliferative disorders, including renal fibrosis, pulmonary fibrosis, and scleroderma.[2] Thus understanding the pathophysiology of HTS applies to other areas of medicine, and developments in treating various fibroproliferative diseases can directly affect scar management. Since an exhaustive discussion of every nuance of abnormal wound healing is impossible, we focus on aspects of HTS formation highlighting well understood pathways or novel developments. It is our hope that a deeper understanding of abnormal wound healing pathophysiology and fibrosis will lead to nonsurgical treatments that improve life not only for burn patients, but for the many patients suffering fibrotic diseases.

Extracellular Matrix

ECM in healing wounds is laid down by fibroblasts and subsequently remodeled as the scar matures. The ECM in HTS displays significant differences from mature scar and normal skin, most notably in the arrangement and composition of collagen bundles and in the relative proportions of several proteoglycans.[3] Owing to the interaction of fibroblasts and ECM, these differences not only result from abnormal fibroblast behavior but also contribute to it.[4]

COLLAGEN

Collagen is the major constituent of ECM, providing a scaffold for cells and mechanical strength to tissues. In HTS the quantity of collagen per unit surface area is increased;[5] however the relative proportion of collagen in HTS is decreased compared to normal skin, owing to much greater increases in proteoglycans and glycoproteins.[3] In normal skin the majority of collagen is type I (80%) with smaller amounts of type III (10–15%) and type V (minimal), resulting in thick, regular collagen fibril bundles running parallel to the skin surface.[6] In contrast, HTS is composed of greatly increased amounts of type III (33%)[7] and type V (10%)[8] collagen, which drastically alters collagen fibrils, making them thinner[6] and disorganized.[9] In normal wound healing, type III collagen appears early then gradually disappears as the scar is remodeled and matures,[10] but this does not occur in HTS, where persistently high levels reflect biological immaturity.[11]

Classic histologic descriptions of HTS highlight "whorls" and "nodules" of poorly organized collagen encapsulated in more normal-appearing collagen fibrils,[6] as seen in Fig. 45.6. However not only are collagen fibril composition and morphology altered in HTS, but interfibrillar spacing is also irregular and greatly increased.[12] This space is filled with proteoglycans and glycoproteins whose composition is markedly different from normal skin and mature scar.

PROTEOGLYCANS AND GLYCOPROTEINS

Proteoglycans are responsible for physical properties of skin such as turgor, resilience, and resistance to compression, resulting from their interaction with collagen. Proteoglycans also modulate the activities of multiple growth factors and cytokines. Glycoproteins, such as fibronectin, are generally involved in cell–matrix adhesion and influence cell behavior via this mechanism. Together proteoglycans and glycoproteins are major constituents of skin, both physically and functionally.

Proteoglycans are formed by a protein core, often with repeating units such as leucine in decorin, and glycosaminoglycan side chains.[13] These side chains are ionized and hydrophilic and thus mainly responsible for tissue water retention.[14] Early studies of HTS demonstrated elevated glycosaminoglycan levels,[15] which are responsible for the hyperhydrated state of HTS that leads to its classically increased turgor. These levels of glycosaminoglycan are not uniformly elevated. Instead certain proteoglycans are downregulated and others upregulated, with unique implications for HTS.

Decorin is a prototypical small, leucine-rich proteoglycan (SLRP) produced in abundance in normal skin and mature scar but reduced by 75% in HTS.[3] Originally named for "decorating" collagen fibrils, decorin affects wound healing via several distinct and complementary pathways. Decorin binds to collagen fibrils, controlling their diameter, morphology,[16] and interfibrillar distance.[17] In decorin knockout mice collagen fibrils are irregular in morphology and have highly variable diameters.[18] Decorin binds to and

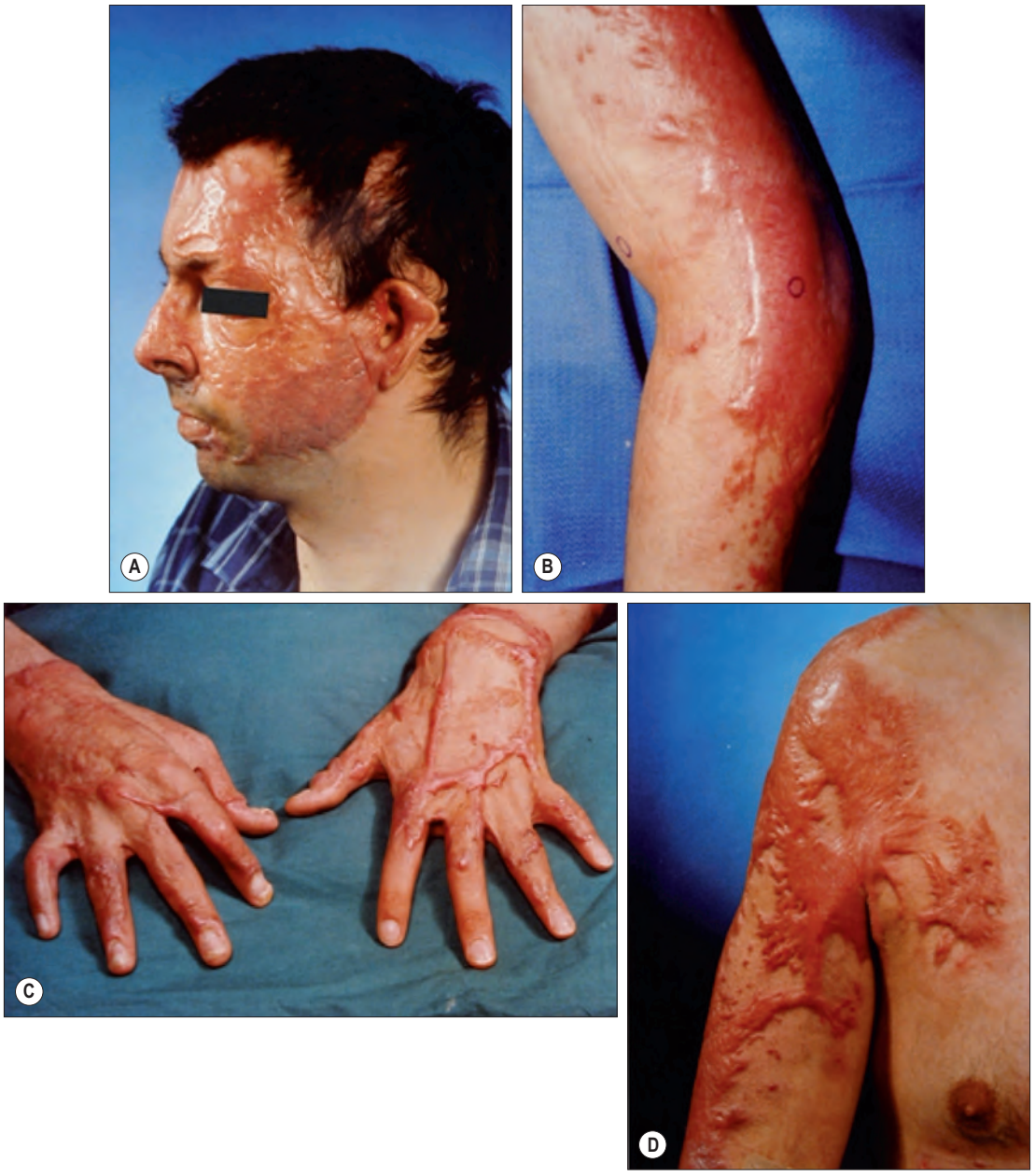

Fig. 45.1 Hypertrophic scarring in a 34-year-old white man, 8 months following a 60% total body surface area burn involving the face, upper extremities, and hands. (From Scott PG, Ghahary A, Chambers MM, Tredget EE. Biological basis of hypertrophic scarring. In: Malhotra SK, ed., *Advances in Structural Biology*, vol. 3. Greenwich, CT: JAI Press, 1994: 157–202.)

inactivates the profibrotic cytokines transforming growth factor-β (TGF-β)[19] and platelet-derived growth factor (PDGF).[20] The effects of this inactivation are most readily visible in fibroblast-populated collagen lattices where decorin significantly reduces contraction by normal and HTS fibroblasts.[21,22] Decorin also binds to and antagonistically downregulates several cell surface receptor tyrosine kinases: epidermal growth factor receptor (EGFR),[23] hepatocyte growth factor receptor (HGFR),[24] and insulin-like growth factor 1 receptor (IGF1R),[25] which reduces cellular proliferation and migration. Decorin production increases significantly as scars mature.[26] In a mouse model of diabetes, renal fibrosis and nephropathy developed significantly faster in decorin knockout than in wild-type mice.[27] Similarly upregulating decorin production via an adenoviral vector in mouse models of bleomycin-induced pulmonary fibrosis reduced fibrosis.[28]

In contrast to decorin downregulation, two other proteoglycans, biglycan and versican, are significantly upregulated in HTS. Biglycan is 57% similar to decorin in amino acid sequence but with two dermatan sulfate chains and is believed to have originated as a gene duplication of decorin.[29] Despite these similarities, biglycan and decorin have significantly different functions in vivo. Biglycan is minimally present in normal skin but significantly upregulated in fibrosis, yet it does not compensate for the lack of decorin.[29,30] Versican is also significantly upregulated in HTS, up to six times higher than in normal skin,[3] where it is normally confined to the proliferating epidermis.[31] As a large proteoglycan with 12–30 glycosaminoglycans

chains, versican is most likely responsible for the increased hydration and turgor leading to the increased volume of HTS.[5]

The most common glycoprotein in ECM is fibronectin, which has effects on cell–matrix interaction via its interaction with integrins. Although the role of fibronectin in HTS is unclear, its upregulation in HTS,[32] influence on the assembly of other ECM proteins, and interaction with cellular integrins[33] suggest that it, too, plays a role in fibroblast behavior and HTS formation.

Cellular Contributions to Hypertrophic Scar

HYPERTROPHIC SCAR FIBROBLASTS

Fibroblasts are the cells primarily responsible for ECM production and remodeling in wound healing. Numerous studies have demonstrated that dermal fibroblasts can be divided into distinct subpopulations—superficial (papillary) and deep (reticular)—based on both physical location and phenotype.[34–36] When characteristics of superficial dermal, deep dermal, and HTS fibroblasts are compared, as in Table 45.1, it becomes clear that HTS fibroblasts most closely resemble deep dermal fibroblasts.[36] These in vitro results correlate directly with a clinically relevant dermal scratch model developed by Dunkin and colleagues.[37] In this model a linear skin wound is created with depth that increases along its length from no injury to full-thickness penetration. This results in regeneration in the superficial portion (depth ≤0.56 mm) with minimal scar; whereas HTS formation occurs in the deeper portion of the wound.[37] Combining these basic science and clinical observations with the tendency of HTS to form following deep partial- to full-thickness burns suggests two possible theories of HTS formation: (1) selective proliferation of deep dermal fibroblasts after fibrogenic cytokine stimulation, or (2) destruction of superficial dermal fibroblasts by thermal injury, leaving only deep dermal fibroblasts to repopulate the wound.[38] Both theories are consistent with an experimental model in which human skin was grafted onto the backs of nude mice and subsequently injured. In this model, deep dermal fibroblasts closed wounds and superficial dermal fibroblasts then remodeled them.[39] It is possible that in deep burns superficial fibroblasts are not present to initiate this remodeling process, leaving the healing wound in a hyperactive state (Fig. 45.2).

Table 45.1 Superficial and Deep Dermal Fibroblasts Compared to Hypertrophic Scar Fibroblasts

	Superficial Dermal Fibroblasts	Deep Dermal Fibroblasts	Hypertrophic Scar Fibroblasts
Collagen production	↓	↑	↑
Collagenase production	↑	↓	↓
Decorin production	↑	↓	↓
TGF-β production	↓	↑	↑
CTGF production	↓	↑	↑
Keratinocyte proliferation	↑	↓	↓
Capillary formation	↑	↓	↓

ROLE OF MYOFIBROBLASTS IN NORMAL AND PATHOLOGICAL SITUATIONS

Myofibroblasts are cells that have acquired a phenotype intermediate between fibroblasts and smooth muscle cells. Presently it is accepted that myofibroblast modulation of fibroblastic cells begins with the appearance of precursor proto-myofibroblasts whose stress fibers contain only β- and γ-cytoplasmic actins. These proto-myofibroblasts acquire de novo contractile bundles whose stress fibers generate sufficient forces to pull cells forward to populate tissue spaces in a migration process and to pre-remodel the ECM. Proto-myofibroblasts evolve, but not necessarily always, into the differentiated myofibroblast.[40] Fully differentiated myofibroblasts express α-smooth muscle actin (α-SMA), the actin isoform present in typical contractile vascular smooth muscle cells (Fig. 45.3). The presence of α-SMA is directly related to the contractile activity of myofibroblasts. A direct correlation has been demonstrated both in vitro and in vivo between the level of α-SMA expression and myofibroblast contraction.[41,42] Myofibroblasts also exhibit some similarities with pericytes.[43] In physiological conditions, after healing, myofibroblasts undergo apoptosis,[44] and only a few fibroblasts are left to ensure renewal of the ECM.

Among the soluble factors, TGF-β1 is a potent inducer of myofibroblast differentiation.[45,46] TGF-β1 action on myofibroblast differentiation is only possible in the presence of ED-A fibronectin, which underlines the fact that ECM components play an important role in soluble factor activity.[47] Granulocyte–macrophage colony-stimulating factor stimulates macrophage proliferation and myofibroblast differentiation, thereby promoting granulation tissue formation.[48,49] Endothelin has also a positive effect on differentiation and activation of myofibroblasts. This peptide also induces myofibroblast contraction and migration.[50] More recently it has been shown that granulation tissue formation is modified by chemical denervation.[51] This peripheral nervous system involvement in tissue repair has likewise been shown in the liver; in this organ, in an experimental model of fibrosis

Fig. 45.2 Injury below a critical depth in skin leads to scarring. (From Kwan P, Hori K, Ding J, Tredget EE. Scar and contracture: biological principles. *Hand Clin.* 2009;25[4]: 11–528.)

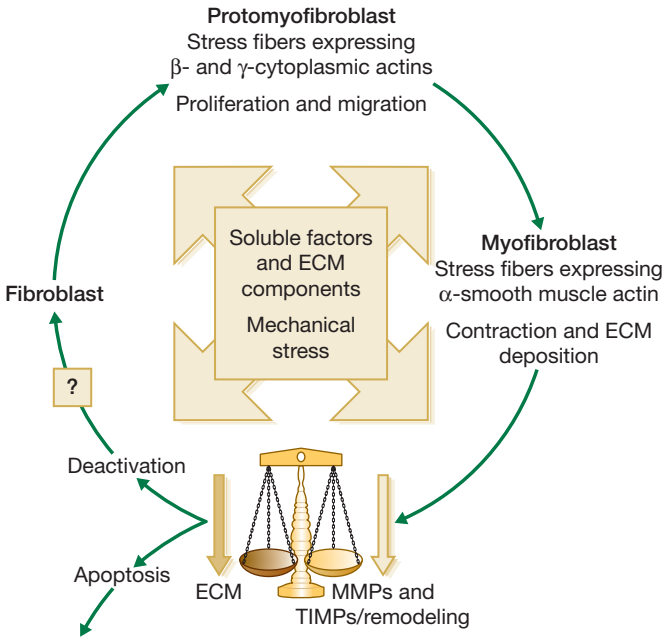

Fig. 45.3 Schematic illustration showing the evolution of the (myo) fibroblast phenotype. The myofibroblast modulation of fibroblastic cells begins with the appearance of the proto-myofibroblast, whose stress fibers contain only β- and γ-cytoplasmic actins and evolves, but not necessarily always, into the appearance of the differentiated myofibroblast, the most common variant of this cell, with stress fibers containing α-smooth muscle actin. Myofibroblasts present a well-developed rough endoplasmic reticulum and are responsible for (excessive) deposition of extracellular matrix (ECM); they also secrete matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) and are involved in granulation tissue remodeling. Soluble factors, particularly transforming growth factor-β1, associated with ECM components (e.g., fibronectin ED-A), play important roles during myofibroblast differentiation. Mechanical stress is also importantly involved in myofibroblast differentiation. The myofibroblast can undergo apoptosis; the deactivation leading to a quiescent phenotype has not been clearly demonstrated at least in vivo. (From Desmoulière A.)

using carbon tetrachloride treatment, chemical denervation significantly reduces matrix deposition and myofibroblast differentiation.[52]

ROLE OF MECHANICAL STRESS AND MYOFIBROBLASTS

Myofibroblast cells, because of their contractile properties and privileged relationships with ECM, can modify their activity depending on the mechanical environment. It has been shown, in gingival fibroblasts, that α-SMA expression induced by TGF-β1 is regulated by the compliance of collagen gels on or in which they are cultured.[53] The direct effects of mechanical stress on fibroblasts can be easily shown in culture using stressed fibroblast-populated collagen lattices (Fig. 45.4). Moreover, myofibroblast differentiation features, such as stress fibers, ED-A fibronectin, or α-SMA expression, appear earlier in granulation tissue subjected to increased mechanical tension by splinting of the full-thickness wound with a plastic frame than in normally healing wounds.[42] It has also been shown that fibroblasts cultured on substrates of variable stiffness present different phenotypes. Cultured fibroblasts do not express stress fibers on soft surfaces, but, when the stiffness of the substrate increases, a sudden change in cell morphology occurs and stress fibers appear.[54,55] Shear forces exerted by fluid flow are also able to induce TGF-β1 production and differentiation of fibroblasts cultured in collagen gels in the absence of other external stimuli, such as cytokine treatment.[56] Intercellular mechanical coupling of stress fibers via adherens junctions improves contraction of collagen gels by myofibroblasts.[57] By assessing spontaneous intracellular Ca^{2+} oscillations, Follonier et al. have shown that intracellular Ca^{2+} oscillations are coordinated between contacting myofibroblasts via adherens junctions, but randomly between fibroblasts and noncontacting cells.[58] They propose the following model of mechanical coupling for myofibroblasts: individual cell contraction is transmitted via adherens junctions and leads to opening of mechanosensitive ion channels in adjacent cells. The resulting Ca^{2+} influx induces a contraction that can feed back on the first cell and/or stimulate other contacting cells, working like a syncytium. This mechanism could improve the remodeling of cell-dense tissue by coordinating the activity of myofibroblasts.[59]

PATHOLOGICAL REPAIR (HYPERTROPHIC SCARS AND KELOIDS)

Pathological wound healing can result from impaired remodeling of the granulation tissue leading to abnormal cutaneous repair in hypertrophic or keloid scars (Fig. 45.5). Keloid and HTS differ in their expression of α-SMA; indeed, in keloids, no α-SMA is observed, although proto-myofibroblasts could account for large amounts of extracellular matrix but are unable to contract, whereas numerous myofibroblasts express this protein in HTS, thus explaining the fact that contracture often appears specifically in HTS.[38,60] Thus the use of α-SMA to differentiate HTS and keloids has been proposed.[61] The presence of contractile myofibroblasts in HTS is responsible for the formation of contractures that interfere with function and may require extensive reconstructive surgery (Fig. 45.6). Moreover, keloids contain thick collagen fibers, whereas HTS contain thin fibers organized in nodules.[60,62] It emphasizes that the different processes involved in collagen maturation together with the effects of the matrix metalloproteinase (MMP)/tissue inhibitor of MMP (TIMP) system play an important role in excessive scar formation. The expression of lysyl hydroxylase-2b (LH-2b), a splice variant of LH-2, an enzyme involved in the cross-linking of the collagen fibrils, has been linked to fibrotic development occurring in pathologic situations.[63] Animal models mimicking this specific expression of LH-2b are available and could be used to test new antiscarring therapies based on the inhibition of LH-2b.[64] In these lesions, the normal healing process cannot be achieved and granulation tissue continues to grow owing to an abnormal and excessive secretion of growth factors and/or lack of molecules inducing apoptosis or ECM remodeling. Interestingly HTS have an excess of microvessels, most of which are partially or totally occluded due to a functional regression of endothelial cells induced by (myo)fibroblast hyperactivity.[65] In excessive scarring, a focal upregulation of p53 expression, which probably inhibits apoptosis, has been observed. ECM modifications also seem to be an important factor in induction of the apoptotic process. In vivo, covering granulation tissue by

Fig. 45.4 Myofibroblast evolution in collagen gels. When myofibroblasts previously cultured in plastic dishes are incorporated in a floating collagen gel, a high proportion rapidly undergo apoptosis (arrows). In contrast, when incorporated in an attached collagen gel, they show a typical elongated morphology, express high amounts of α-smooth muscle actin, and proliferate. (From Coulomb B, Inserm U970, Université Paris Descartes, France and Desmoulière A, unpublished data.)

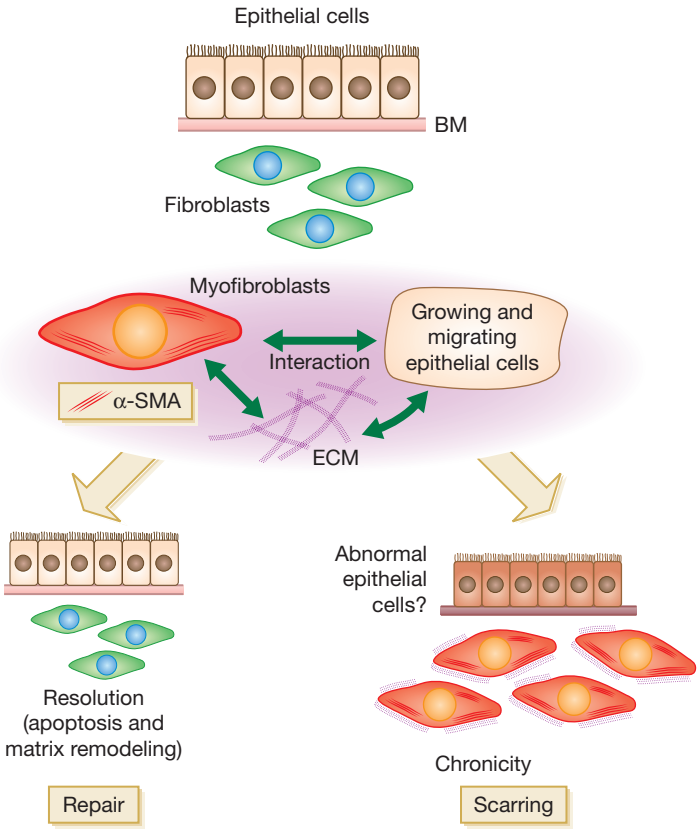

Fig. 45.5 Processes leading to normal repair or pathological scarring. In normal tissue repair, myofibroblasts disappear by apoptosis during the transition between granulation tissue and scar. In pathological situations, myofibroblasts proliferate and participate in the excessive deposition of extracellular matrix. In all these situations, not only interaction between fibroblasts/myofibroblasts and extracellular matrix, but also the dialogue between epithelial cells and mesenchymal cells play a major role. BM: basement membrane; SMA: smooth muscle actin; ECM: extracellular matrix. (Modified from Sarrazy et al. Wound repair and regeneration: mechanisms of pathological scarring: role of myofibroblasts and current developments. *Wound Repair Regen.* 2011;19[1]: s10–s15.)

a vascularized skin flap induces an upregulation of MMP together with a decrease in TIMP, leading to a rapid loss of granulation tissue cells by apoptosis.[66] In vitro, the matrix environment can modulate fibroblast apoptosis. Furthermore, in HTS, the mechanical forces obtained by compression of the scar are able to restore the classic organization observed in normal wounds and trigger the disappearance of myofibroblasts by apoptosis.[67] Thus mechanical stress can maintain myofibroblast differentiation. It has been shown that mechanical loading early in the proliferative phase of wound healing produces HTS by inhibiting cellular apoptosis.[68] In contrast, it is suggested that mechanical challenge could be a clinically relevant strategy to improve ischemic and chronic wound healing by supporting myofibroblast formation.[69] Interestingly oncogenic-Ras-transformed human fibroblasts lose growth factor selectivity and cell matrix density-dependent inhibition of migration.[70] In the liver and certain other organs, stiffness appears to result from matrix cross-linking and possibly other unknown variables in addition to matrix quantity, suggesting that increased stiffness may play an important role in initiating the early stages of fibrosis.[71] The epithelium could also be involved in the development of excessive scarring.[72] Hakvoort et al. have shown that, in HTS, keratinocytes expressed an activated $CD36^+$ phenotype.[73] They suggest that HTS formation is not only due to dermal dysfunction, but is also the result of a perturbation affecting dermal–epidermal interactions involving neurohormonal factors. Indeed, a "neurogenic inflammation hypothesis" has been suggested.[74] Mechanical stress stimulates mechanosensitive nociceptors in skin sensory fibers, which release neuropeptides involved in vessel modifications and fibroblast activation.

ORIGIN OF (MYO)FIBROBLASTS

It is now accepted that myofibroblasts can originate from various cell types, as illustrated in Fig. 45.7. The majority of these cells originate from local recruitment of connective tissue fibroblasts. For example, in skin, dermal fibroblasts located in the edges of the wound can acquire a myofibroblast phenotype and participate in tissue repair.[75,76] In diffuse cutaneous systemic sclerosis, microvascular pericytes constitute a cellular link between microvascular damage and fibrosis by transdifferentiating into myofibroblasts.[77] In the liver, the role of hepatic perisinusoidal hepatic stellate cells has been widely studied, and their key role during fibrogenesis has been clearly demonstrated.[78] Recently it has also been shown that portal fibroblasts are involved in the formation of portal septa.[79] Vascular smooth muscle cells residing in the walls of portal vein branches and portal arteries have been implicated in fibrosis observed in chronic schistosomiasis.[80] In the kidney, both mesangial cells and interstitial fibroblasts of the medulla can acquire a myofibroblast phenotype and participate in ECM deposition after damage.[81,82] Moreover the involvement in tissue repair of local mesenchymal stem cells is becoming better understood. These progenitor cells have been described in the dermal sheath that surrounds the outside of the hair follicle facing the epithelial stem cells, constituting a niche of stem cells. They are involved in the regeneration of the dermal papilla and can also become wound healing (myo) fibroblasts after an injury.[83] This concept of a cell association able to reconstitute the different organ cell populations and constituting a niche of stem cells is currently discussed in diverse organs, notably the liver, in the periportal zone containing Hering's canals.[84,85] Recent data have shown the implication of circulating cells, called fibrocytes, in the tissue repair process[88] tissue repair process, another type of circulating cell originating from bone marrow participates in tissue repair. These mesenchymal stem cells are bone marrow-derived nonhematopoietic precursor cells[89,90] that contribute to the maintenance and regeneration of connective tissues through engraftment. Indeed, they have the capacity to engraft into several organs and to differentiate into wound-healing myofibroblasts. However, recently it has been suggested that fibroblasts/myofibroblasts that participate in cutaneous wound healing are not derived from circulating progenitor cells.[91] Finally, epithelial- and endothelial-to-mesenchymal transition (EMT), a process by which differentiated (or malignant) epithelial cells and endothelial cells undergo a phenotypic conversion that gives rise to the matrix-producing fibroblasts and myofibroblasts, is increasingly recognized as an integral part of tissue fibrogenesis after injury, particularly in the kidney[92]

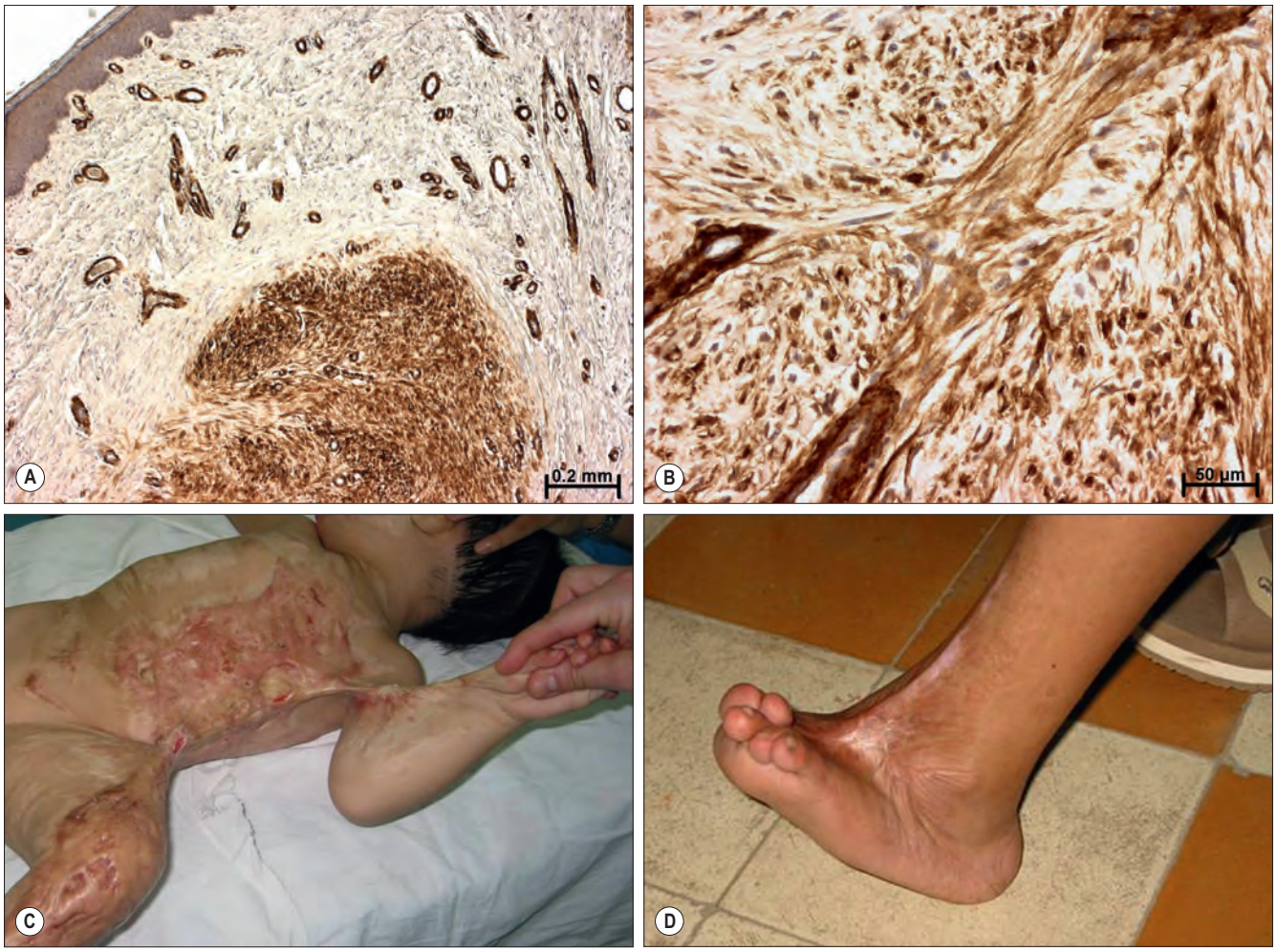

Fig. 45.6 Myofibroblasts in hypertrophic scars. In hypertrophic scar nodules myofibroblasts express large amounts of α-smooth muscle actin (A,B, immunohistochemistry for α-smooth muscle actin) and develop huge contractile activity in scars after burn injury (C,D) (From Desmoulière A; C,D are from Casoli P, Plastic Surgery and Burns Unit, University Hospital of Bordeaux, France.)

and during stroma reaction formation. However the degree to which this process contributes to fibrosis and stroma reaction in the skin remains a matter of intense debate and is likely to be context dependent. Altogether mesenchymal stem cells, fibrocytes, bone marrow-derived cells, and cells derived from EMT may represent alternative sources of myofibroblasts when local fibroblasts are not able to respond. These diverse cell types probably contribute to the appearance of myofibroblast subpopulations whose phenotype can be modulated by their interactions with neighboring cells and ECM.[93,94]

THE ROLE OF FIBROCYTES IN HYPERTROPHIC SCAR

Fibrocytes are a bloodborne, $CD14^+$ monocyte subpopulation[86] that mediate wound healing, first identified in 1994 by Bucala et al. in mouse wound chambers.[95] Although originally defined as collagen$^+$/vimentin$^+$/$CD34^+$ cells, other accepted markers include combinations of collagen$^+$ and $CD45^+$ or $LSP1^+$ markers.[87,96] Fibrocytes have been found in normal wound healing[86] and also in a wide variety of fibrotic diseases, including pulmonary fibrosis,[97] renal fibrosis,[98] and hypertrophic burn scars.[87] Fibrocytes traffic to wounds via a secondary lymphoid chemokine gradient, and differentiate under the influence of T cells and TGF-β.[86] It has been noted that $CD4^+$ T cells producing TGF-β are present in high levels in burn wounds,[99] where fibrocyte levels in burn patients are also increased.[100] In contrast, Pilling et al. demonstrated that fibrocyte differentiation is blocked by serum amyloid P (SAP), a constitutive plasma protein related to C-reactive protein, by using SAP to inhibit fibrocytes in a mouse bleomycin-induced pulmonary fibrosis model.[101] It appears that fibrocytes contribute to ECM formation and fibrosis through two mechanisms. Exposure to profibrotic cytokines causes fibrocytes to secrete collagen and differentiate into myofibroblasts via Smad2/3 and SAPK/JNK MAPK pathway activation.[102] Fibrocytes also modulate the activity of local fibroblasts in burn wounds via secretion of TGF-β and connective tissue growth factor (CTGF)[103] and may serve as a crucial link between healing wounds and the immune system. Like leukocytes, fibrocytes can act as antigen-presenting cells to prime naïve T cells[104] and also express Toll-like receptors, allowing them to function as part of the innate immune system.[105] Fibrocytes also induce revascularization of wounds through MMP-9 secretion, which degrades ECM and promotes endothelial invasion and the production of vascular endothelial growth

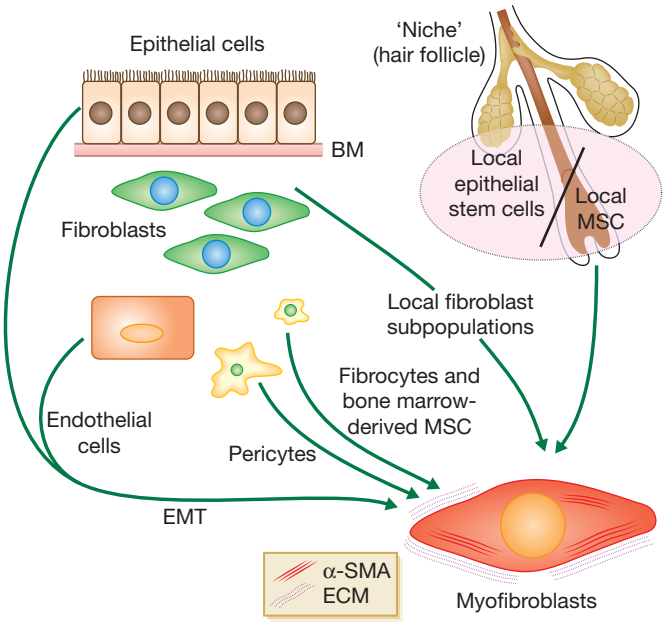

Fig. 45.7 Schematic illustration showing the different origins of the myofibroblast cells. Various cell types can acquire a myofibroblast phenotype; these diverse origins lead to distinct myofibroblast subpopulations. Circulating fibrocytes and bone marrow-derived mesenchymal stem cells (MSCs) are important sources of myofibroblasts when the dermis, source of local fibroblasts, is destroyed (second- and third-degree burns). A local source can also be local stem cells (both epithelial stem cells and MSCs forming a niche located at the level of hair follicles). The hypothesis suggesting that a major source of fibrosis- and tumor-associated myofibroblasts is through transdifferentiation from nonmalignant epithelial cells, from epithelial-derived carcinoma cells or from endothelial cells through epithelial- and endothelial-to-mesenchymal transition (EMT), requires further studies. SMA: smooth muscle actin; ECM: extracellular matrix. (From Desmoulière A.)

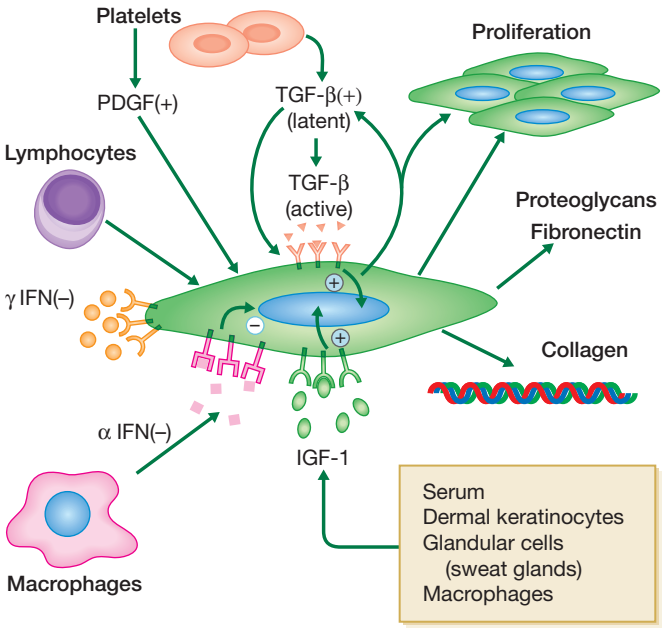

Fig. 45.8 Balance of pro- and antifibrotic cytokines in wound healing. The fibrogenic and antifibrogenic factors that modulate fibroblast function during wound healing. (From Tredget EE, Nedelec B, Scott PG, Ghahary A, Hypertrophic scars, keloids and molecular basis for therapy. *Surg Clin N Am*. 1997;77:701–730.)

factor.[106] Our understanding of fibrocytes as profibrotic mediators of wound healing continues to evolve, with several recent descriptions of alternate fibrocyte subpopulations[107] and the ability to reprogram fibrocytes into an antifibrotic phenotype.[108] Although this appears to complicate the fibrocyte picture, it does highlight the importance of systemic responses to wound healing and suggests that the initial cytokine signals that bone marrow-derived cells receive as they leave the circulation can have a significant impact on their role in HTS formation.

HYPERTROPHIC SCAR KERATINOCYTES

Keratinocytes are an important component of wound healing. Classically the remodeling phase of wound healing begins once reepithelialization of the wound is complete,[109] and wounds taking longer than 2 weeks to reepithelialize are more likely to form HTS.[110] Keratinocytes regulate fibroblast activity and vice versa,[109] suggesting that they play key roles in normal wound healing and HTS formation.[111] Experiments with keratinocyte-conditioned media in skin-equivalent models show that keratinocytes downregulate fibroblast production of the profibrotic cytokines TGF-β and CTGF.[112] Normally keratinocytes increase fibroblast proliferation but simultaneously reduce collagen production[113] and increase collagen breakdown by upregulating MMP-1 via factors such as stratifin.[114] In contrast, keratinocytes from HTS promote increased fibrosis in normal dermal fibroblasts,[72] display an activated phenotype similar to early wound-healing keratinocytes,[115] and have higher proliferation rates in the basal layer many months after reepithelialization is complete.[116] This may be due, in part, to elevated PDGF production by HTS keratinocytes.[117] This suggests that normal keratinocytes promote normal wound healing and abnormal keratinocytes promote HTS formation. It is also possible that HTS fibroblasts alter the normal wound-healing keratinocyte phenotype to a HTS phenotype, and these HTS keratinocytes in turn reinforce the HTS fibroblast phenotype. Thus therapies for HTS must address not only wound fibroblasts but also wound keratinocytes.

The Role of Cytokines in Hypertrophic Scar

Cytokines serve as signals for communication between cells, in paracrine signaling, and for cells to signal themselves in autocrine signaling. While the number of cytokines, and hence the diversity of signals, is immense, there are several key cytokines whose prototypic role in fibrosis and HTS has been extensively studied and whose actions account for a wide variety of fibroses. The roles of these cytokines are illustrated in Fig. 45.8.

TGF-β

TGF-β is one of the most studied profibrotic cytokines and belongs to a large superfamily of related proteins regulating processes as diverse as embryonic development, chemotaxis,

cell cycle, homeostasis, and wound healing. When produced by cells, TGF-β is secreted in an inactive form bound to latent TGF-β-binding protein. This bond is subsequently cleaved by enzymes in the milieu of healing wounds, including several matrix metalloproteinases (MMP-2, MMP-9) and plasmin (present in blood). Mammals produce three known isoforms: TGF-β_1, TGF-β_2, and TGF-β_3.[118] These are produced by many cells involved in wound healing, including degranulating platelets, macrophages, T lymphocytes, endothelial cells, fibroblasts, and keratinocytes.[119] The actions of TGF-β_1 and -β_2 are mediated by the intracellular Smad pathway and have directly profibrotic actions on mesenchymal cells.[120] TGF-β is upregulated locally in wounds and systemically in the blood of burn patients with HTS.[121] HTS fibroblasts produce greater amounts of TGF-β than normal fibroblasts[122] and regenerative fetal fibroblasts.[123] In fact, normally regenerative fetal fibroblasts can be induced to form scar following TGF-β exposure.[123] TGF-β has direct effects on the ECM by upregulating collagen production[124] and downregulating decorin production[125] by fibroblasts. This decrease in dermal decorin is profibrotic because decorin binds to TGF-β in the ECM, blocking its activity.[126] TGF-β promotes not only the transformation of fibroblasts into myofibroblasts[46] but also the transdifferentiation of epithelial cells into mesenchymal cells,[127] and it reduces apoptosis in the healing wound.[128] In this context, TGF-β is a highly profibrotic cytokine playing a unique role in HTS initiation. Interestingly, it has been suggested that the isoform TGF-β_3 acts as an antifibrotic cytokine. Clinical trials of TGF-β_3 have shown promise in improving wound healing,[129] and it is noteworthy that TGF-β_3, which is upregulated in the remodeling phase of wound healing, reduces ECM deposition.[130] Many effects of other cytokines in wound healing can be directly related to activation by or interaction with TGF-β.

CTGF/CCN2

Connective tissue growth factor (CTGF or CCN2) is a prototypic member of the CCN family of cytokines. The CCN family motif consists of four linked regions: an IGF-binding domain, a von Willebrand type C domain, a thrombospondin-1 domain, and a cysteine knot heparin-binding domain.[131] This configuration and multiple studies suggest that CTGF does not act simply as a growth factor, but rather as an important cofactor for TGF-β and as an interface between cells and the ECM by binding to cellular integrins and matrix proteoglycans.[132] Independent stimulation by TGF-β or CTGF alone induces only transient fibrotic upregulation in fibroblasts, whereas co-stimulation by both cytokines leads to prolonged fibrosis,[133] and in chronic fibrosis CTGF remains elevated after TGF-β returns to basal levels.[134] Thus one can surmise that TGF-β serves to initiate fibrosis and CTGF serves to continue the process as a downstream mediator of TGF-β.[124] In keeping with this hypothesis, CTGF is upregulated in HTS, scleroderma,[135] and other fibrotic diseases.[136] TGF-β induces CTGF through the Ras/MEK/ERK pathway, and blocking this activation with iloprost (a synthetic prostacyclin PGI_2 analog) reduces fibrosis.[137] Other methods of targeting CTGF, such as anti-CTGF antibodies and CTGF siRNA, have also proved effective in reducing fibrosis.[138]

PLATELET-DERIVED GROWTH FACTOR

PDGF is delivered to wounds by platelets from injured capillary vessels and is also produced by local fibroblasts.[139] There are four isoforms of PDGF: A, B, C, and D, which form dimers to activate two structurally related tyrosine kinase receptors[140] leading to fibroblast proliferation and actin filament reorganization that induces a transformation into myofibroblasts.[45] PDGF also increases ECM production and inhibits myofibroblast apoptosis.[141] PDGF activity contributes to pulmonary fibrosis, hepatic fibrosis, renal fibrosis, and scleroderma.[142] PDGF has been shown to upregulate TGF-β receptors in scleroderma fibroblasts,[139] and its multiple effects are magnified in HTS and keloid fibroblasts.[143] Recent research into the causes of nephrogenic systemic fibrosis, a disorder of dermal fibrosis occurring after gadolinium contrast administration in patients with impaired renal function, shows that blocking PDGF receptors using antibodies inhibits the proliferative effects of gadolinium on fibroblasts.[144] Other researchers have shown that blocking PDGF action using tyrosine kinase inhibitors reduces fibrosis in murine models of radiation-induced pulmonary fibrosis[145] and scleroderma.[146] Thus although PDGF is an independently profibrotic cytokine, it also serves to reinforce and magnify the effects of TGF-β, and blocking its activity can reduce fibrosis.

INSULIN-LIKE GROWTH FACTOR 1

Insulin-like growth factor 1 (IGF-1) was originally described in chondrocytes, where it regulates glycosaminoglycan production.[147] IGF-1 is a mitogen for fibroblasts[148] and endothelial cells,[149] and it induces collagen production in pulmonary[150] and dermal[151] fibroblasts. IGF-1 upregulates TGF-β gene transcription in fibroblasts, accounting for observed similarities in their profibrotic actions.[151] It has been shown that IGF-1 also downregulates collagenase mRNA levels and activity in dermal fibroblasts.[152] This increase in collagen production and decrease in breakdown shift the balance of ECM remodeling toward fibrosis. IGF-1 is upregulated in a number of fibrotic conditions, including post-burn HTS,[153] scleroderma, pulmonary fibrosis, and hepatic fibrosis.[5] Interestingly in unwounded skin IGF-1 is produced exclusively in epidermal sweat and sebaceous glands and is thus sequestered from dermal fibroblasts.[153] One may hypothesize that when these structures are disrupted, as in burns and other wounds, dermal fibroblasts are then directly exposed to IGF-1. Prolonged inflammation and delayed re-epithelialization would increase the duration of fibroblast stimulation with IGF-1 and could help explain the formation of HTS. Although IGF-1 is certainly not the only cause of HTS, its relationship to TGF-β and its unique distribution in skin suggest a key role in the pathogenesis of abnormal scarring.

INTERFERONS

HTS is not simply the result of overexpression of profibrotic signals, but also results from a disturbance in the delicate balance between pro- and antifibrotic cytokines. The interferons (IFN) are cytokines classically produced by immune cells to activate the host defense system.[154] IFNs

can be divided into type I (IFN-α and IFN-β produced by leukocytes and fibroblasts, respectively) and type II (IFN-γ produced by activated T lymphocytes).[154] Of these, the two antifibrotic cytokines whose roles in wound healing and HTS have been best studied are IFN-α_{2b} and IFN-γ. Treatment of fibroblasts with these IFNs inhibits cell proliferation and also downregulates collagen,[155] fibronectin,[155] and TGF-β production.[121] IFN-α_{2b} also upregulates collagenase production and reduces TIMP-1,[156] making it a good candidate to promote scar remodeling.[121] IFN-α_{2b} reduces in vitro collagen lattice contraction rates[157] and in vivo wound contraction in guinea pigs.[158] IFN-α_{2b} also reduces myofibroblast populations and increases the numbers of apoptotic fibroblasts in later stages of wound healing,[158] a finding also demonstrated in several other cell types.[159,160] A prospective clinical trial of IFN-α_{2b} in post-burn HTS patients demonstrated reductions in scar volume, normalized TGF-β levels, and reduced scar angiogenesis.[121] It is suggested that abnormal scar results, at least in part, from reduced levels of endogenous IFN in burn patients. An examination of the peripheral blood mononuclear cells (PBMCs) of patients forming keloids after trauma compared to those with normal scarring showed decreased production of IFN-α and IFN-γ,[161] which is consistent with this hypothesis. Therefore an understanding of IFNs highlights the important balance between pro- and antifibrotic cytokines and suggests possible therapeutic treatments for HTS.

The Immune System Regulates Wound Healing

Mast cells, neutrophils, and macrophages have long been recognized as playing important roles in the inflammatory phase of wound healing.[162] Macrophages produce classic immune cytokines interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α), which stimulate keratinocytes and fibroblasts,[45] and classic profibrotic cytokines TGF-β, PDGF, and IGF-1.[163] Recently the importance of the immune response type rather than degree of inflammation in determining the risk of HTS formation has been recognized. HTS are highly infiltrated by lymphocytes,[6] of which activated $CD4^+$ T-helper (T_H) cells are an important subgroup.[99] These T_H cells can be generally classified as one of at least four groups: T_H1, T_H2, T_H17, and T-regulatory cells, based on cytokine production patterns.[164] Of these, the T_H1–T_H2 axis in wound healing and burn patients is the most studied. T_H1 cells produce IFN-γ, IL-2, and TNF-β and are involved in cell-mediated immunity, whereas T_H2 cells produce IL-4, IL-5, and IL-10 and are involved in antibody-mediated

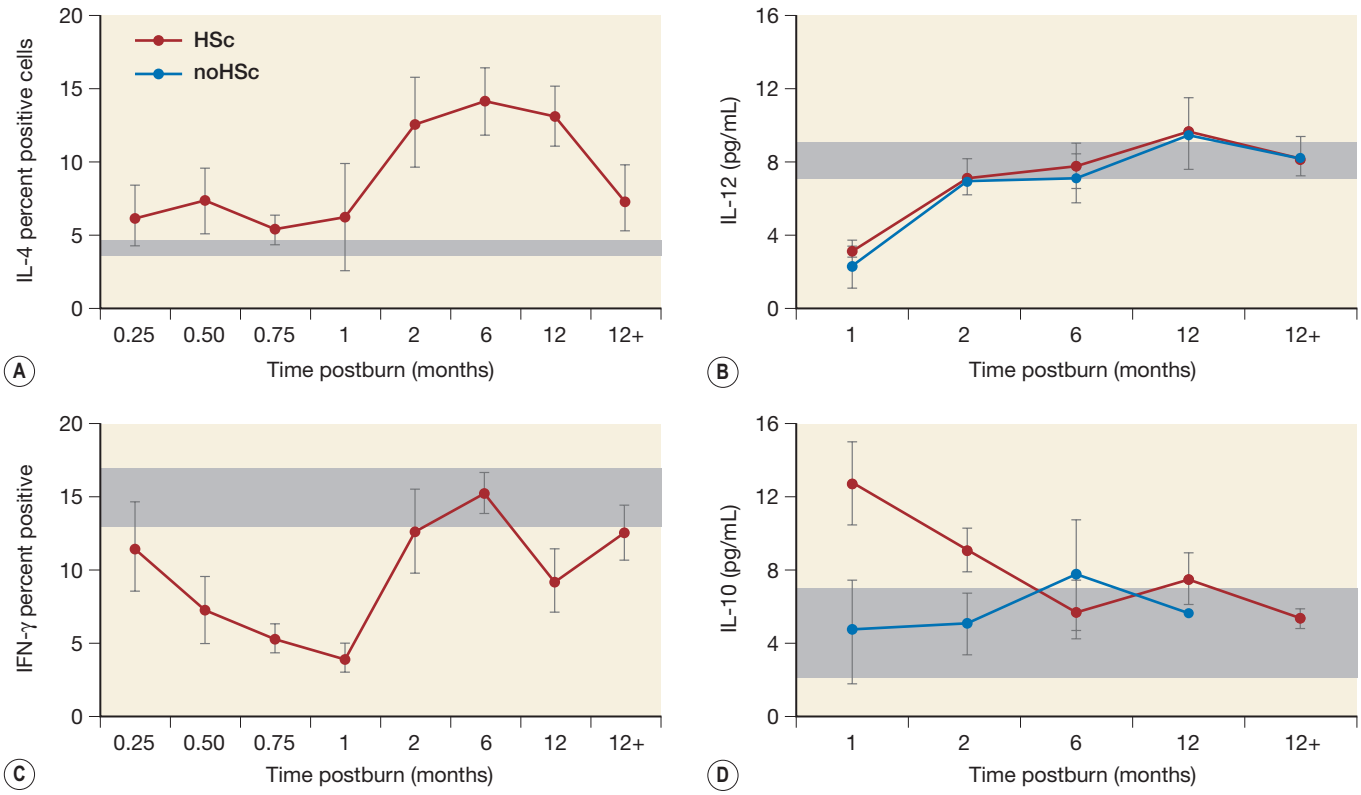

Fig. 45.9 Cytokine production in burn patients. Cytokine production by lymphocytes from burn patients as a function of time after injury. The percentages of lymphocytes producing IFN-γ (A) or IL-4 (C) were estimated by flow cytometry analysis of cells stained for intracellular cytokines using fluorescent-labeled antibodies (n = 22). Panels B and D show the time course of IL-12 (B) and IL-10 (D) production by peripheral blood mononuclear cells (PBMCs) cultured from burn patients who developed hypertrophic scar (HSc) and those who did not (noHSc), measured by enzyme-linked immunosorbent assay (ELISA: n = 16). The values measured for cells from normal human volunteers are shown in the shaded boxes (mean ± SD). (From Tredget EE, Nedelec B, Ghahary A. Hypertrophic scar, keloids and contracture: The cellular and molecular basis for therapy. *Surg Clin N Am*. 1997;77(3):701–730.)

immunity.[165] Interestingly these cytokine profiles are involved not only in specific immune responses, but are also anti- or profibrotic.[166] The T_H2 cytokine IL-10 stimulates activated naïve T_H cells to secrete TGF-β, and this is more pronounced in IFN-γ (T_H1) knockout mice and reduced in IL-4 (T_H2) knockout mice.[167] In a burn mouse model T_H2 cytokines (IL-5) were upregulated and T_H1 cytokines (IFN-γ and IL-2) were coordinately downregulated.[168] A similar T_H2 type response is seen in human burn patients using stimulated PBMC from those with burns of 25% or more total body surface area (TBSA),[169] a finding confirmed by another study in burn and major trauma patients.[170] The severity of fibrosis in animal models has also been linked to the type of T_H-cell response. In a model of liver fibrosis BALB/c mice developed a T_H2 response to chemically induced liver injury and displayed more severe fibrosis than did C57BL/6 mice, which developed a T_H1 response. This effect was abrogated by administration of IL-4 antibodies or IFN-γ, which induced a T_H1 response in the BALB/c mice.[171] A longitudinal study of recovering burn patients demonstrated a predominant T_H2 response to burn injury, as demonstrated by increased IL-4 and IL-10 levels from PBMC and in scar tissue (Fig. 45.9). Interestingly this response was significantly higher in burn patients who went on to develop HTS than in those who developed normal scars, whereas those patients developing normal scar had higher levels of IFN-γ-producing PBMC.[172] Recently it was found that IFN-α blocks T_H2 development and inhibits cytokine secretion by committed T_H2 cells.[164] This suggests that IFN-α_{2b} has effects not only on fibroblasts, as discussed previously, but also the T_H2 cells that modulate them.

Conclusion

HTS is a fibrotic disorder resulting from derangement of the normal wound-healing process and shares many common features with other fibrotic diseases. As discussed, HTS is markedly different from normal skin and mature scar in terms of the structure and composition of ECM, active cellular phenotypes, and cytokine messages displayed. This results in a mass of disorganized connective tissue with thin, irregular collagen bundles in whorls and nodules instead of thick, organized fibers parallel to the surface. The concomitant decrease in decorin and increase in other proteoglycans not only contributes to this disorganized ECM but also allows profibrotic signals to propagate in the dermis. The fibrotic, hypercellular nature of HTS both contributes to and results from elevated profibrotic (e.g., TGF-β, CTGF) and decreased antifibrotic (IFN-γ) cytokine levels. The resulting local HTS fibroblast is modulated by systemic fibrocytes and T_H cells, which migrate to the wound. The resulting pathogenesis of HTS is complex, with many aspects that serve to reinforce the fibrotic process. Although this complexity makes elucidating the mechanisms of HTS formation difficult, it also provides multiple targets for medical therapy. It is our hope that this will provide therapies to improve the quality of life for both burn patients and others with fibroproliferative conditions.

Complete references available online at
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Further Reading

Desmoulière A, Chaponnier C, Gabbiani G. Tissue repair, contraction, and the myofibroblast. *Wound Repair Regen*. 2005;13(1):7-12.

Dunkin CSJ, Pleat JM, Gillespie PH, et al. Scarring occurs at a critical depth of skin injury: precise measurement in a graduated dermal scratch in human volunteers. *Plast Reconstr Surg*. 2007;119(6):1722-1732.

Ignotz RA, Massague J. Transforming growth factor-beta stimulates the expression of fibronectin and collagen and their incorporation into the extracellular matrix. *J Biol Chem*. 1986;261(9):4337-4345.

Leask A, Abraham DJ. TGF-beta signaling and the fibrotic response. *FASEB J*. 2004;18(7):816-827.

Schmidt M, Sun G, Stacey MA, et al. Identification of circulating fibrocytes as precursors of bronchial myofibroblasts in asthma. *J Immunol*. 2003;171(1):380-389.

Tredget EE, Yang L, Delehanty M, et al. Polarized Th2 cytokine production in patients with hypertrophic scar following thermal injury. *J Interferon Cytokine Res*. 2006;26(3):179-189.

Wang J, Dodd C, Shankowsky HA, et al. Deep dermal fibroblasts contribute to hypertrophic scarring. *Lab Invest*. 2008;88(12):1278-1290.

References

1. Niessen FB, Spauwen PH, Schalkwijk J, et al. On the nature of hypertrophic scars and keloids: a review. *Plast Reconstr Surg*. 1999;104(5):1435-1458.
2. Wynn TA. Cellular and molecular mechanisms of fibrosis. *J Pathol*. 2008;214(2):199-210.
3. Scott PG, Dodd CM, Tredget EE, et al. Chemical characterization and quantification of proteoglycans in human post-burn hypertrophic and mature scars. *Clin Sci*. 1996;90(5):417-425.
4. Wang H, Pieper J, Peters F, et al. Synthetic scaffold morphology controls human dermal connective tissue formation. *J Biomed Mater Res A*. 2005;74(4):523-532.
5. Scott PG, Ghahary A, Tredget EE. Molecular and cellular aspects of fibrosis following thermal injury. *Hand Clin*. 2000;16(2):271-287.
6. Linares HA, Kischer CW, Dobrkovsky M, et al. The histiotypic organization of the hypertrophic scar in humans. *J Invest Dermatol*. 1972;59(4):323-331.
7. Bailey AJ, Bazin S, Sims TJ, et al. Characterization of the collagen of human hypertrophic and normal scars. *Biochim Biophys Acta*. 1975;405(2):412-421.
8. Ehrlich HP, White BS. The identification of alpha A and alpha B collagen chains in hypertrophic scar. *Exp Mol Pathol*. 1981;34(1):1-8.
9. Hayakawa T, Hashimoto Y, Myokei Y, et al. Changes in type of collagen during the development of human post-burn hypertrophic scars. *Clin Chim Acta*. 1979;93(1):119-125.
10. Gay S, Vijanto J, Raekallio J, et al. Collagen types in early phases of wound healing in children. *Acta Chir Scand*. 1978;144(4):205-211.
11. Zhang LQ, Laato M, Muona P, et al. Normal and hypertrophic scars: quantification and localization of messenger RNAs for type I, III and VI collagens. *Br J Dermatol*. 1994;130(4):453-459.
12. Kischer CW. Collagen and dermal patterns in the hypertrophic scar. *Anat Rec*. 1974;179(1):137-145.
13. Iozzo RV, Murdoch AD. Proteoglycans of the extracellular environment: clues from the gene and protein side offer novel perspectives in molecular diversity and function. *FASEB J*. 1996;10(5):598-614.
14. Hardingham TE, Fosang AJ. Proteoglycans: many forms and many functions. *FASEB J*. 1992;6(3):861-870.
15. Shetlar MR, Dobrkovsky M, Linares H, et al. The hypertrophic scar. Glycoprotein and collagen components of burn scars. *Proc Soc Exp Biol Med*. 1971;138(1):298-300.
16. Zhang G, Ezura Y, Chervoneva I, et al. Decorin regulates assembly of collagen fibrils and acquisition of biomechanical properties during tendon development. *J Cell Biochem*. 2006;98(6):1436-1449.
17. Orgel JP, Eid A, Antipova O, et al. Decorin core protein (decoron) shape complements collagen fibril surface structure and mediates its binding. *PLoS ONE*. 2009;4(9):e7028.
18. Danielson KG, Baribault H, Holmes DF, et al. Targeted disruption of decorin leads to abnormal collagen fibril morphology and skin fragility. *J Cell Biol*. 1997;136(3):729-743.
19. Zhang Z, Li X-J, Liu Y, et al. Recombinant human decorin inhibits cell proliferation and downregulates TGF-beta1 production in hypertrophic scar fibroblasts. *Burns*. 2007;33(5):634-641.
20. Nili N, Cheema AN, Giordano FJ, et al. Decorin inhibition of PDGF-stimulated vascular smooth muscle cell function: potential mechanism for inhibition of intimal hyperplasia after balloon angioplasty. *Am J Pathol*. 2003;163(3):869-878.
21. Bittner K, Liszio C, Blumberg P, et al. Modulation of collagen gel contraction by decorin. *Biochem J*. 1996;314(Pt 1):159-166.
22. Zhang Z, Garron TM, Li XJ, et al. Recombinant human decorin inhibits TGF-beta1-induced contraction of collagen lattice by hypertrophic scar fibroblasts. *Burns*. 2009;35(4):527-537.
23. Zhu JX, Goldoni S, Bix G, et al. Decorin evokes protracted internalization and degradation of the epidermal growth factor receptor via caveolar endocytosis. *J Biol Chem*. 2005;280(37):32468-32479.
24. Goldoni S, Humphries A, Nystrom A, et al. Decorin is a novel antagonistic ligand of the Met receptor. *J Cell Biol*. 2009;185(4):743-754.
25. Schonherr E, Sunderkotter C, Iozzo RV, et al. Decorin, a novel player in the insulin-like growth factor system. *J Biol Chem*. 2005;280(16):15767-15772.
26. Sayani K, Dodd CM, Nedelec B, et al. Delayed appearance of decorin in healing burn scars. *Histopathology*. 2000;36(3):262-272.
27. Williams KJ, Qiu G, Usui HK, et al. Decorin deficiency enhances progressive nephropathy in diabetic mice. *Am J Pathol*. 2007;171(5):1441-1450.
28. Kolb M, Margetts PJ, Galt T, et al. Transient transgene expression of decorin in the lung reduces the fibrotic response to bleomycin. *Am J Respir Crit Care Med*. 2001;163(3 Pt 1):770-777.
29. Ameye L, Young MF. Mice deficient in small leucine-rich proteoglycans: novel in vivo models for osteoporosis, osteoarthritis, Ehlers-Danlos syndrome, muscular dystrophy, and corneal diseases. *Glycobiology*. 2002;12(9):107R-116R.
30. Jarvelainen H, Puolakkainen P, Pakkanen S, et al. A role for decorin in cutaneous wound healing and angiogenesis. *Wound Repair Regen*. 2006;14(4):443-452.
31. Zimmermann DR, Dours-Zimmermann MT, Schubert M, et al. Versican is expressed in the proliferating zone in the epidermis and in association with the elastic network of the dermis. *J Cell Biol*. 1994;124(5):817-825.
32. Kischer CW, Hendrix MJ. Fibronectin (FN) in hypertrophic scars and keloids. *Cell Tissue Res*. 1983;231(1):29-37.
33. Leiss M, Beckmann K, Giros A, et al. The role of integrin binding sites in fibronectin matrix assembly in vivo. *Curr Opin Cell Biol*. 2008;20(5):502-507.
34. Sorrell JM, Baber MA, Caplan AI. Human dermal fibroblast subpopulations; differential interactions with vascular endothelial cells in coculture: nonsoluble factors in the extracellular matrix influence interactions. *Wound Repair Regen*. 2008;16(2):300-309.
35. Sorrell JM, Caplan AI. Fibroblast heterogeneity: more than skin deep. *J Cell Sci*. 2004;117(Pt 5):667-675.
36. Wang J, Dodd C, Shankowsky HA, et al. Deep dermal fibroblasts contribute to hypertrophic scarring. *Lab Invest*. 2008;88(12):1278-1290.
37. Dunkin CSJ, Pleat JM, Gillespie PH, et al. Scarring occurs at a critical depth of skin injury: precise measurement in a graduated dermal scratch in human volunteers. *Plast Reconstr Surg*. 2007;119(6):1722-1732.
38. Kwan P, Hori K, Ding J, et al. Scar and contracture: biological principles. *Hand Clin*. 2009;25(4):511-528.
39. Rossio-Pasquier P, Casanova D, Jomard A, et al. Wound healing of human skin transplanted onto the nude mouse after a superficial excisional injury: human dermal reconstruction is achieved in several steps by two different fibroblast subpopulations. *Arch Dermatol Res*. 1999;291(11):591-599.
40. Tomasek JJ, Gabbiani G, Hinz B, et al. Myofibroblasts and mechano-regulation of connective tissue remodelling. *Nat Rev Mol Cell Biol*. 2002;3(5):349-363.
41. Hinz B, Celetta G, Tomasek JJ, et al. Alpha-smooth muscle actin expression upregulates fibroblast contractile activity. *Mol Biol Cell*. 2001;12(9):2730-2741.
42. Hinz B, Mastrangelo D, Iselin CE, et al. Mechanical tension controls granulation tissue contractile activity and myofibroblast differentiation. *Am J Pathol*. 2001;159(3):1009-1020.
43. Bergers G, Song S. The role of pericytes in blood-vessel formation and maintenance. *Neuro Oncol*. 2005;7(4):452-464.
44. Desmouliere A, Redard M, Darby I, et al. Apoptosis mediates the decrease in cellularity during the transition between granulation tissue and scar. *Am J Pathol*. 1995;146(1):56-66.
45. Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. *Physiol Rev*. 2003;83(3):835-870.
46. Desmouliere A, Geinoz A, Gabbiani F, et al. Transforming growth factor-beta 1 induces alpha-smooth muscle actin expression in granulation tissue myofibroblasts and in quiescent and growing cultured fibroblasts. *J Cell Biol*. 1993;122(1):103-111.
47. Serini G, Bochaton-Piallat ML, Ropraz P, et al. The fibronectin domain ED-A is crucial for myofibroblastic phenotype induction by transforming growth factor-beta1. *J Cell Biol*. 1998;142(3):873-881.
48. Rubbia-Brandt L, Sappino AP, Gabbiani G. Locally applied GM-CSF induces the accumulation of alpha-smooth muscle actin containing myofibroblasts. *Virchows Arch B Cell Pathol Incl Mol Pathol*. 1991;60(2):73-82.
49. Vyalov S, Desmouliere A, Gabbiani G. GM-CSF-induced granulation tissue formation: relationships between macrophage and myofibroblast accumulation. *Virchows Arch B Cell Pathol Incl Mol Pathol*. 1993;63(4):231-239.
50. Appleton I, Tomlinson A, Chander CL, et al. Effect of endothelin-1 on croton oil-induced granulation tissue in the rat. A pharmacologic and immunohistochemical study. *Lab Invest*. 1992;67(6):703-710.
51. Souza BR, Cardoso JF, Amadeu TP, et al. Sympathetic denervation accelerates wound contraction but delays reepithelialization in rats. *Wound Repair Regen*. 2005;13(5):498-505.

52. Dubuisson L, Desmouliere A, Decourt B, et al. Inhibition of rat liver fibrogenesis through noradrenergic antagonism. *Hepatology*. 2002;35(2):325-331.
53. Arora PD, Narani N, McCulloch CA. The compliance of collagen gels regulates transforming growth factor-beta induction of alpha-smooth muscle actin in fibroblasts. *Am J Pathol*. 1999;154(3):871-882.
54. Wells RG. The role of matrix stiffness in hepatic stellate cell activation and liver fibrosis. *J Clin Gastroenterol*. 2005;39(4 suppl 2):S158-S161.
55. Yeung T, Georges PC, Flanagan LA, et al. Effects of substrate stiffness on cell morphology, cytoskeletal structure, and adhesion. *Cell Motil Cytoskeleton*. 2005;60(1):24-34.
56. Ng CP, Hinz B, Swartz MA. Interstitial fluid flow induces myofibroblast differentiation and collagen alignment in vitro. *J Cell Sci*. 2005;118(Pt 20):4731-4739.
57. Hinz B, Pittet P, Smith-Clerc J, et al. Myofibroblast development is characterized by specific cell-cell adherens junctions. *Mol Biol Cell*. 2004;15(9):4310-4320.
58. Follonier L, Schaub S, Meister JJ, et al. Myofibroblast communication is controlled by intercellular mechanical coupling. *J Cell Sci*. 2008;121(Pt 20):3305-3316.
59. Follonier Castella L, Gabbiani G, McCulloch CA, et al. Regulation of myofibroblast activities: calcium pulls some strings behind the scene. *Exp Cell Res*. 2010;316(15):2390-2401.
60. Ehrlich HP, Desmouliere A, Diegelmann RF, et al. Morphological and immunochemical differences between keloid and hypertrophic scar. *Am J Pathol*. 1994;145(1):105-113.
61. Lee JY, Yang CC, Chao SC, et al. Histopathological differential diagnosis of keloid and hypertrophic scar. *Am J Dermatopathol*. 2004;26(5):379-384.
62. Verhaegen PD, van Zuijlen PP, Pennings NM, et al. Differences in collagen architecture between keloid, hypertrophic scar, normotrophic scar, and normal skin: an objective histopathological analysis. *Wound Repair Regen*. 2009;17(5):649-656.
63. van der Slot AJ, Zuurmond AM, van den Bogaerdt AJ, et al. Increased formation of pyridinoline cross-links due to higher telopeptide lysyl hydroxylase levels is a general fibrotic phenomenon. *Matrix Biol*. 2004;23(4):251-257.
64. Ulrich MM, Verkerk M, Reijnen L, et al. Expression profile of proteins involved in scar formation in the healing process of full-thickness excisional wounds in the porcine model. *Wound Repair Regen*. 2007;15(4):482-490.
65. Xi-Qiao W, Ying-Kai L, Chun Q, et al. Hyperactivity of fibroblasts and functional regression of endothelial cells contribute to microvessel occlusion in hypertrophic scarring. *Microvasc Res*. 2009;77(2):204-211.
66. Darby IA, Bisucci T, Pittet B, et al. Skin flap-induced regression of granulation tissue correlates with reduced growth factor and increased metalloproteinase expression. *J Pathol*. 2002;197(1):117-127.
67. Costa AM, Peyrol S, Porto LC, et al. Mechanical forces induce scar remodeling. Study in non-pressure-treated versus pressure-treated hypertrophic scars. *Am J Pathol*. 1999;155(5):1671-1679.
68. Aarabi S, Bhatt KA, Shi Y, et al. Mechanical load initiates hypertrophic scar formation through decreased cellular apoptosis. *FASEB J*. 2007;21(12):3250-3261.
69. Modarressi A, Pietramaggiori G, Godbout C, et al. Hypoxia impairs skin myofibroblast differentiation and function. *J Invest Dermatol*. 2010;130(12):2818-2827.
70. Menezes GC, Miron-Mendoza M, Ho CH, et al. Oncogenic Ras-transformed human fibroblasts exhibit differential changes in contraction and migration in 3D collagen matrices. *Exp Cell Res*. 2008;314(16):3081-3091.
71. Georges PC, Hui JJ, Gombos Z, et al. Increased stiffness of the rat liver precedes matrix deposition: implications for fibrosis. *Am J Physiol Gastrointest Liver Physiol*. 2007;293(6):G1147-G1154.
72. Bellemare J, Roberge CJ, Bergeron D, et al. Epidermis promotes dermal fibrosis: role in the pathogenesis of hypertrophic scars. *J Pathol*. 2005;206(1):1-8.
73. Hakvoort TE, Altun V, Ramrattan RS, et al. Epidermal participation in post-burn hypertrophic scar development. *Virchows Arch B Cell Pathol Incl Mol Pathol*. 1999;434(3):221-226.
74. Akaishi S, Ogawa R, Hyakusoku H. Keloid and hypertrophic scar: neurogenic inflammation hypotheses. *Med Hypotheses*. 2008;71(1):32-38.
75. Ross R, Everett NB, Tyler R. Wound healing and collagen formation. VI. The origin of the wound fibroblast studied in parabiosis. *J Cell Biol*. 1970;44(3):645-654.
76. Wang J, Dodd C, Shankowsky HA, et al. Deep dermal fibroblasts contribute to hypertrophic scarring. *Lab Invest*. 2008;88(12):1278-1290.
77. Rajkumar VS, Howell K, Csiszar K, et al. Shared expression of phenotypic markers in systemic sclerosis indicates a convergence of pericytes and fibroblasts to a myofibroblast lineage in fibrosis. *Arthritis Res Ther*. 2005;7(5):R1113-R1123.
78. Reeves HL, Friedman SL. Activation of hepatic stellate cells—a key issue in liver fibrosis. *Front Biosci*. 2002;7:d808-d826.
79. Guyot C, Lepreux S, Combe C, et al. Hepatic fibrosis and cirrhosis: the (myo)fibroblastic cell subpopulations involved. *Int J Biochem Cell Biol*. 2006;38(2):135-151.
80. Andrade ZA, Guerret S, Fernandes AL. Myofibroblasts in schistosomal portal fibrosis of man. *Mem Inst Oswaldo Cruz*. 1999;94(1):87-93.
81. Hewitson TD. Renal tubulointerstitial fibrosis: common but never simple. *Am J Physiol Renal Physiol*. 2009;296(6):F1239-F1244.
82. Pozzi A, Voziyan PA, Hudson BG, et al. Regulation of matrix synthesis, remodeling and accumulation in glomerulosclerosis. *Curr Pharm Des*. 2009;15(12):1318-1333.
83. Jahoda CA, Reynolds AJ. Hair follicle dermal sheath cells: unsung participants in wound healing. *Lancet*. 2001;358(9291):1445-1448.
84. Theise ND, Saxena R, Portmann BC, et al. The canals of Hering and hepatic stem cells in humans. *Hepatology*. 1999;30(6):1425-1433.
85. Saxena R, Theise N. Canals of Hering: recent insights and current knowledge. *Semin Liver Dis*. 2004;24(1):43-48.
86. Abe R, Donnelly SC, Peng T, et al. Peripheral blood fibrocytes: differentiation pathway and migration to wound sites. *J Immunol*. 2001;166(12):7556-7562.
87. Yang L, Scott PG, Dodd C, et al. Identification of fibrocytes in postburn hypertrophic scar. *Wound Repair Regen*. 2005;13(4):398-404.
88. Okada H, Kalluri R. Cellular and molecular pathways that lead to progression and regression of renal fibrogenesis. *Curr Mol Med*. 2005;5(5):467-474.
89. Prockop DJ. Marrow stromal cells as stem cells for nonhematopoietic tissues. *Science*. 1997;276(5309):71-74.
90. Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. *Science*. 1999;284(5411):143-147.
91. Barisic-Dujmovic T, Boban I, Clark SH. Fibroblasts/myofibroblasts that participate in cutaneous wound healing are not derived from circulating progenitor cells. *J Cell Physiol*. 2010;222(3):703-712.
92. Liu Y. New insights into epithelial-mesenchymal transition in kidney fibrosis. *J Am Soc Nephrol*. 2010;21(2):212-222.
93. Hinz B, Phan SH, Thannickal VJ, et al. The myofibroblast: one function, multiple origins. *Am J Pathol*. 2007;170(6):1807-1816.
94. Watsky MA, Weber KT, Sun Y, et al. New insights into the mechanism of fibroblast to myofibroblast transformation and associated pathologies. *Int Rev Cell Mol Biol*. 2010;282:165-192.
95. Bucala R, Spiegel LA, Chesney J, et al. Circulating fibrocytes define a new leukocyte subpopulation that mediates tissue repair. *Mol Med*. 1994;1(1):71-81.
96. Pilling D, Fan T, Huang D, et al. Identification of markers that distinguish monocyte-derived fibrocytes from monocytes, macrophages, and fibroblasts. *PLoS ONE*. 2009;4(10):e7475.
97. Andersson-Sjoland A, de Alba CG, Nihlberg K, et al. Fibrocytes are a potential source of lung fibroblasts in idiopathic pulmonary fibrosis. *Int J Biochem Cell Biol*. 2008;40(10):2129-2140.
98. Sakai N, Wada T, Matsushima K, et al. The renin-angiotensin system contributes to renal fibrosis through regulation of fibrocytes. *J Hypertens*. 2008;26(4):780-790.
99. Wang J, Jiao H, Stewart TL, et al. Increased TGF-beta-producing CD4+T lymphocytes in postburn patients and their potential interaction with dermal fibroblasts in hypertrophic scarring. *Wound Repair Regen*. 2007;15(4):530-539.
100. Yang L, Scott PG, Giuffre J, et al. Peripheral blood fibrocytes from burn patients: identification and quantification of fibrocytes in adherent cells cultured from peripheral blood mononuclear cells. *Lab Invest*. 2002;82(9):1183-1192.
101. Pilling D, Roife D, Wang M, et al. Reduction of bleomycin-induced pulmonary fibrosis by serum amyloid P. *J Immunol*. 2007;179(6):4035-4044.
102. Hong KM, Belperio JA, Keane MP, et al. Differentiation of human circulating fibrocytes as mediated by transforming growth factor-beta

and peroxisome proliferator-activated receptor gamma. *J Biol Chem*. 2007;282(31):22910-22920.
103. Wang JF, Jiao H, Stewart TL, et al. Fibrocytes from burn patients regulate the activities of fibroblasts. *Wound Repair Regen*. 2007;15(1):113-121.
104. Chesney J, Bacher M, Bender A, et al. The peripheral blood fibrocyte is a potent antigen-presenting cell capable of priming naive T cells in situ. *Proc Natl Acad Sci USA*. 1997;94(12):6307-6312.
105. Balmelli C, Alves MP, Steiner E, et al. Responsiveness of fibrocytes to toll-like receptor danger signals. *Immunobiology*. 2007;212(9-10):693-699.
106. Hartlapp I, Abe R, Saeed RW, et al. Fibrocytes induce an angiogenic phenotype in cultured endothelial cells and promote angiogenesis in vivo. *FASEB J*. 2001;15(12):2215-2224.
107. Curnow SJ, Fairclough M, Schmutz C, et al. Distinct types of fibrocyte can differentiate from mononuclear cells in the presence and absence of serum. *PLoS ONE*. 2010;5(3):e9730.
108. Medina A, Ghahary A. Fibrocytes can be reprogrammed to promote tissue remodeling capacity of dermal fibroblasts. *Mol Cell Biochem*. 2010;344(1-2):11-21.
109. Werner S, Krieg T, Smola H. Keratinocyte–fibroblast interactions in wound healing. *J Investig Dermatol*. 2007;127(5):998-1008.
110. Deitch EA, Wheelahan TM, Rose MP, et al. Hypertrophic burn scars: analysis of variables. *J Trauma*. 1983;23(10):895-898.
111. Ghahary A, Ghaffari A. Role of keratinocyte-fibroblast cross-talk in development of hypertrophic scar. *Wound Repair Regen*. 2007;15(suppl 1):S46-S53.
112. Amjad SB, Carachi R, Edward M. Keratinocyte regulation of TGF-beta and connective tissue growth factor expression: a role in suppression of scar tissue formation. *Wound Repair Regen*. 2007;15(5):748-755.
113. Harrison CA, Gossiel F, Bullock AJ, et al. Investigation of keratinocyte regulation of collagen I synthesis by dermal fibroblasts in a simple in vitro model. *Br J Dermatol*. 2006;154(3):401-410.
114. Ghahary A, Marcoux Y, Karimi-Busheri F, et al. Differentiated keratinocyte-releasable stratifin (14–3-3 sigma) stimulates MMP-1 expression in dermal fibroblasts. *J Invest Dermatol*. 2005;124(1):170-177.
115. Machesney M, Tidman N, Waseem A, et al. Activated keratinocytes in the epidermis of hypertrophic scars. *Am J Pathol*. 1998;152(5):1133-1141.
116. Andriessen MP, Niessen FB, Van de Kerkhof PC, et al. Hypertrophic scarring is associated with epidermal abnormalities: an immunohistochemical study. *J Pathol*. 1998;186(2):192-200.
117. Niessen FB, Andriessen MP, Schalkwijk J, et al. Keratinocyte-derived growth factors play a role in the formation of hypertrophic scars. *J Pathol*. 2001;194(2):207-216.
118. Leask A, Abraham DJ. TGF-beta signaling and the fibrotic response. *FASEB J*. 2004;18(7):816-827.
119. Roberts AB. Molecular and cell biology of TGF-beta. *Miner Electrolyte Metab*. 1998;24(2-3):111-119.
120. Cutroneo KR. TGF-beta-induced fibrosis and SMAD signaling: oligo decoys as natural therapeutics for inhibition of tissue fibrosis and scarring. *Wound Repair Regen*. 2007;15(suppl 1):S54-S60.
121. Tredget EE, Shankowsky HA, Pannu R, et al. Transforming growth factor-beta in thermally injured patients with hypertrophic scars: effects of interferon alpha-2b. *Plast Reconstr Surg*. 1998;102(5):1317-1328, discussion 1329-1330.
122. Wang R, Ghahary A, Shen Q, et al. Hypertrophic scar tissues and fibroblasts produce more transforming growth factor-beta1 mRNA and protein than normal skin and cells. *Wound Repair Regen*. 2000;8(2):128-137.
123. Lanning DA, Nwomeh BC, Montante SJ, et al. TGF-beta1 alters the healing of cutaneous fetal excisional wounds. *J Pediatr Surg*. 1999;34(5):695-700.
124. Grotendorst GR. Connective tissue growth factor: a mediator of TGF-beta action on fibroblasts. *Cytokine Growth Factor Rev*. 1997;8(3):171-179.
125. Scott PG, Dodd CM, Ghahary A, et al. Fibroblasts from post-burn hypertrophic scar tissue synthesize less decorin than normal dermal fibroblasts. *Clin Sci*. 1998;94(5):541-547.
126. Yamaguchi Y, Mann DM, Ruoslahti E. Negative regulation of transforming growth factor-beta by the proteoglycan decorin. *Nature*. 1990;346(6281):281-284.
127. Willis BC, Liebler JM, Luby-Phelps K, et al. Induction of epithelial-mesenchymal transition in alveolar epithelial cells by transforming growth factor-beta1: potential role in idiopathic pulmonary fibrosis. *Am J Pathol*. 2005;166(5):1321-1332.
128. Arora PD, McCulloch CA. The deletion of transforming growth factor-beta-induced myofibroblasts depends on growth conditions and actin organization. *Am J Pathol*. 1999;155(6):2087-2099.
129. Occleston NL, Laverty HG, O'Kane S, et al. Prevention and reduction of scarring in the skin by Transforming Growth Factor beta 3 (TGFbeta3): from laboratory discovery to clinical pharmaceutical. *J Biomater Sci Polym Ed*. 2008;19(8):1047-1063.
130. Bock O, Yu H, Zitron S, et al. Studies of transforming growth factors beta 1–3 and their receptors I and II in fibroblast of keloids and hypertrophic scars. *Acta Derm Venereol*. 2005;85(3):216-220.
131. Leask A, Abraham DJ. All in the CCN family: essential matricellular signaling modulators emerge from the bunker. *J Cell Sci*. 2006;119(Pt 23):4803-4810.
132. Chen CC, Lau LF. Functions and mechanisms of action of CCN matricellular proteins. *Int J Biochem Cell Biol*. 2009;41(4):771-783.
133. Mori T, Kawara S, Shinozaki M, et al. Role and interaction of connective tissue growth factor with transforming growth factor-beta in persistent fibrosis: a mouse fibrosis model. *J Cell Physiol*. 1999;181(1):153-159.
134. Leask A, Abraham DJ. The role of connective tissue growth factor, a multifunctional matricellular protein, in fibroblast biology. *Biochem Cell Biol*. 2003;81(6):355-363.
135. Colwell AS, Phan T-T, Kong W, et al. Hypertrophic scar fibroblasts have increased connective tissue growth factor expression after transforming growth factor-beta stimulation. *Plast Reconstr Surg*. 2005;116(5):1387-1390, discussion 1391-1392.
136. Shi-Wen X, Leask A, Abraham D. Regulation and function of connective tissue growth factor/CCN2 in tissue repair, scarring and fibrosis. *Cytokine Growth Factor Rev*. 2008;19(2):133-144.
137. Stratton R, Shiwen X, Martini G, et al. Iloprost suppresses connective tissue growth factor production in fibroblasts and in the skin of scleroderma patients. *J Clin Invest*. 2001;108(2):241-250.
138. Abraham D. Connective tissue growth factor: growth factor, matricellular organizer, fibrotic biomarker or molecular target for anti-fibrotic therapy in SSc? *Rheumatology (Oxford)*. 2008;47(suppl 5):v8-v9.
139. Trojanowska M. Role of PDGF in fibrotic diseases and systemic sclerosis. *Rheumatology (Oxford)*. 2008;47(suppl 5):v2-v4.
140. Andrae J, Gallini R, Betsholtz C. Role of platelet-derived growth factors in physiology and medicine. *Genes Dev*. 2008;22(10):1276-1312.
141. Powell DW, Mifflin RC, Valentich JD, et al. Myofibroblasts. I. Paracrine cells important in health and disease. *Am J Physiol*. 1999;277(1 Pt 1):C1-C9.
142. Bonner JC. Regulation of PDGF and its receptors in fibrotic diseases. *Cytokine Growth Factor Rev*. 2004;15(4):255-273.
143. Younai S, Venters G, Vu S, et al. Role of growth factors in scar contraction: an in vitro analysis. *Ann Plast Surg*. 1996;36(5):495-501.
144. Bhagavathula N, Dame MK, Dasilva M, et al. Fibroblast response to gadolinium: role for platelet-derived growth factor receptor. *Invest Radiol*. 2010;45(12):769-777.
145. Abdollahi A, Li M, Ping G, et al. Inhibition of platelet-derived growth factor signaling attenuates pulmonary fibrosis. *J Exp Med*. 2005;201(6):925-935.
146. Distler JHW, Jungel A, Huber LC, et al. Imatinib mesylate reduces production of extracellular matrix and prevents development of experimental dermal fibrosis. *Arthritis Rheum*. 2007;56(1):311-322.
147. Makower AM, Wroblewski J, Pawlowski A. Effects of IGF-I, EGF, and FGF on proteoglycans synthesized by fractionated chondrocytes of rat rib growth plate. *Exp Cell Res*. 1988;179(2):498-506.
148. Rolfe KJ, Cambrey AD, Richardson J, et al. Dermal fibroblasts derived from fetal and postnatal humans exhibit distinct responses to insulin like growth factors. *Arthritis Rheum*. 2007;7:124.
149. Miele C, Rochford JJ, Filippa N, et al. Insulin and insulin-like growth factor-I induce vascular endothelial growth factor mRNA expression via different signaling pathways. *J Biol Chem*. 2000;275(28):21695-21702.
150. Goldstein RH, Poliks CF, Pilch PF, et al. Stimulation of collagen formation by insulin and insulin-like growth factor I in cultures of human lung fibroblasts. *Endocrinology*. 1989;124(2):964-970.
151. Ghahary A, Shen Q, Shen YJ, et al. Induction of transforming growth factor beta 1 by insulin-like growth factor-1 in dermal fibroblasts. *J Cell Physiol*. 1998;174(3):301-309.
152. Ghahary A, Shen YJ, Nedelec B, et al. Collagenase production is lower in post-burn hypertrophic scar fibroblasts than in normal

fibroblasts and is reduced by insulin-like growth factor-1. *J Invest Dermatol*. 1996;106(3):476-481.
153. Ghahary A, Shen YJ, Wang R, et al. Expression and localization of insulin-like growth factor-1 in normal and post-burn hypertrophic scar tissue in human. *Mol Cell Biochem*. 1998;183(1-2):1-9.
154. Pestka S, Krause CD, Walter MR. Interferons, interferon-like cytokines, and their receptors. *Immunol Rev*. 2004;202:8-32.
155. Tredget EE, Shen YJ, Liu G, et al. Regulation of collagen synthesis and messenger RNA levels in normal and hypertrophic scar fibroblasts in vitro by interferon alfa-2b. *Wound Repair Regen*. 1993;1(3):156-165.
156. Ghahary A, Shen YJ, Nedelec B, et al. Interferons gamma and alpha-2b differentially regulate the expression of collagenase and tissue inhibitor of metalloproteinase-1 messenger RNA in human hypertrophic and normal dermal fibroblasts. *Wound Repair Regen*. 1995;3(2):176-184.
157. Dans MJ, Isseroff R. Inhibition of collagen lattice contraction by pentoxifylline and interferon-alpha, -beta, and -gamma. *J Invest Dermatol*. 1994;102(1):118-121.
158. Nedelec B, Dodd CM, Scott PG, et al. Effect of interferon-alpha2b on guinea pig wound closure and the expression of cytoskeletal proteins in vivo. *Wound Repair Regen*. 1998;6(3):202-212.
159. Dao T, Ariyasu T, Holan V, et al. Natural human interferon-alpha augments apoptosis in activated T cell line. *Cell Immunol*. 1994;155(2):304-311.
160. Rodriguez-Villanueva J, McDonnell TJ. Induction of apoptotic cell death in non-melanoma skin cancer by interferon-alpha. *Int J Cancer*. 1995;61(1):110-114.
161. McCauley RL, Chopra V, Li YY, et al. Altered cytokine production in black patients with keloids. *J Clin Immunol*. 1992;12(4):300-308.
162. van der Veer WM, Bloemen MCT, Ulrich MMW, et al. Potential cellular and molecular causes of hypertrophic scar formation. *Burns*. 2009;35(1):15-29.
163. Sunderkotter C, Steinbrink K, Goebeler M, et al. Macrophages and angiogenesis. *J Leukoc Biol*. 1994;55(3):410-422.
164. Huber JP, Ramos HJ, Gill MA, et al. Cutting edge: type I IFN reverses human Th2 commitment and stability by suppressing GATA3. *J Immunol*. 2010;185(2):813-817.
165. Mosmann TR, Coffman RL. TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annu Rev Immunol*. 1989;7:145-173.
166. Wynn TA. Fibrotic disease and the T(H)1/T(H)2 paradigm. *Nat Rev Immunol*. 2004;4(8):583-594.
167. Seder RA, Marth T, Sieve MC, et al. Factors involved in the differentiation of TGF-beta-producing cells from naive CD4+ T cells: IL-4 and IFN-gamma have opposing effects, while TGF-beta positively regulates its own production. *J Immunol*. 1998;160(12):5719-5728.
168. Hunt JP, Hunter CT, Brownstein MR, et al. The effector component of the cytotoxic T-lymphocyte response has a biphasic pattern after burn injury. *J Surg Res*. 1998;80(2):243-251.
169. Horgan AF, Mendez MV, O'Riordain DS, et al. Altered gene transcription after burn injury results in depressed T-lymphocyte activation. *Ann Surg*. 1994;220(3):342-351, discussion 351-352.
170. O'Sullivan ST, Lederer JA, Horgan AF, et al. Major injury leads to predominance of the T helper-2 lymphocyte phenotype and diminished interleukin-12 production associated with decreased resistance to infection. *Ann Surg*. 1995;222(4):482-490, discussion 490-492.
171. Shi Z, Wakil AE, Rockey DC. Strain-specific differences in mouse hepatic wound healing are mediated by divergent T helper cytokine responses. *Proc Natl Acad Sci USA*. 1997;94(20):10663-10668.
172. Tredget EE, Yang L, Delehanty M, et al. Polarized Th2 cytokine production in patients with hypertrophic scar following thermal injury. *J Interferon Cytokine Res*. 2006;26(3):179-189.

46 Pathophysiology of the Burn Scar

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Introduction

PREHISTORIC AND HISTORIC PERSPECTIVES

Wounds due to combat, hunting injuries, accidents, and thermal injuries have been the leading causes of death in humans for millennia, whereas prolonged survival of large full-thickness wounds is a recent phenomenon. Complex biological responses to cutaneous injury have evolved over time without evolutionary pressure to evolve appropriate healing responses to large wounds. There are records of human attempts to improve wound healing in ancient texts from Mesopotamia and Egypt. Guido Majno has explored what can be learned from archeology and paleontology regarding wounds and their treatment in ancient times and provides an accurate description of the wound healing process in lay terms.[1] In the development of modern medicine, the advances in wound treatment advocated by Ambroise Pare (1520–1590) stand out, together with the antisepsis campaign of Joseph Lister (1827–1912) and the development of antibiotics and other modern methods of treatment described in this book.

INCISIONAL WOUNDS WITH PRIMARY CLOSURE

The essential components of wound healing are easily understood. They are: (1) activation of tissue repair in the wound by fibroblasts and small blood vessels and an inflammatory response initiated by vascular leakage and (2) entry into the wound of circulating polymorphonuclear neutrophils, lymphocytes, and macrophages.[2] When a sharp incision is closed while still sterile, minimal vascular leakage and inflammation occur, and the predominant reaction to injury occurs in the fibroblasts present in the dermis and subcutaneous tissue. These resting connective tissue cells are rapidly activated to secrete collagen, which quickly bridges the small remaining gap to restore the resistance of the skin to tearing. Vascular continuity is restored by budding and remodeling of blood vessels, and the basal keratinocytes of the epidermis divide briefly to restore the complete structure of the epidermal barrier. All that remains to indicate the site of injury is a linear ribbon of dense collagen with little flexibility that marks the site of the incision, as well as small scars that mark the suture sites. This process of incisional wound healing was well described in humans by Ross and colleagues.[3,4]

DELAYED WOUND CLOSURE "BY SECOND INTENTION" AND WOUND CONTRACTION

If the epidermis and dermis are incised or removed and the edges of the wound remain separated, then the resultant inflammatory and reparative events are prolonged and more prominent. Extensive leakage of blood plasma by damaged small blood vessels maintains an outward flow that serves to keep the wound clean but causes deposition of coagulated fibrin and other desiccated proteins on the wound surface. Conversion of fibrinogen into fibrin fills the gap in the epidermis and provides a gelatinous matrix capable of sustaining migrating cells. Thrombin stimulates expression of interleukin-6 (IL-6) in connective tissue cells.[5] Degranulation of platelets releases platelet-derived growth factor (PDGF) and other proinflammatory cytokines.[6] Fibrin degradation releases peptides that stimulate fibroblast proliferation and secretion, division of vascular endothelial cells, and production of cytokines by other cells.[7–9] Dermal fibroblasts, together with circulating stem cells, divide rapidly in the wound bed and secrete large quantities of collagen and proteoglycans, with predominance of type III collagen.[10,11] Simultaneously the endothelial cells of small blood vessels proliferate rapidly and form numerous small capillary loops that extend upward toward the surface. Together these cells form a mass of granulation tissue that covers the wound. These activities of fibroblasts and endothelial cells are stimulated by cytokines and other peptides, largely secreted by monocytes and lymphoid cells that infiltrate the wound bed. Certain proteins and peptides that are normally present in blood plasma also stimulate and enable formation of the wound matrix, notably fibronectin and vitronectin.[12–14] Polymorphonuclear neutrophils also enter the wound bed in large numbers where they phagocytize and kill bacteria and fungi that gained entry to the dermis and subcutis through the open wound. Next the fibroblasts develop interconnections among themselves and produce and assemble the contractile machinery of actin and myosin within the cytoplasm of each cell.[15] These interconnected myofibroblasts contract to shrink the size of the open wound, pulling adjacent intact skin to cover the wound bed. Wound contraction is most dramatic in experimental wounds of rodents; however the effects of wound contracture in applying tension to surrounding tissues can be seen in humans as well. Simultaneously with these processes, the basal keratinocytes of the cut edges of the epidermis proliferate and change to a migratory and secretory phenotype and begin to invade the wound bed between the granulation tissue layer and the scab of dried proteins on the surface.[16] Once they make contact to seal the center of the wound, the migrating keratinocytes change phenotype again and restore the normal laminated structure of the epidermis and produce a new basal lamina.[17,18] Melanocytes also migrate during healing of large wounds and establish a degree of pigmentation in the healed wound that approximates the pigmentation of the uninjured skin. It

should be noted that only the epidermis regenerates to resemble the normal epidermis. Hair follicles, sweat glands, and other epidermal appendages do not regenerate. Thus the part of the wound that was not closed by contracture remains dry, hairless, and flat. Furthermore the restored dermis in a fully healed scar is composed of collagen type I fibers running in straight lines adjacent to one another and parallel to the surface, providing strength (though somewhat less than the native skin) but far less elasticity and flexibility than the connective tissue of the normal dermis.

FIRST-DEGREE OR SUPERFICIAL INJURY OF SKIN

Superficial burn wounds are those in which part or all of the epidermis is lost, but the epidermal basal lamina remains intact and the dermis is uninjured. In these areas, only epidermal regeneration is required, hair follicles and sweat glands remain intact, and healing can occur with little or no disfigurement.[19]

SECOND-DEGREE OR PARTIAL-THICKNESS INJURY

In partial-thickness wounds, the entire epidermis and the upper part of the dermis become necrotic. If left intact, the presence of a large quantity of devitalized tissue requires prolonged activity of macrophages to clear the necrotic debris. Granulation tissue forms underneath the necrotic dermal tissue, and epidermal migration occurs under the eschar formed by dead tissue, leading to restoration of the epidermis and production of dermal connective tissue in the form of a thin scar. The deep portions of the hair follicles remain viable, and the keratinocytes lining the hair follicles become migratory and undergo mitosis behind the migrating cells, eventually covering the surface with new epidermis derived from the hair follicle.[16,20] In severe cases, loss of hair follicles may lead to insufficient regenerative activity to cover the surface.[21–23] Multipotent stem cells within the hair follicles generate cells that can multiply, migrate, and regenerate the surface epidermis.[24] The stem cell population that was first identified is slowly cycling, expresses the conventional stem cell surface marker CD34, and resides in the bulge region of the follicle near the attachment of the arrector pili muscle.[25,26] More recently, additional stem cell populations have been identified that reside in the isthmus region and the hair germ region of the follicle and express distinct markers.[27–29] Much is being learned about the function of these stem cells by studying knockout and overexpressing mice. The changes in follicular stem cells during healing of burn wounds, however, remain to be described.

One new aspect of hair follicle biology that is of great interest for burn surgeons is the delineation of the role of the dermal papilla, the tiny cluster of mesenchymal cells within the hair bulb.[30] Fetal development of hair follicles depends on interaction between epithelial cells of the epidermis and mesenchymal cells. The mesenchymal cells of the dermal papilla, which can be amplified in culture using keratinocyte-conditioned medium, can induce formation of hair follicles from interfollicular skin. Formation of new hair follicles, complete with hair, has been induced in hairless nipple skin of the mouse and in the renal capsule.[31,32] Since one of the major problems in long-term care of burn patients is alopecia, the possibility that hair follicles could be induced to regenerate is very appealing.[33]

THIRD-DEGREE OR FULL-THICKNESS INJURY

In full-thickness burns, thermal injury extends deep enough to destroy all of the hair follicles that have the capacity to regenerate the epidermis and some of the upper subcutaneous tissue may also become necrotic. In this case regeneration of the epidermis from hair follicles is not possible, and the wound can develop an epidermal covering only slowly as the epidermis lateral to the wound spreads out over the entire wound surface.[2] During this time, the necrotic tissue in the wound bed is at risk of infection, and extensive activity of tissue macrophages is required to eventually remove it.

Biology of Wound Healing

CHANGES IN VASCULAR PERMEABILITY

In order to review current understanding of the processes important in wound healing, each will be considered separately. Changes in local blood vessels are the earliest component of the wound's response to injury and are essential for the succeeding steps. Plasma exudation is due to increased permeability of venules to proteins, largely due to local release of histamine and vascular endothelial growth factor (VEGF) from mast cells and substance P from local sensory nerve endings. With burn injury, there is an added component of plasma leakage that occurs for several hours throughout the body in response to unknown stimuli. Of course, both plasma and red blood cells enter the wound through broken or necrotic blood vessels. Infection triggers further plasma exudation by constantly stimulating and prolonging the vascular phase of acute inflammation. Additionally the newly formed capillaries of granulation tissue allow passage of plasma proteins and fluid until they mature. Certain plasma proteins, notably fibronectin and vitronectin, are important in stimulating reparative responses in the wound.

GRANULATION TISSUE AND THE PROLIFERATIVE PHASE OF WOUND HEALING

Massive proliferation of fibroblasts and vascular endothelial cells is characteristic of the early phase of wound healing. These cells, and the fine fibrils of collagen and the gel provided by mucopolysaccharides and proteoglycans, make up the granulation tissue that is a major feature of all wounds that remain open. The most important of many peptides that stimulate fibroblast growth appear to be transforming growth factor-β (TGF-β) and basic fibroblast growth factor (bFGF/FGF2), whereas the most important peptide that stimulates growth of endothelial cells appears to be VEGF.[34–39] In order for wound contraction to occur, fibroblasts form networks within the dermis that allow the wound to contract. Interactions between the extracellular matrix and the cellular cytoskeleton are important in controlling cellular differentiation and function.[40–42] When

wound healing is abnormal and hypertrophic scars (HTS) develop, this process of interlinking fibroblasts to form a meshwork that supports tension parallel to the surface is disrupted since nodules of collagen result that do not flatten out normally.

INFLUX OF CIRCULATING CELLS

Many circulating cells actively migrate into wound beds and play roles in defense against bacteria and fungi, clearance of devitalized tissue components, and stimulation of later phases of healing of the dermis and epidermis. Based on experiments with partially selective ablation of individual cell types, the cells most important in stimulating and maintaining tissue repair appear to be the T lymphocytes and monocytes.[43] Monocytes, which differentiate into tissue macrophages, are responsible for synthesis and release of many of the cytokines important in wound healing, as are connective tissue cells and epithelial cells. Mast cell abundance increases in the healing wound, and mediators secreted by the mast cells recruit neutrophils and other circulating inflammatory cells to the wound. At the same time, mast cells induce an inflammatory response in the healing tissue by acting on keratinocytes. In addition, circulating stem cells enter healing wounds, where they can differentiate to form fibroblasts and other connective tissue cells needed to restore tissue integrity.[44,45]

MIGRATION OF KERATINOCYTES TO COVER THE WOUND (EPIBOLY)

When the epidermis is transected, changes take place rapidly in the basal cells of the epidermis adjacent to the wound. The process of epidermal regeneration has been well studied by Stenn and his colleagues.[16,46,47] Altered basal keratinocytes send out thin sheets and undergo ameboid motion not over the wound bed, but under the nonviable eschar and/or scab, secreting a provisional matrix as they go.[48,49] Development of this migratory phenotype is stimulated by the plasma protein vitronectin and requires the presence of albumin as a cofactor.[16,47,50] Cell division occurs to support this migration, not among migratory cells, but among their precursors in the residual epidermis. Similar processes stimulate migration and replacement of epithelial cells from hair follicles in partial-thickness wounds. After a sheet of epithelial cells is established over the entire wound surface, they begin to divide and eventually create a multilayered stratified squamous epithelium with a granular layer and keratinization. Epidermal cells secrete substantial quantities of IL-1β and other cytokines.[51,52] The new proliferative epidermal basal cells also secrete a new basal lamina composed of laminin, type IV collagen, and bullous pemphigoid antigen; adhere tightly to that basal lamina; and develop attachments of type VII collagen between the basal lamina and the underlying fibers of type I collagen in the scarred dermis. Also, just after the newly formed epithelial layer completely covers the wound, the phenotype of the connective tissue cells in the matrix undergoes a series of changes and much less fibronectin is found in the wound matrix.[17] As noted earlier, in second-degree burns, epidermal cells from the hair follicles regenerate the epidermis on the surface.

COLLAGEN MATRIX FORMATION AND MATURATION

Scars gradually increase in their strength, as measured by their resistance to tearing, but never reach the strength of normal dermis. During this process, the delicate fibers of newly secreted collagens I and III are replaced by large collagen I fibers that are oriented parallel to each other and to the skin surface (Figs. 46.1 and 46.2). Maturation of collagen fibers is largely a chemical process of remodeling that involves covalent crosslinking of adjacent polypeptide chains. Collagen fibers normally form and are degraded continuously in normal skin and in scars, but the processes that control the rates of formation and degradation and the orientation of the mature fibers are not fully understood. Prolonged activation of the keratinocytes in the wounds leads to reduced regulation of fibroblast collagen production by the keratinocytes and prolonged inflammation, both of which contribute to fibrosis. At the same time, mast cells act to induce fibrosis through the release of histamine, tryptase, and chymase, which stimulate collagen production, procollagen synthesis, and procollagen cleavage, respectively.

CYTOKINES AND GROWTH FACTORS

Many short polypeptides, mostly cytokines and growth factors, are responsible for the changes in cells that lead to the stages of wound healing, including the transition from the inflammatory to the proliferative phases, and the formation and organization of a scar, or the maturation phase. Among the most important are TGF-β, bFGF, platelet-derived growth factor (PDGF), and VEGF.[53–60] Frequently the response of a particular cell type to a specific mediator depends not only on binding to the precise cell surface receptor, but also on simultaneous signals from other cellular receptors. Thus the network of peptide signaling is complex, and the range of possible cellular responses is large enough to allow generation of complex structures and considerable fine-tuning.[56,61] There are many opportunities for reparative processes to go wrong, to proceed in an unbalanced fashion, or to fail to complete an appropriate cycle of activation and regression.[62–64]

BIOPHYSICS OF THERMAL INJURY

Human skin cells die when their temperature is increased, largely because of the sensitivity of the cell surface membrane to disruption outside fairly narrow temperature limits. Flame, electrical, and contact burns often lead to pyrolysis and disruption and oxidation of some tissues as well. Among the various cell types present in the skin, some are likely to be more sensitive to temperature than others. The degree of temperature elevation at a given site in the skin also depends on the rate of heat transfer within the tissue. The thermal conductivity of the dermis is much greater than that of the subcutis since fat is a good insulator. Perhaps for this reason thermal injury often leads to necrosis of the entire dermis with little cell death in the subcutis, as seen in wound biopsies. Hair follicles in some sites typically extend well beyond the dermis into the adipose tissue of the upper subcutis, and eccrine sweat glands are also often present in the subcutaneous fat. Despite the

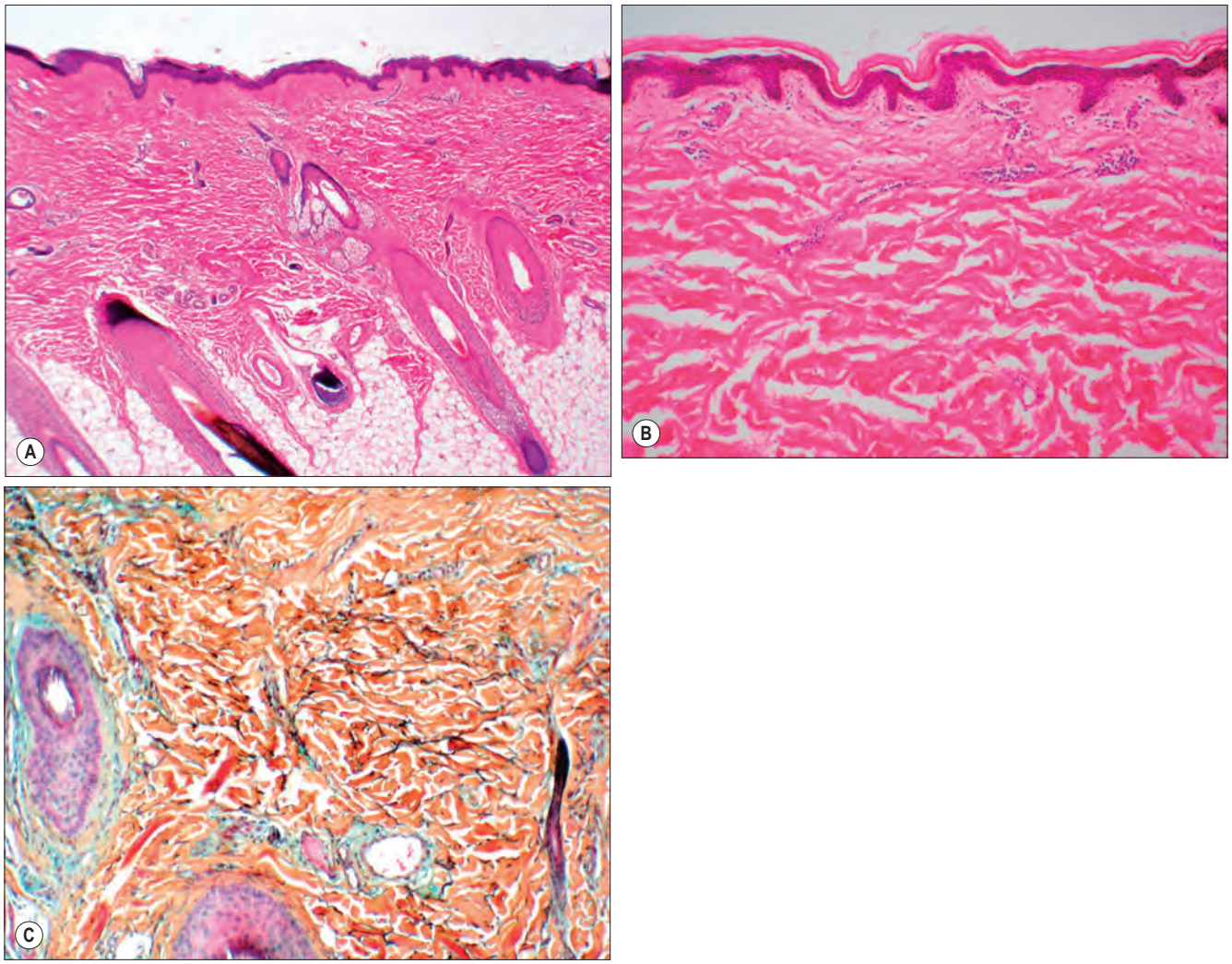

Fig. 46.1 Photomicrographs of normal skin, stained with hematoxylin and eosin. (A) The hair follicles often extend through the dermis into the subcutaneous adipose tissue. The epidermis forms irregular rete ridges at its base. (B) The reticular dermis of normal skin has an orderly arrangement of collagen fibers with no preferred orientation. (C) With the Movat pentachrome stain, normal collagen fibers stain yellow-orange, and delicate interconnecting black elastin fibers are present between collagen fibers.

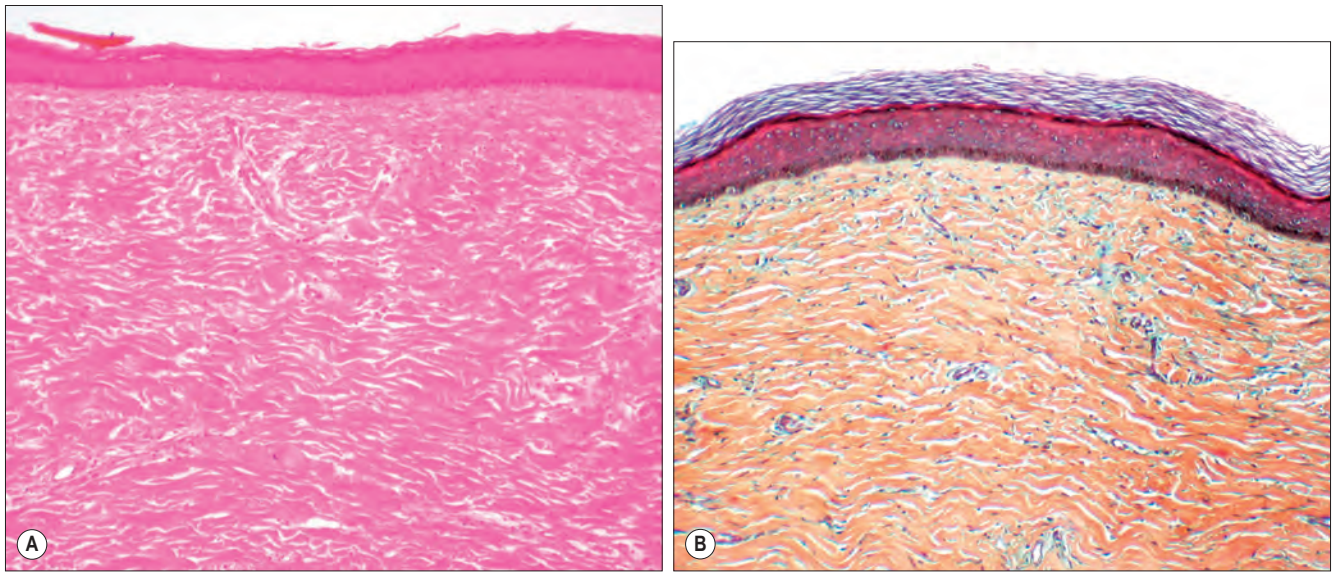

Fig. 46.2 (A) In a normal flat scar, the epidermis is flat and does not have any rete ridges and the dermis is replaced by collagen fibers that are oriented parallel to the skin surface. (B) A Movat pentachrome stain of a normal scar shows mature collagen fibers stained yellow-orange and does not demonstrate any elastin fibers.

presence of adipose tissue around follicles, regenerative capacity is frequently entirely destroyed by burns even though there is little or no apparent necrosis in the upper subcutis. In the most severe burns, however, the entire subcutis may become necrotic, and cell death may occur in the underlying fascia and skeletal muscle or even in underlying internal organs.

Factors That Alter Wound Healing

CHANGES IN BLOOD SUPPLY AND PERFUSION

The study of local blood supply by ultrasound led to the discovery that there is usually a zone of greatly increased blood flow below a burn wound, which is not surprising as part of a local inflammatory response to tissue injury. Above this zone of hyperemia is a zone of tissue ischemia, in which blood flow is less than normal. Remarkably, during the first 24 hours after a burn wound, the zone of ischemia typically becomes significantly deeper, indicating that ischemic injury of dermal tissues actually leads to a depth of tissue necrosis greater than that produced by the immediate thermal injury.[65] Experiments in animals have shown that neutrophils are involved in this progressive ischemic cell death in injured but viable tissue deep to a burn wound.[66] Altered blood flow may lead to vascular thrombosis in a burn wound, also contributing to the risk of ischemic tissue injury. In normal skin, there is a plexus of arteries and veins immediately below the dermis in the upper layer of subcutaneous adipose tissue. This subdermal plexus is at risk of thrombosis in deep partial-thickness burns and in full-thickness burns, and it is vulnerable to damage in the process of tangential wound excision, with further loss of blood supply to the wound.

COMPROMISED WOUND HEALING: REQUIREMENTS FOR OPTIMAL WOUND HEALING

Long clinical experience has demonstrated clearly that wound healing is greatly slowed and impaired when there is deficiency of essential ingredients for construction of the scar or of an adequate energy supply. Vitamin C deficiency and protein-calorie malnutrition are characterized by deficient wound healing, and provision of sufficient calories and reversal of the usual protein catabolism are major goals of general burn care. Vitamin D deficiency can impair wound healing, whereas vitamin D addition increases migration of fibroblasts and collagen production. Diabetic vasculopathy is associated with deficient wound healing, demonstrating the importance of an adequate microcirculation. Heart failure similarly compromises wound healing. Radiation, cigarette smoking, and hypoxemia also have been associated with delayed wound healing.[67] Advanced age is associated with increased mortality from large burns but does not in itself prevent good wound healing.[19,68]

BIOLOGIC RESPONSES TO WOUND EXCISION AND GRAFTING

The current standard of treatment in our institution is early excision of the burn wound, normally within 24 hours of admission, with removal of all necrotic tissue using either tangential excision to leave most of the subcutaneous fat or fascial excision which removes the entire subcutis. The wound is initially covered with meshed cadaver skin from the skin bank. Within a few days autografting is done using meshed partial-thickness grafts from unburned regions. Over the face and the hands, unmeshed sheet autografts are often used to obtain the best cosmetic result. The epidermis of the cadaveric homograft slowly degenerates, but the dermal matrix often is incorporated into the healing wound. The interstices of the autograft fill with granulation tissue derived partly from the underlying fibrous or adipose tissue and partly by migration of fibroblasts from the strands of autograft. The autograft's epidermis migrates over the granulation tissue matrix, under the fibrin layer, and reconstitutes the epidermis without any follicles or other epidermal appendages. The pattern of the meshed grafts is usually visible in the healed wound. The incorporation of dermal connective tissue elements from the donor site may enhance the pliability of the final scar. Occasionally epidermal inclusion cysts develop within grafted burn wounds, and they may rupture. These cysts could develop from residual hair roots that had lost their connection to the surface, from aberrant migration of epidermal cells during wound resurfacing, or from trapping of epidermis by expanding connective tissue. In addition, tiny bits of hair shaft are sometimes encountered in healing wounds, associated with a giant cell foreign body reaction, perhaps representing hairs left behind after necrosis of the hair follicles that originally produced them.

WOUND INFECTION

Bacterial infection frequently complicates wound healing. The risk is increased in burn patients since large amounts of necrotic cells and tissue are present in the wound and provide a good culture medium for bacteria. When infection occurs, the inflammatory component of wound healing is greatly amplified and the processes of conversion of granulation tissue to a dense scaffolding of collagen, wound contraction, and regeneration of the epidermis are all delayed. Frequently the wound suppurates. Some bacteria cause additional tissue necrosis, and some bacteria can invade into normal tissues, leading to hyperemia around the original wound and/or enlargement and deepening of the original wound. In response to the bacterial infection and the enhanced inflammatory reaction, the cytokine milieu of the wound is altered.[69–71] Grafts placed over wounds with residual infected tissue typically do not take, and when large numbers of bacteria are present deep in the wound bed there is always the hazard that the bacteria may enter the bloodstream, incite septicemia, and invade remote tissues. These processes, which were common in the era before antibiotics and before the practice of early wound excision became common, are now being seen again due to infection with highly antibiotic-resistant strains of bacteria, particularly *Pseudomonas* and *Acinetobacter*.

Hypertrophic Wound Healing

In most patients with large burns treated in our institution, healing of the burn wounds is complicated by development

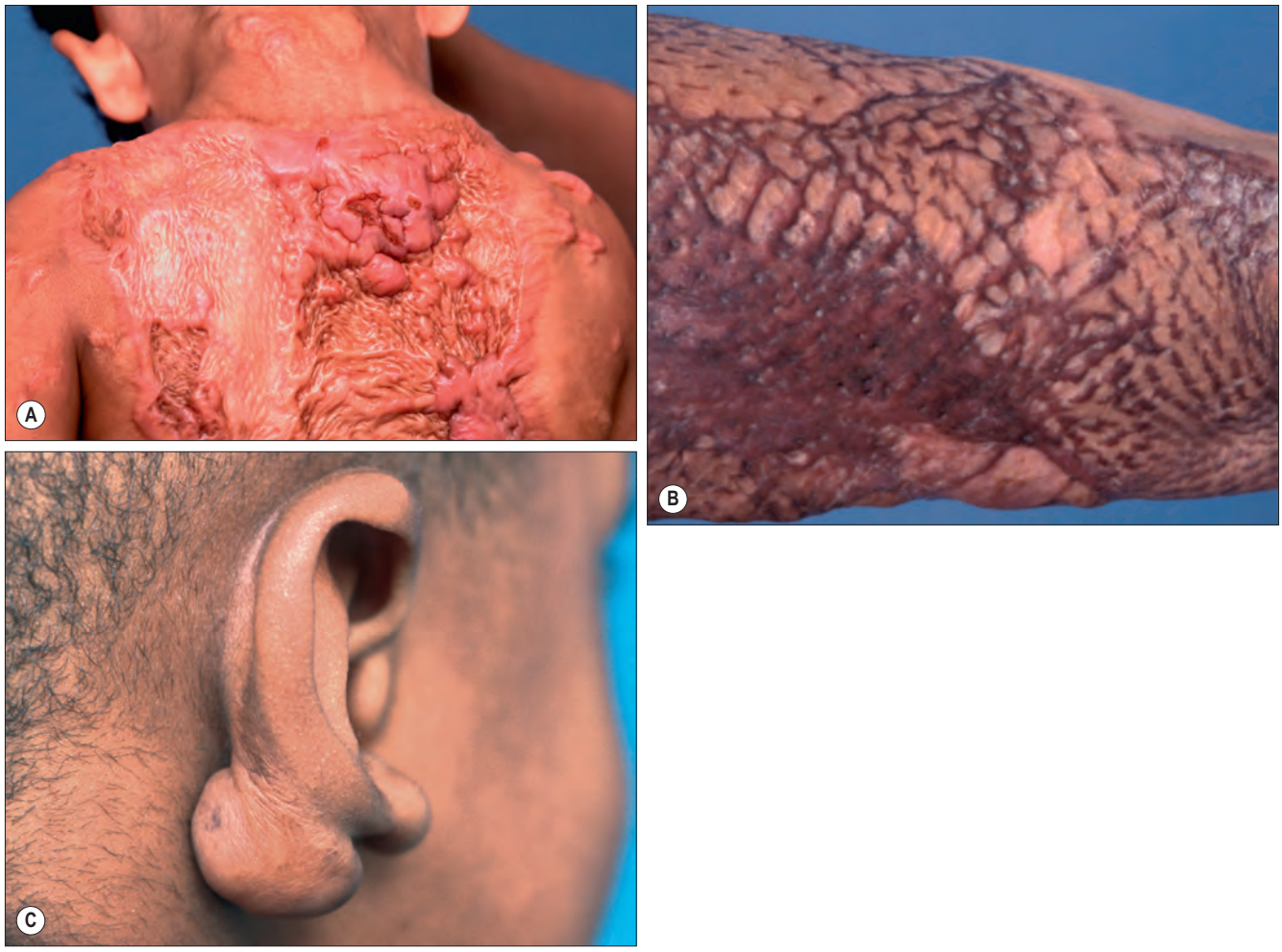

Fig. 46.3 Typical appearances of hypertrophic scars of burn patients. (A) The hypertrophic scar is raised above the surrounding normal skin, has sharp borders, and is very firm to the touch. This scar recurred after complete excision. (B) Hypertrophic scars often have patterns corresponding to meshed grafts and often are hyperpigmented, as shown here, or hypopigmented. (C) This round firm lesion developed from a minor burn on the patient's ear. It did not recur after excision.

of elevated, thick, firm, reddish scars that itch constantly. These hypertrophic cicatrices occur more commonly in wounds that had become infected or took longer than usual to become fully covered. They may cover large areas, but do not usually extend beyond the original burn wound. These abnormal wounds also are associated with more severe wound contraction. In the great majority of affected cases, these HTS enlarge for a period of months, then gradually regress over a period of a few years, eventually becoming flat scars with no further symptoms. In wounds that develop HTS, there are often abnormalities of skin pigmentation, either depigmentation or hyperpigmentation, that evolve over time (Fig. 46.3). The largest HTS impairing function are surgically excised, often with creation of Z-plasties or sheet grafting to release scar contractures or the use of lasers to ablate the scar. Generally new HTS do not develop again. There does not appear to be a link with ethnicity for this type of hypertrophic scarring, which occurs in about 75% of Caucasian, black, and Hispanic patients.[72]

Clearly this experience is quite different from that described in the literature with keloids, which frequently occur spontaneously or in response to puncture wounds or clean incisions that were closed primarily.[73–75] Keloids extend beyond the initial site of injury, respond poorly to medical therapy, persist for many years, and usually recur after surgical excision. There is often a positive family history of keloidal scarring, and keloids are 10–15 times more common in dark-skinned people of African ancestry than in northern Europeans and their descendants. Elaborate patterns of raised scars are a symbol of status in many African tribes, leading one to wonder whether this practice may have exerted selective pressure during human evolution.

HISTOLOGIC FEATURES OF HYPERTROPHIC SCARS

Numerous HTS have been examined histologically in our laboratory. The abnormal elevated scars consistently show several distinct differences from uncomplicated flat scars. The most striking is the presence of rounded whorls of immature collagen that consist of delicate collagen fibrils, mostly of type III collagen, small blood vessels, and plentiful acid mucopolysaccharide. These nodules are very sharply

demarcated from the surrounding scar tissue, which may be composed of similar material or may be composed of mature thick collagen fibers that are oriented parallel to each other and to the wound surface, typical of mature scars. Although the collagen fibers are clearly visible with routine H&E staining, they are most distinctly seen with the Movat stain, which stains mucopolysaccharides blue-green and mature collagen fibers yellow-orange. The nodules of HTS vary from 0.5 mm to more than 1 cm in diameter and can be spherical, ovoid, or cylindrical in shape. The abnormal dermal tissue is very firm and may reach a thickness of several centimeters. Both normal and HTS are characterized by lack of elastin, which is also visible using the Movat stain. However there are often residual elastin fibers in the deepest part of the dermis below zones of hypertrophic scarring, and sometimes there is a narrow zone of normal elastin fibers above the HTS, perhaps derived from the applied skin grafts. Occasionally small rounded nodules of HTS tissue are seen scattered between intact hair follicles. It is not unusual to see residual eccrine sweat glands in the adipose tissue beneath a large HTS, suggesting that these scars may originate in deep partial-thickness burns. These features are illustrated in Figs. 46.4 and 46.5. In addition, in a minority of HTS, an additional histologic feature is seen consisting of very broad, hypereosinophilic collagen fibers oriented parallel to each other but at varying angles with the skin surface. In some cases such broad, dense fibers dominate the wound. Generally they are surrounded by whorls of circularly oriented, immature collagen typical of HTS. These features are illustrated in Fig. 46.6. These are the features that have been described as typical of the histology of keloids. However, in our patient population, typical keloids are distinctly unusual, and there is no evidence to suggest that the patients with these thick, eosinophilic collagen fibers have a worse prognosis or a more delayed course of scar maturation than other patients with HTS. Thus, in our extensive experience with the histology of scars from large burns in children, the histologic features typical of keloids are seen as part of the spectrum of hypertrophic scarring.

The distinction between HTS and keloids was first made by Mancini and Quaife in 1962.[76–79] The features typical of HTS were further described by Linares, Kischer, and others.[80–83] The literature on HTS and keloids was thoroughly reviewed by Niessen[84] and Huang.[118]

Because the etiology and pathogenesis of HTS are different from that of keloids, we limit our discussion to HTS.

A number of differences distinguish between normal scars and HTS. HTS contain more type III collagen, fibronectin, and hyaluronic acid, all characteristic of the early phases of wound repair, than do normal flat scars. HTS are more vascular with higher cutaneous blood flow. HTS contain significantly more T cells and macrophages than normal scars. Larger numbers of mast cells have been found in HTS, and indeed a clinical history of atopy and higher levels of circulating IgE have been found in patients with HTS. Recently much larger numbers of epidermal Langerhans cells have been identified in association with HTS.[85,86]

Immunohistochemical staining has demonstrated additional striking differences between HTS and normal scars. Staining for α-smooth-muscle actin has consistently demonstrated this contractile protein within spindle cells in the characteristic collagen nodules of HTS. The sulfated proteoglycans of HTS are quite different from those of normal scars in that much less decorin is present, and versican is predominant in the rounded nodules. More VEGF immunostaining is seen in HTS. Larger numbers of small nerve fibers have been identified by immunostaining in HTS. These consistent findings may be providing important clues to the pathogenesis of hypertrophic scarring, but, at this time, they are difficult to incorporate into a single hypothesis. Although the lack of a suitable animal model and the scarcity of human tissue, in addition to the confusion surrounding the proper identification of hypertrophic scarring, have hampered research in this field, in recent years the study of the biology of HTS has been enabled by the

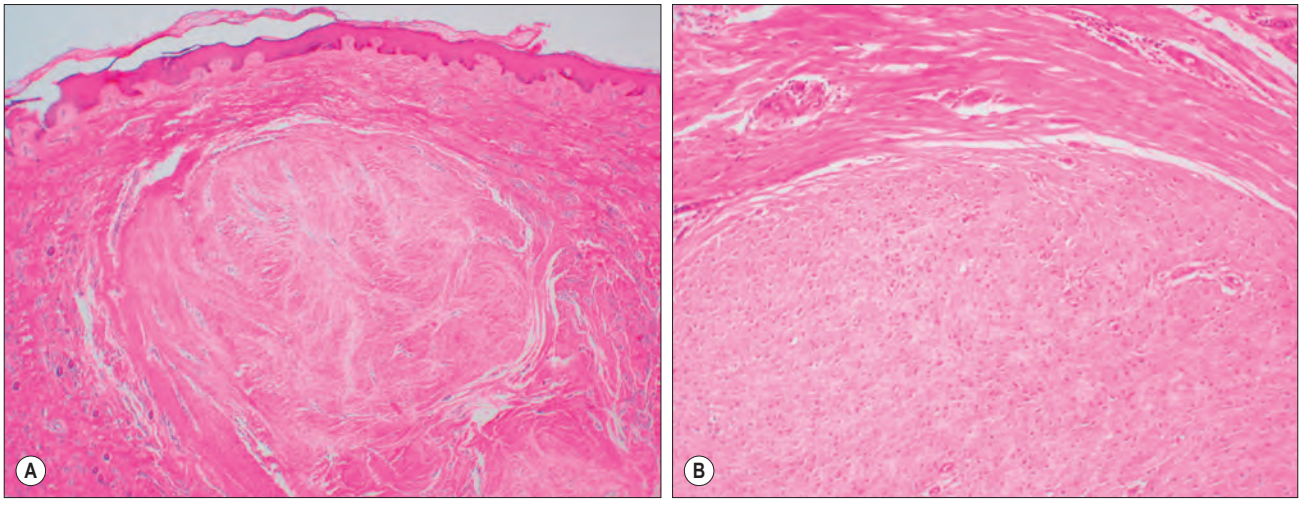

Fig. 46.4 Photomicrographs of hypertrophic scars. (A) Within the dermis there is a rounded nodule of collagen that has a sharp border and is distinct from the surrounding scar tissue. (B) The border of a collagenous nodule in a hypertrophic scar. In the surrounding scar tissue, collagen fibers are oriented parallel to the skin surface. Within the nodule, collagen fibers are very thin and are oriented circumferentially.

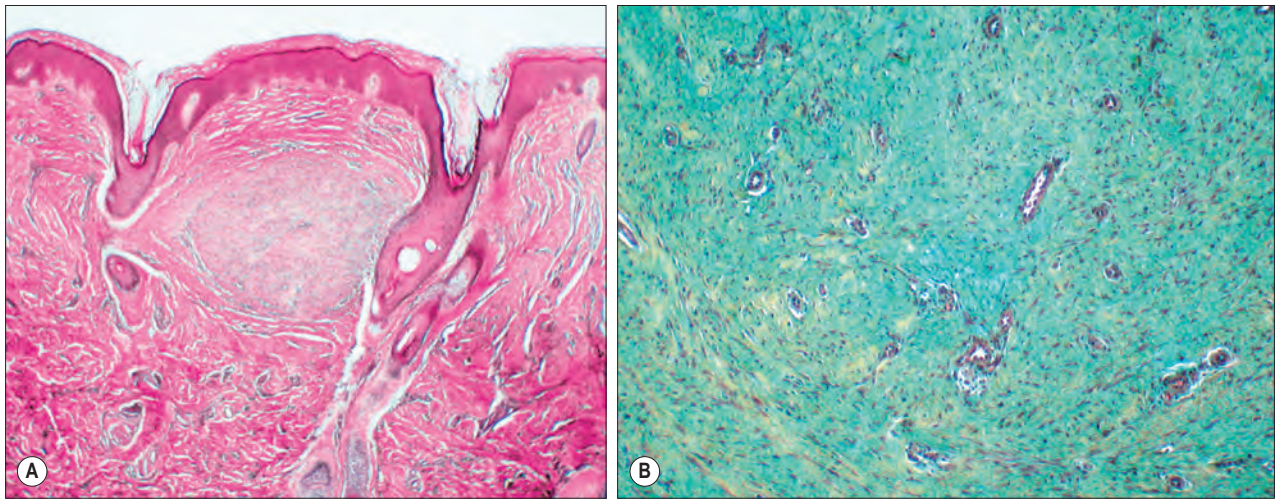

Fig. 46.5 (A) This Movat-stained slide shows a minimal hypertrophic scar consisting of a single round nodule between hair follicles. The nodule stains light green, in contrast to the yellow-orange color of the surrounding mature collagen fibers. The greenish color reflects a larger quantity of sulfated proteoglycans within the collagen nodule. (B) At higher magnification, numerous small blood vessels can be seen within a large, green-staining nodule from a hypertrophic scar.

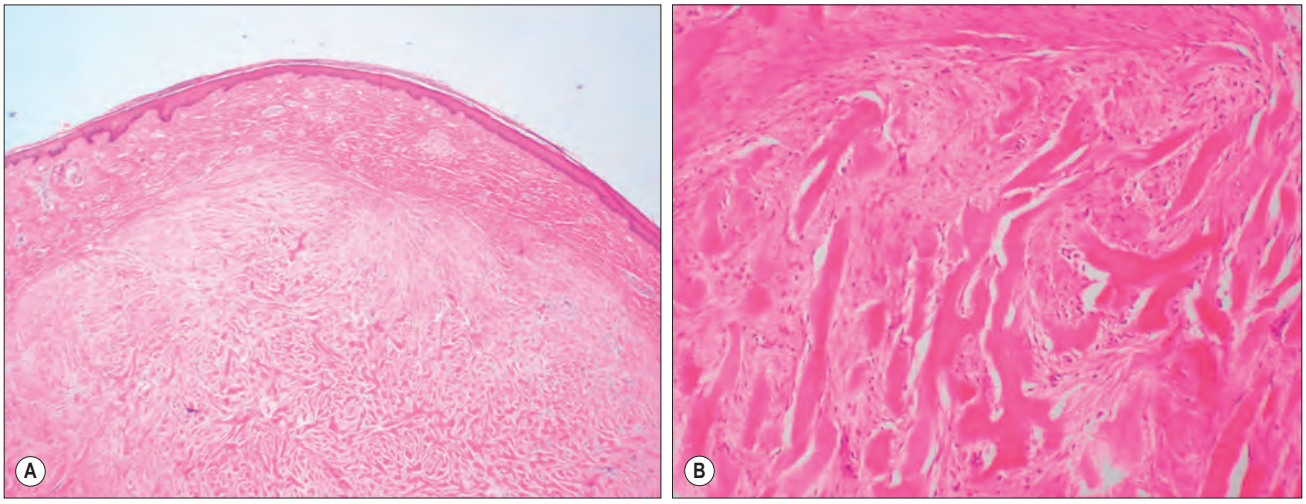

Fig. 46.6 (A) Some otherwise typical dermal nodules in hypertrophic scars contain very broad, hypereosinophilic collagen fibers similar to those typical of keloids. This specimen is from the patient shown in Fig. 46.3C. (B) The typical appearance of the thick, dense collagen fibers that stain intensely with eosin can be seen at higher magnification.

development of new experimental models. Adoption of cell culture models, culture of whole-tissue biopsies, use of immune-deficient mice, and establishment of hypertrophic scarring in the red Duroc pig have yielded important information on biologic processes underlying human hypertrophic scarring.

EXPERIMENTAL MODELS OF HYPERTROPHIC HEALING

The first animal model of keloids was described in 1959, based on immunization of experimental animals with autologous skin, followed by induction of wounds.[87] Extensive work has been done in which normal and abnormal human scar tissue have been implanted into the athymic nude mouse, which allows testing of potential therapies and modification of the biological milieu in vivo.[88–91] In this model, it is even possible to irradiate the mouse and transplant human bone marrow to study interactions between immune reactions involving human cells and the human skin grafts. Engrav and his colleagues developed a model in the female red Duroc pig that mimics many of the features of human hypertrophic scarring.[92–100] Recent studies by their group and others have elucidated molecular mechanisms underlying HTS development as well as the effects of antiscarring therapies at the molecular level.

PHENOTYPIC ABNORMALITIES OF HYPERTROPHIC SCAR FIBROBLASTS

There have been many studies of the functions and molecular biology of fibroblasts derived from HTS and keloids in tissue culture. It does appear from these studies that there is a significantly different phenotype of fibroblasts from HTS that persists in culture. HTS fibroblasts have been found consistently to secrete more TGF-β and collagen more rapidly than fibroblasts derived from normal skin or normal scars.[101] Furthermore the depth of residence of the fibroblast also determines the fibrotic phenotype, with deep dermal fibroblasts characterized by increased collagen secretion with reduced collagenase expression, slower proliferation, and an increase in α-smooth muscle actin expression when compared to superficial fibroblasts. Genomic analysis has been done in several laboratories on HTS fibroblasts, with identification of numerous differences in gene expression. In a genomic study from our institution, cultured fibroblasts from HTS showed a reduced response to IL-6 as compared to fibroblasts from adjacent normal skin, suggesting that decreased receptor activation might be a factor in hypertrophic scarring.[102]

GENE EXPRESSION IN HYPERTROPHIC SCARS

Studies of gene expression and regulatory pathways in HTS tissue have begun to provide much better understanding of both normal and hypertrophic wound healing. Initial studies of HTS gene expression using transcriptome analysis showed consistent differences in the expression of multiple collagen isoforms, growth factors, and metalloproteinases.[103] Similar studies demonstrated the similarities between human and porcine hypertrophic scarring.[104] In several experimental studies in animals, interventions have been applied that alter wound expression of important genes or signaling pathways, with substantial change in size of the resulting wound.[105–110] Studies in human patients have shown that variation in a gene's sequence can be associated with decreased severity of postburn hypertrophic scarring; although the role of CUB and Sushi multiple domains 1 (CSMD1) in hypertrophic scarring is not yet known, a potential modification of the TGF-β signaling pathway has been proposed. Although more research is needed, such studies promise possible therapeutic intervention in the processes that lead to hypertrophic scarring.

INTERPLAY OF SYSTEMIC AND LOCAL INFLAMMATORY RESPONSES

Both local and systemic cytokine expression impact the development of hypertrophic scarring. In burned children who do not develop HTS, active and total TGF-β1 levels in plasma increased during the first 2 weeks following the burn injury before dropping to levels below those found in nonburned patients. In burned children who later developed HTS, however, active and total TGF-β1 levels in plasma were diminished from the day of burn until at least 180 days later.[111] Augmented levels of systemic TGFβ1 have been correlated with increased circulating fibrocytes.[112] Although elevated systemic levels of TGF-β1 may be beneficial following a burn injury, prolonged expression locally within the burn wound may lead to hypertrophic scarring with increased fibrosis, downregulation of decorin, upregulation of versican, increased neovascularization, and decreased collagenase[113] The type of inflammatory response, in addition to the magnitude and location of the inflammation, play a role in hypertrophic scarring. Characterization of $CD4^+$ T-helper cells revealed that, following a burn, polarization of lymphocyte populations leads to a shift from a T_H1/antifibrotic phenotype to a T_H2/profibrotic response.[114] Decreased systemic expression of interferon-γ (IFN-γ) and IL-4 and increased IL-4-producing lymphocytes persist for a year following a burn injury.

PATHOGENIC CONCEPTS

Understanding of the biology of hypertrophic scarring has been hampered by multiple factors, including problems in gaining consensus on the definition of the lesion, the underuse of a suitable animal model, and the consequent inability to test hypotheses by altering the course of the disease. Multiple concepts of pathogenesis have been proposed, with some gaining wide acceptance while others have yet to be experimentally excluded. It does seem clear that development of an HTS represents an abnormality in regulation of the normal processes of wound healing, which may occur early, as Linares and Larson suggested.[72] Failure of the normal processes limiting collagen secretion and matrix formation is apparent in HTS. One might suppose that the normal processes by which tensions in the matrix signal cellular responses have become defective in HTS.[40,42] The roles of the mast cell and other inflammatory cells in scar development have become better defined; use of the mast cell stabilizers ketotifen and sodium cromoglycate demonstrates decreased fibrosis and wound contraction with inhibition of mast cell activity, indicating new targets for antiscarring therapies. Myofibroblasts are more prominent in immature and active HTS than in normal or mature scars and are thought to play a role in excessive wound contraction. Dermal fibroblasts within the HTS differentiate into myofibroblasts. The fibrous nodules of HTS might represent persistence and uncontrolled growth of a separate population of connective tissue cells perhaps related to the perifollicular cells that normally express versican. The formation of these nodules may represent abnormal epithelial–mesenchymal interactions; epidermal cells, such as Langerhans cells, and increased IL-4 with decreased IL-1α expression have been shown to influence dermal remodeling resulting in hypertrophic scarring. Since burn patients have higher circulating levels of glucocorticoids and IL-6 than do nonburned individuals, selection of cells resistant to the usual effects of these agents may occur following burn injury, leaving fibroblasts that are able to withstand the normal suppressive action on fibroblast proliferation. Metabolic differences, such as higher adenosine triphosphate (ATP) concentrations and greater oxygen consumption apparent within the hypertrophic scarring, may be the emphasis on metabolic differences. Finally, abnormal macromolecular expression by the covering epithelium may lead to abnormal development of the dermal scar or fail to suppress inappropriate fibroblast functions.[117] Clearly it continues to be important to develop and test many hypotheses until the problem of hypertrophic scarring is finally solved.

Conclusion

Healing of burn wounds requires activation of several host processes, including fibrin clotting and lysis, deposition of an immature connective tissue matrix and its reorganization into a mature scar, and epithelial outgrowth and interaction between the epidermis and the dermal matrix. In many burn patients, excessive scar tissue forms, with adverse consequences. Continued study of this problem will continue to be important until more effective modes of treatment are developed.

Complete references available online at http://www.expertconsult.inkling.com

Further Reading

Clark RA. Basics of cutaneous wound repair. *J Dermatol Surg Oncol*. 1993;19:693-706.

Ingber DE. Mechanical control of tissue growth: function follows form. *Proc Natl Acad Sci USA*. 2005;102:11571-11572.

Finnerty CC, Jeschke MG, Branski LK, et al. Hypertrophic scarring: the greatest unmet challenge following burn injury. *Lancet*. 2016; 388(10052):1427-1436.

Tran KT, Griffith L, Wells A. Extracellular matrix signaling through growth factor receptors during wound healing. *Wound Repair Regen*. 2004;12:262-268.

Zhu KQ, Engrav LH, Armendariz R, et al. Changes in VEGF and nitric oxide after deep dermal injury in the female, red Duroc pig – further similarities between female, Duroc scar and human hypertrophic scar. *Burns*. 2005;31:5-10.

Zhu Z, Ding J, Shankowsky HA, Tredget EE. The molecular mechanism of hypertrophic scar. *J Cell Commun Signal*. 2013;7:239-252.

References

1. Majno G. *The Healing Hand – Man and Wound in the Ancient World*. Cambridge: Harvard University Press; 1975.
2. Clark RA. Basics of cutaneous wound repair. *J Dermatol Surg Oncol*. 1993;19(8):693-706.
3. Ross R. Wound healing. *Sci Am*. 1969;220(6):40-50.
4. Ross R, Odland G. Human wound repair. II. Inflammatory cells, epithelial-mesenchymal interrelations, and fibrogenesis. *J Cell Biol*. 1968;39(1):152-168.
5. Sower LE, Froelich CJ, Carney DH, et al. Thrombin induces IL-6 production in fibroblasts and epithelial cells. Evidence for the involvement of the seven-transmembrane domain (STD) receptor for alpha-thrombin. *J Immunol*. 1995;155(2):895-901.
6. Ross R, Bowen-Pope DF, Raines EW. Platelet-derived growth factor: its potential roles in wound healing, atherosclerosis, neoplasia, and growth and development. *Ciba Found Symp*. 1985;116:98-112.
7. Naldini A, Pucci A, Carney DH, et al. Thrombin enhancement of interleukin-1 expression in mononuclear cells: involvement of proteinase-activated receptor-1. *Cytokine*. 2002;20(5):191-199.
8. Naldini A, Carney DH, Bocci V, et al. Thrombin enhances T cell proliferative responses and cytokine production. *Cell Immunol*. 1993; 147(2):367-377.
9. Carney DH, Mann R, Redin WR, et al. Enhancement of incisional wound healing and neovascularization in normal rats by thrombin and synthetic thrombin receptor-activating peptides. *J Clin Invest*. 1992;89(5):1469-1477.
10. Clark RA. Biology of dermal wound repair. *Dermatol Clin*. 1993; 11(4):647-666.
11. Clark RA. Fibrin and wound healing. *Ann N Y Acad Sci*. 2001; 936:355-367.
12. Grinnell F. Fibronectin and wound healing. *Am J Dermatopathol*. 1982;4:185-188.
13. Greiling D, Clark RA. Fibronectin provides a conduit for fibroblast transmigration from collagenous stroma into fibrin clot provisional matrix. *J Cell Sci*. 1997;110(Pt 7):861-870.
14. Swerlick RA, Brown EJ, Xu J, et al. Expression and modulation of the vitronectin receptor on human dermal microvascular endothelial cells. *J Invest Dermatol*. 1992;99(6):715-722.
15. Gabbiani G, Ryan GD, Majno G. Presence of modified fibroblasts in granulation tissue and their possible role in wound contraction. *Experientia*. 1971;27:549-553.
16. Stenn KS, Depalma L. Re-epithelialization. In: Clark RA, ed. *The Molecular and Cellular Biology of Wound Repair*. 2nd ed. New York: Plenum Press; 1996:321-335.
17. Clark RA. Fibronectin matrix deposition and fibronectin receptor expression in healing and normal skin. *J Invest Dermatol*. 1990;94(suppl 6):128S-134S.
18. Staiano-Coico L, Carano K, Allan VM, et al. PAI-1 gene expression is growth state-regulated in cultured human epidermal keratinocytes during progression to confluence and postwounding. *Exp Cell Res*. 1996;227(1):123-134.
19. Gamelli RL, He LK. Incisional wound healing. Model and analysis of wound breaking strength. *Methods Mol Med*. 2003;78:37-54.
20. Daly TJ. The repair phase of wound healing – re-epithelialization and contraction. In: Kloth LC, McCullough J, Feedar JA, eds. *Wound Healing*. Philadelphia: FA Davis; 1990:14-30.
21. Barret JP, Dziewulski P, Wolf SE, et al. Outcome of scalp donor sites in 450 consecutive pediatric burn patients. *Plast Reconstr Surg*. 1999;103(4):1139-1142.
22. Chang LY, Yang JY, Chuang SS, et al. Use of the scalp as a donor site for large burn wound coverage: review of 150 patients. *World J Surg*. 1998;22(3):296-299.
23. McCauley RL, Oliphant JR, Robson MC. Tissue expansion in the correction of burn alopecia: classification and methods of correction. *Ann Plast Surg*. 1990;25(2):103-115.
24. Levy V, Lindon C, Zheng Y, et al. Epidermal stem cells arise from the hair follicle after wounding. *FASEB J*. 2007;21(7):1358-1366.
25. Oshima H, Rochat A, Kedzia C, et al. Morphogenesis and renewal of hair follicles from adult multipotent stem cells. *Cell*. 2001;104(2):233-245.
26. Morris RJ, Liu Y, Marles L, et al. Capturing and profiling adult hair follicle stem cells. *Nat Biotechnol*. 2004;22(4):411-417.
27. Jensen UB, Yan X, Triel C, et al. A distinct population of clonogenic and multipotent murine follicular keratinocytes residing in the upper isthmus. *J Cell Sci*. 2008;121(Pt 5):609-617.
28. Blanpain C. Stem cells: skin regeneration and repair. *Nature*. 2010; 464(7289):686-687.
29. Jaks V, Kasper M, Toftgard R. The hair follicle: a stem cell zoo. *Exp Cell Res*. 2010;316(8):1422-1428.
30. Yang CC, Cotsarelis G. Review of hair follicle dermal cells. *J Dermatol Sci*. 2010;57(1):2-11.
31. Inamatsu M, Matsuzaki T, Iwanari H, et al. Establishment of rat dermal papilla cell lines that sustain the potency to induce hair follicles from afollicular skin. *J Invest Dermatol*. 1998;111(5): 767-775.
32. Mayer JA, Foley J, De La CD, et al. Conversion of the nipple to hair-bearing epithelia by lowering bone morphogenetic protein pathway activity at the dermal-epidermal interface. *Am J Pathol*. 2008;173(5):1339-1348.
33. Stenn K, Parimoo S, Zheng Y, et al. Bioengineering the hair follicle. *Organogenesis*. 2007;3(1):6-13.
34. Spindler KP, Murray MM, Detwiler KB, et al. The biomechanical response to doses of TGF-beta 2 in the healing rabbit medial collateral ligament. *J Orthop Res*. 2003;21(2):245-249.
35. Broadley KN, Aquino AM, Hicks B, et al. Growth factors bFGF and TGF beta accelerate the rate of wound repair in normal and in diabetic rats. *Int J Tissue React*. 1988;10(6):345-353.
36. Bennett NT, Schultz GS. Growth factors and wound healing: Part II. Role in normal and chronic wound healing. *Am J Surg*. 1993;166:74-81.
37. Broadley KN, Aquino AM, Woodward SC, et al. Monospecific antibodies implicate basic fibroblast growth factor in normal wound repair. *Lab Invest*. 1989;61(5):571-575.
38. Davidson JM, Broadley KN. Manipulation of the wound-healing process with basic fibroblast growth factor. *Ann N Y Acad Sci*. 1991; 638:306-315.
39. Falanga V. Growth factors and wound healing. *J Dermatol Surg Oncol*. 1993;19(8):711-714.
40. Ingber DE. Cellular tensegrity: defining new rules of biological design that govern the cytoskeleton. *J Cell Sci*. 1993;104:613-627.
41. Ingber DE. Mechanical control of tissue growth: function follows form. *Proc Natl Acad Sci USA*. 2005;102(33):11571-11572.
42. Huang S, Ingber DE. The structural and mechanical complexity of cell-growth control. *Nat Cell Biol*. 1999;1(5):E131-E138.
43. Barbul A, Breslin RJ, Woodyard JP, et al. The effect of in vivo T helper and T suppressor lymphocyte depletion on wound healing. *Ann Surg*. 1989;209(4):479-483.
44. Quan TE, Cowper S, Wu SP, et al. Circulating fibrocytes: collagen-secreting cells of the peripheral blood. *Int J Biochem Cell Biol*. 2004;36(4):598-606.
45. Mori L, Bellini A, Stacey MA, et al. Fibrocytes contribute to the myofibroblast population in wounded skin and originate from the bone marrow. *Exp Cell Res*. 2005;304(1):81-90.
46. Stenn KS. The role of serum in the epithelial outgrowth of mouse skin explants. *Br J Dermatol*. 1978;98(4):411-416.
47. Stenn KS. Epibolin: a protein of human plasma that supports epithelial cell movement. *Proc Natl Acad Sci USA*. 1981;78(11):6907-6911.
48. Kubo M, Van de WL, Plantefaber LC, et al. Fibrinogen and fibrin are anti-adhesive for keratinocytes: a mechanism for fibrin eschar slough during wound repair. *J Invest Dermatol*. 2001;117(6):1369-1381.
49. Stenn KS, Madri JA, Roll FJ. Migrating epidermis produces AB2 collagen and requires continued collagen synthesis for movement. *Nature*. 1979;277:229-232.
50. Stenn KS. Coepibolin, the activity of human serum that enhances the cell spreading properties of epibolin, associates with albumin. *J Invest Dermatol*. 1987;89(1):59-63.
51. Qwarnstrom EE, Jarvelainen HT, Kinsella MG, et al. Interleukin-1β regulation of fibroblast proteoglycan synthesis involves a decrease in versican steady state mRNA levels. *Biochem J*. 1993;294:613-620.
52. Niessen FB, Andriessen MP, Schalkwijk J, et al. Keratinocyte-derived growth factors play a role in the formation of hypertrophic scars. *J Pathol*. 2001;194(2):207-216.
53. Karr BP, Bubak PJ, Sprugel KH, et al. Platelet-derived growth factor and wound contraction in the rat. *J Surg Res*. 1995;59(6):739-742.
54. Savage K, Siebert E, Swann D. The effect of platelet-derived growth factor on cell division and glycosaminoglycan synthesis by human skin and scar fibroblasts. *J Invest Dermatol*. 1987;89(1):93-99.
55. Tredget EE. Pathophysiology and treatment of fibroproliferative disorders following thermal injury. *Ann N Y Acad Sci*. 1999;888:165-182.
56. Scott PG, Ghahary A, Tredget EE. Molecular and cellular aspects of fibrosis following thermal injury. *Hand Clin*. 2000;16(2):271-287.

57. Tran KT, Griffith L, Wells A. Extracellular matrix signaling through growth factor receptors during wound healing. *Wound Repair Regen*. 2004;12(3):262-268.
58. Younai S, Venters G, Vu S, et al. Role of growth factors in scar contraction: an in vitro analysis. *Ann Plast Surg*. 1996;36(5):495-501.
59. Tonnesen MG, Feng X, Clark RA. Angiogenesis in wound healing. *J Invest Dermatol Symp Proc*. 2000;5(1):40-46.
60. Grinnell F. Fibroblasts, myofibroblasts, and wound contraction. *J Cell Biol*. 1994;124(4):401-404.
61. Roberts AB. The ever-increasing complexity of TGF-beta signaling. *Cytokine Growth Factor Rev*. 2002;13(1):3-5.
62. Barrientos S, Stojadinovic O, Golinko MS, et al. Growth factors and cytokines in wound healing. *Wound Repair Regen*. 2008; 16(5):585-601.
63. Kondo T, Ishida Y. Molecular pathology of wound healing. *Forensic Sci Int*. 2010;203:93-98.
64. Kwan P, Hori K, Ding J, et al. Scar and contracture: biological principles. *Hand Clin*. 2009;25(4):511-528.
65. Burns JL, Mancoll JS, Phillips LG. Impairments to wound healing. *Clin Plast Surg*. 2003;30(1):47-56.
66. Mileski WJ, Borgstrom D, Lightfoot E, et al. Inhibition of leukocyte-endothelial adherence following thermal injury. *J Surg Res*. 1992;52:334-339.
67. Burns JL, Mancoll JS, Phillips LG. Impairments to wound healing. *Clin Plast Surg*. 2003;30(1):47-56.
68. Ono I. The effects of basic fibroblast growth factor (bFGF) on the breaking strength of acute incisional wounds. *J Dermatol Sci*. 2002;29(2):104-113.
69. Hunt TK, Hopf H, Hussain Z. Physiology of wound healing. *Adv Skin Wound Care*. 2000;13(suppl 2):6-11.
70. Thornton FJ, Schaffer MR, Barbul A. Wound healing in sepsis and trauma. *Shock*. 1997;8(6):391-401.
71. van den Boom R, Wilmink JM, O'Kane S, et al. Transforming growth factor-beta levels during second-intention healing are related to the different course of wound contraction in horses and ponies. *Wound Repair Regen*. 2002;10(3):188-194.
72. Linares HA, Larson DL. Early differential diagnosis between hypertrophic and nonhypertrophic healing. *J Invest Dermatol*. 1974; 62(5):514-516.
73. Burd A, Huang L. Hypertrophic response and keloid diathesis: two very different forms of scar. *Plast Reconstr Surg*. 2005;116(7): 150e-157e.
74. Ketchum LD, Cohen IK, Masters FW. Hypertrophic scars and keloids. A collective review. *Plast Reconstr Surg*. 1974;53(2):140-154.
75. Murray JC, Pollack SV, Pinnell SR. Keloids: a review. *J Am Acad Dermatol*. 1981;4(4):461-470.
76. Mancini RE, Quaife JV. Histogenesis of experimentally produced keloids. *J Invest Dermatol*. 1962;38:143-181.
77. Peacock EE Jr, Madden JW, Trier WC. Biologic basis for the treatment of keloids and hypertrophic scars. *South Med J*. 1970;63(7): 755-760.
78. Blackburn WR, Cosman B. Histologic basis of keloid and hypertrophic scar differentiation. *Arch Pathol*. 1966;82:65-71.
79. Ehrlich HP, Desmouliere A, Diegelmann RF, et al. Morphological and immunochemical differences between keloid and hypertrophic scar. *Am J Pathol*. 1994;145(1):105-113.
80. Linares HA, Kischer CW, Dobrkovsky M, et al. On the origin of the hypertrophic scar. *J Trauma*. 1973;13(1):70-75.
81. Linares HA, Kischer CW, Dobrkovsky M, et al. The histiotypic organization of the hypertrophic scar in humans. *J Invest Dermatol*. 1972;59(4):323-331.
82. Kischer CW. Collagen and dermal patterns in the hypertrophic scar. *Anat Rec*. 1974;179(1):137-145.
83. Kischer CW, Shetlar MR, Chvapil M. Hypertrophic scars and keloids: a review and new concept concerning their origin. *Scan Electron Microsc*. 1982;(Pt 4):1699-1713.
84. Niessen FB, Spauwen PH, Schalkwijk J, et al. On the nature of hypertrophic scars and keloids: a review. *Plast Reconstr Surg*. 1999;104(5):1435-1458.
85. Niessen FB, Schalkwijk J, Vos H, et al. Hypertrophic scar formation is associated with an increased number of epidermal Langerhans cells. *J Pathol*. 2004;202(1):121-129.
86. Cracco C, Stella M, Teich AS, et al. Comparative study of Langerhans cells in normal and pathological human scars. II. Hypertrophic scars. *Eur J Histochem*. 1992;36(1):53-65.
87. Chytilova M, Kulhankek V, Horn V. Experimental production of keloids after immunization with autologous skin. *Acta Chir Plast*. 1959;1:72-79.
88. Shetlar MR, Shetlar CL, Hendricks L, et al. The use of athymic nude mice for the study of human keloids. *Proc Soc Exp Biol Med*. 1985;179(4):549-552.
89. Kischer CW, Sheridan D, Pindur J. Use of nude (athymic) mice for the study of hypertrophic scars and keloids: vascular continuity between mouse and implants. *Anat Rec*. 1989;225(3):189-196.
90. Kischer CW, Pindur J, Shetlar MR, et al. Implants of hypertrophic scars and keloids into the nude (athymic) mouse: viability and morphology. *J Trauma*. 1989;29(5):672-677.
91. Barbul A, Shawe T, Rotter SM, et al. Wound healing in nude mice: a study on the regulatory role of lymphocytes in fibroplasia. *Surgery*. 1989;105(6):764-769.
92. Zhu KQ, Engrav LH, Armendariz R, et al. Changes in VEGF and nitric oxide after deep dermal injury in the female, red Duroc pig—further similarities between female, Duroc scar and human hypertrophic scar. *Burns*. 2005;31(1):5-10.
93. Zhu KQ, Engrav LH, Tamura RN, et al. Further similarities between cutaneous scarring in the female, red Duroc pig and human hypertrophic scarring. *Burns*. 2004;30(6):518-530.
94. Liang Z, Engrav LH, Muangman P, et al. Nerve quantification in female red Duroc pig (FRDP) scar compared to human hypertrophic scar. *Burns*. 2004;30(1):57-64.
95. Zhu KQ, Engrav LH, Gibran NS, et al. The female, red Duroc pig as an animal model of hypertrophic scarring and the potential role of the cones of skin. *Burns*. 2003;29(7):649-664.
96. de Hemptinne I, Gallant-Behm CL, et al. Dermal fibroblasts from red Duroc and Yorkshire pigs exhibit intrinsic differences in the contraction of collagen gels. *Wound Repair Regen*. 2008;16(1): 132-142.
97. Xie Y, Zhu KQ, Deubner H, et al. The microvasculature in cutaneous wound healing in the female red Duroc pig is similar to that in human hypertrophic scars and different from that in the female Yorkshire pig. *J Burn Care Res*. 2007;28(3):500-506.
98. Harunari N, Zhu KQ, Armendariz RT, et al. Histology of the thick scar on the female, red Duroc pig: final similarities to human hypertrophic scar. *Burns*. 2006;32(6):669-677.
99. Zhu KQ, Carrougher GJ, Gibran NS, et al. Review of the female Duroc/Yorkshire pig model of human fibroproliferative scarring. *Wound Repair Regen*. 2007;15(suppl 1):S32-S39.
100. Gallant-Behm CL, Olson ME, Hart DA. Cytokine and growth factor mRNA expression patterns associated with the hypercontracted, hyperpigmented healing phenotype of red Duroc pigs: a model of abnormal human scar development? *J Cutan Med Surg*. 2005;9(4):165-177.
101. Xue H, McCauley RL, Zhang W, et al. Altered interleukin-6 expression in fibroblasts from hypertrophic burn scars. *J Burn Care Rehabil*. 2000;21(2):142-146.
102. Dasu MR, Hawkins HK, Barrow RE, et al. Gene expression profiles from hypertrophic scar fibroblasts before and after IL-6 stimulation. *J Pathol*. 2004;202(4):476-485.
103. Tsou R, Cole JK, Nathens AB, et al. Analysis of hypertrophic and normal scar gene expression with cDNA microarrays. *J Burn Care Rehabil*. 2000;21(6):541-550.
104. Zhu KQ, Carrougher GJ, Couture OP, et al. Expression of collagen genes in the cones of skin in the Duroc/Yorkshire porcine model of fibroproliferative scarring. *J Burn Care Res*. 2008;29(5):815-827.
105. Sisco M, Kryger ZB, O'Shaughnessy KD, et al. Antisense inhibition of connective tissue growth factor (CTGF/CCN2) mRNA limits hypertrophic scarring without affecting wound healing in vivo. *Wound Repair Regen*. 2008;16(5):661-673.
106. Song B, Zhang W, Guo S, et al. Adenovirus-mediated METH1 gene expression inhibits hypertrophic scarring in a rabbit ear model. *Wound Repair Regen*. 2009;17(4):559-568.
107. Tan J, Peng X, Luo G, et al. Investigating the role of P311 in the hypertrophic scar. *PLoS ONE*. 2010;5(4):e9995.
108. Reid RR, Roy N, Mogford JE, et al. Reduction of hypertrophic scar via retroviral delivery of a dominant negative TGF-beta receptor II. *J Plast Reconstr Aesthet Surg*. 2007;60(1):64-72.
109. Dabiri G, Tumbarello DA, Turner CE, et al. TGF-beta1 slows the growth of pathogenic myofibroblasts through a mechanism requiring the focal adhesion protein, Hic-5. *J Invest Dermatol*. 2008; 128(2):280-291.

110. Hakkinen L, Koivisto L, Gardner H, et al. Increased expression of beta6-integrin in skin leads to spontaneous development of chronic wounds. *Am J Pathol*. 2004;164(1):229-242.
111. Rorison P, Thomlinson A, Hassan Z, et al. Longitudinal changes in plasma transforming growth factor beta-1 and post-burn scarring in children. *Burns*. 2010;36(1):89-96.
112. Yang L, Scott PG, Giuffre J, et al. Peripheral blood fibrocytes from burn patients: identification and quantification of fibrocytes in adherent cells cultured from peripheral blood mononuclear cells. *Lab Invest*. 2002;82(9):1183-1192.
113. Ladak A, Tredget EE. Pathophysiology and management of the burn scar. *Clin Plast Surg*. 2009;36(4):661-674.
114. Tredget EE, Yang L, Delehanty M, et al. Polarized Th2 cytokine production in patients with hypertrophic scar following thermal injury. *J Interferon Cytokine Res*. 2006;26(3):179-189.
115. Reference deleted at revises.
116. Reference deleted at revises.
117. Andriessen MP, Niessen FB, Van de Kerkhof PC, et al. Hypertrophic scarring is associated with epidermal abnormalities: an immunohistochemical study. *J Pathol*. 1998;186(2):192-200.
118. Huang C, Murphy GF, Akaishi S, et al. Keloids and hypertrophic scars: update and future directions. *Plast Reconstr Surg Glob Open*. 2013;1:e25.

47 Burn Rehabilitation Along the Continuum of Care

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Introduction

The physical rehabilitation of patients who have sustained a burn injury is a serious undertaking and requires, among other disciplines, the involvement of physical therapy, occupational therapy, and exercise physiology in order to produce the best functional and cosmetic outcomes. Recent advances in medicine have significantly contributed to increased patient survival rates, and this necessitates faster, more comprehensive, and prolonged burn rehabilitation. With severe burn injuries, as perhaps with any other order of trauma, there is an urgent need for immediate and aggressive initiation of patient-specific rehabilitation programs. The distribution and depth of the burn injury clearly predict the patterns of deformity and joint contractures and mandate the establishment of therapeutic goals and the initiation of treatment as soon as possible. As stated previously, the more extensive the burn injury, the greater the rehabilitation challenge becomes. A seriously burned extremity in an otherwise modestly burned patient is much easier to restore to function than an extremity similarly burned in a patient with full-thickness burns involving multiple anatomical surfaces. In the case of seriously burned patients, the immediate and primary focus will always be preservation of life and wound coverage. Today, burn rehabilitation specialists intervene early on in the patient recovery process through the development and implementation of rehabilitation programs intended to maximize the potential of functional and cosmetic patient recovery.

The primary short-term rehabilitation goal is to preserve the patient's range of motion (ROM) and functional ability. Long-term rehabilitation goals include returning patients to independent living and teaching patients to compensate for any permanent functional loss suffered as a result of the burn injury while contributing toward acceptable cosmetic outcomes.

This chapter addresses the evaluation, positioning, splinting/orthotics, serial casting, prosthetics, scar management, exercise, performance of activities of daily living (ADL), and patient and caregiver education utilized in burn rehabilitation along the continuum of care.

Evaluation of the Burn Patient

Upon admission to the burn center, patients undergo a comprehensive evaluation by burn rehabilitation therapists (physical and/or occupational therapists) in order to assess their medical status and formulate a plan of care. It is crucial that therapists document the findings of their evaluation in the patient's medical record because these findings will serve as the baseline upon which progress will be determined. A good burn evaluation should include (1) the history of how the accident occurred; (2) an interview with the patient's caregiver to gather information regarding the patient's preinjury functional status and activity level; (3) documentation of the etiology, classification, and total body surface area (TBSA) of the burn injury; (4) documentation of associated injuries such as fractures, smoke inhalation injury, and exposed tendons and bone; (5) measurement of edema, ROM, strength, and sensation if appropriate; (6) assessment of ADL performance; (7) need for positioning of affected areas, including splinting; (8) development of short- and long-term treatment goals; and (9) development and documentation of a treatment plan. The patient's status should be reassessed on a regular basis and after each surgical procedure to update the plan of care as needed. Therapists should communicate the results of their evaluation and the treatment plan to the burn team and to the patients and their families.

Positioning and Splinting of the Burn Patient

In a study of burn survivor perceptions about rehabilitation, positioning and splinting routines were viewed positively and identified as useful in order to improve movement.[1] Positioning of the burned patient is fundamental to bringing about the best functional outcomes in burn rehabilitation.[2–4] Positioning programs should begin immediately upon admission to the burn center and continue throughout the rehabilitative process. The role of the burn rehabilitation therapist is invaluable in designing a patient-centered positioning program, one that reduces edema, enables wound care, facilitates joint alignment, minimizes the risk of peripheral neuropathy,[2,3] and counteracts all contractile forces without compromising function. In planning and implementing an effective patient-specific positioning program, the therapist should be aware of the patient's TBSA of burns, the depth of all injuries, respiratory status, and associated injuries such as exposed tendons/joints or fractures. Individualized positioning programs are monitored closely for any necessary adjustments depending on the patient's medical status. The quote that "the position of comfort is the position of deformity" applies to every burned patient who has sustained a serious injury. The risk

of deformity after burn injury is real, and burn scar contractures should be anticipated and dealt with proactively.[5,6]

Anti-deformity positioning can be achieved through multiple means: splinting, mechanical traction, cut-out foam troughs and mattresses, pillows, strapping mechanisms, serial casting, and, in some cases, through surgical application of pins. The burn therapist needs to be aware of physician-specific protocols and work closely with the entire burn team to design the most effective positioning program. Orthotics and splinting devices are vital in burn rehabilitation because they are utilized extensively to obtain appropriate positioning of the entire body and to counteract the contractile forces of scarring that lead to deformity. The application of positioning strategies is used to influence soft-tissue lengths to limit the loss of ROM due to scar formation and contraction.[2,3] No matter how the burn therapist approaches splinting (material choice, design, and application schedules), the goal is to achieve the best functional outcome at the completion of rehabilitation. When fabricating a splint or an orthosis, the burn therapist must be aware of the anatomy and kinesiology of the body surface to be splinted. Also, the therapist should be well aware of all mechanical principles of splinting as they relate to pressure, mechanical advantage, torque, rotational forces, first-class levers, friction, reciprocal parallel forces, and material strength.[7]

The general outcomes for the use of splints in a burn rehabilitation setting have been identified as protection of vulnerable structures, preservation of ROM, suppression of scar, and correction of soft-tissue contractures.[8] The goals for positioning and splinting will vary with the phase of burn rehabilitation. In the acute phase, the goal is edema control and pressure relief; in the intermediate phase, the aim is tissue elongation and graft protection; and, for long-term rehabilitation, the target is tissue elongation.[9] Positioning and splinting must be designed in a way to:

- Allow for edema reduction
- Maintain joint alignment
- Support, protect, and immobilize joints
- Maintain and/or increase ROM
- Maintain tissue elongation
- Remodel joint and tendon adhesions
- Promote wound healing
- Relieve pressure points
- Protect newly operated sites (grafts/flaps)
- Stabilize and/or position one or more joints, enabling other joints to function correctly
- Assist weak muscles to counteract the effects of gravity and assist in functional activity
- Strengthen weak muscles by exercising against springs or rubber bands.[7]

Devices should:

- Not cause pain
- Be designed with function in mind
- Be cosmetically appealing
- Be easy to apply and remove
- Be lightweight and low-profile
- Be constructed out of appropriate materials
- Allow for ventilation to prevent skin/wound maceration.[7]

Typical burn care positioning protocols describe the supine position in great detail. More emphasis is now being placed on the use of side-lying and prone positioning for patients with large burns who must be immobilized for extended periods due to newer grafting techniques that cover larger areas with fragile skin substitutes. When designing positioning programs, the joint angles are aligned in neutral postures and the supporting surfaces are modified to maximize the surface area to body contact while protecting bony prominences from compression.

Side-lying may be used on a rotating basis for patients at risk for sacral or scapular skin breakdown. In a preventive program, the rotation is right side to supine to left side. The order is then reversed on a 1- to 2-hour schedule. Full side-lying at 90 degrees from supine should not be allowed for any significant length of time due to excessive pressure over the greater trochanter. A more appropriate position for side-lying is approximately 30–40 degrees from the supine position, which distributes pressure more evenly between the head of the femur and the lateral portion of the sacrum.

The mechanics of a side-lying position can be accomplished using pillows or wedges made of foam or wood. The advantage of foam or wooden wedges is that they can be placed directly under the mattress with less manipulation of the patient. As the rotation schedule is completed, the wedge can either be removed for the supine position or transferred to the opposite side of the mattress to achieve side-lying on the opposite surface.

Prone positioning strategies are usually the position of last resort (Fig. 47.1) and are reserved for patients who are not successfully managed in supine or side-lying. For example, there may be nonhealing grafts or wounds in the rectal region that increase the risk of sepsis due to the introduction of fecal matter. Other candidates for this protocol include those with sacral pressure ulcers or posterior trunk grafts that are not healing.

The clinician faces a host of issues that must be considered when instituting a prone positioning program. The airway is always the first issue that must be considered when designing a prone position mattress. The supporting surface is cut from a solid open-cell foam mattress that is

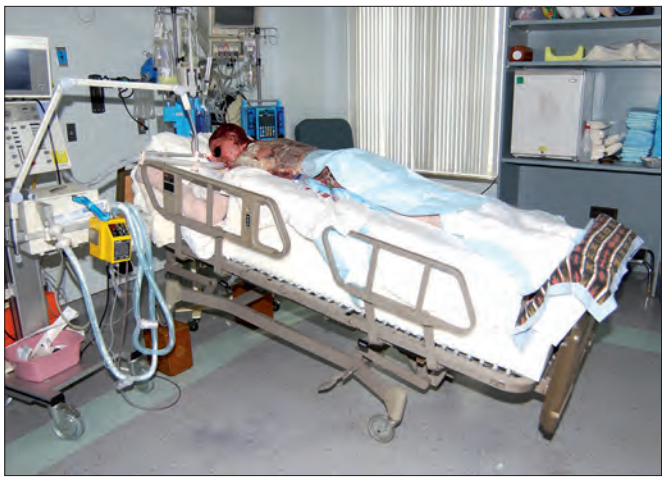

Fig. 47.1 Patients may be positioned prone to protect posterior grafts from shearing.

placed on a wire mesh bed frame. Airway concerns are addressed first, and the patient is evaluated for mode of respiration. Nasal and tracheal intubation are issues to consider, but these are not contraindications for the prone position. A trough should be provided so that direct access can be obtained for routine airway care and if breaths are needed using an Ambu-bag. If the airway becomes compromised, the prone position should be abandoned immediately until proper respiration is established.

The facial opening should be cut in a manner that maximizes weight distribution without allowing the head to enter into the opening. Using this protocol places direct weight-bearing pressure on the brow ridge, zygomatic arches, and the anterior mandible. These structures should be monitored closely, and the patient should be educated that breakdown is likely to occur due to the limited subcutaneous tissue protecting the face. If burn scars are encroaching on the eyelids, then the corneas should be evaluated as well. Corneal abrasion can be avoided with due diligence and prevention of the foam from contacting the unprotected eye. Countersinking a gel cushion into the upper portion of the foam mattress can protect the forehead and brow ridge.

The sternum, pelvic region, and patellae are protected with the use of an air-cell mattress that is inserted into the mattress in a lengthwise manner. The air-cell segments are typically supplied in standard lengths and may not reach from the sternum to the ankles. If there is an unsupported area between the distal portion of the mattress and the dorsum of the foot, then the area can be supported with open-cell egg-crate-type foam. The feet are supported at the distal end of the mattress with a foam footboard. Extra precautions should be taken to evaluate the elevation of the great toe from the supporting bed frame.

In the prone position, all traditional joint alignment suggestions are maintained with the possible exception of the elbows. Shoulder mobility dictates the style of prone mattress that can be made for the individual burn patient. If the patient has greater than 115 degrees of abduction, then the mattress is modified to horizontally adduct and externally rotate the shoulder while flexing the elbow to allow for elevation of the hands. This minimizes edema in the hands and allows for greater function once the prone position is no longer needed. If the shoulders have limited abduction, then a "butterfly" cut is used to allow for horizontal adduction of the shoulder to protect the brachial plexus, with the hands remaining slightly dependent. This will result in some hand edema, which can be addressed with pressure wrapping (Coban glove) and active exercise.

HEAD

Acutely, in aiding with facial edema reduction, the head should be positioned by placing it in midline and elevating the head of the bed at 30–45 degrees if the patient's hips are not involved. In cases where the hips are burned, the entire bed may be elevated at the head with the use of shock blocks (wooden blocks, 12–16 inches, with recessed slots for bed legs) or the use of the reverse Trendelenburg position. These methods avoid positioning the hips in the flexed position that promotes contracture formation and deformity if persistent (Fig. 47.2).

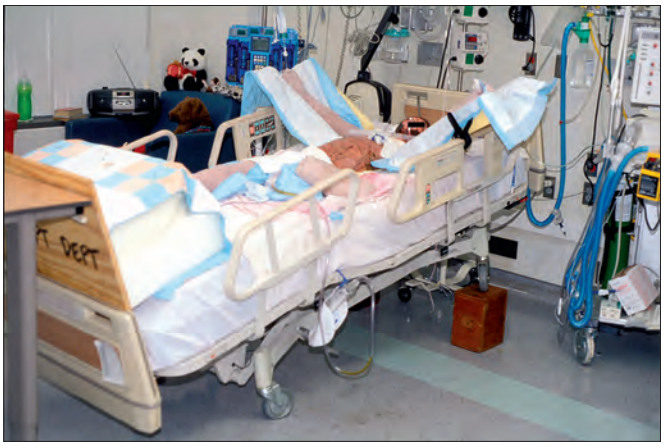

Fig. 47.2 Wooden blocks are utilized to place the bed on an incline to help with edema reduction and prevent hip contractures.

In those cases where the ears are burned, they may be protected by strapping ear cups made of thermoplastic materials or foam.[10] An ear conformer may be constructed to prevent the rim of the ear from contracting toward the head. Internal ear canal splints may also be fabricated and serially adjusted as the circumference of the canal increases. In addition, if the ear is affected, a soft circular foam can be positioned posteriorly to the head to elevate the ears off the surface of the bed. A nasal obturator may be required to maintain the nostrils open. These obturators may be serially adjusted as the circumference of the nostril increases. Mouth splints are utilized for the prevention of oral microstomia. These devices are custom-made by the therapist, or they may be obtained commercially. Mouth splints may be fabricated static or dynamic for horizontal or vertical opening of the mouth.[11–15] In cases of severe microstomia, where compliance is an issue, an orthodontic commissure appliance that attaches to the teeth may be fabricated by an orthodontist.[16] The use of stacked tongue blades is an acceptable technique to aid in reversing oral microstomia. Ongoing research looks at the development of a microstomia device that circumferentially opens the mouth according to its anatomy (Fig. 47.3). In the post-acute phase, facial scar hypertrophy may require fabricating a high thermoplastic transparent mask, such as the Uvex and W-clear masks, or a silicone elastomer facemask.[17–19] A semi-rigid low thermoplastic opaque mask may also be fabricated depending on the state of scar maturation.

NECK

The neck is positioned in neutral or in slight extension of approximately 15 degrees without any rotation. The amount of neck extension must not be so great that traction on the chin causes the mouth to open. Positioning may be achieved with a short mattress supine, a rolled towel, or foam cushion placed behind the upper back on the scapular line. Pillows should be avoided in the cases of anterior neck burns because they may lead to flexion contractures. In the case of anterior neck burns, a conforming custom thermoplastic collar may be fabricated (Fig. 47.4).[20] For burns along the lateral surface of the neck and some long-term

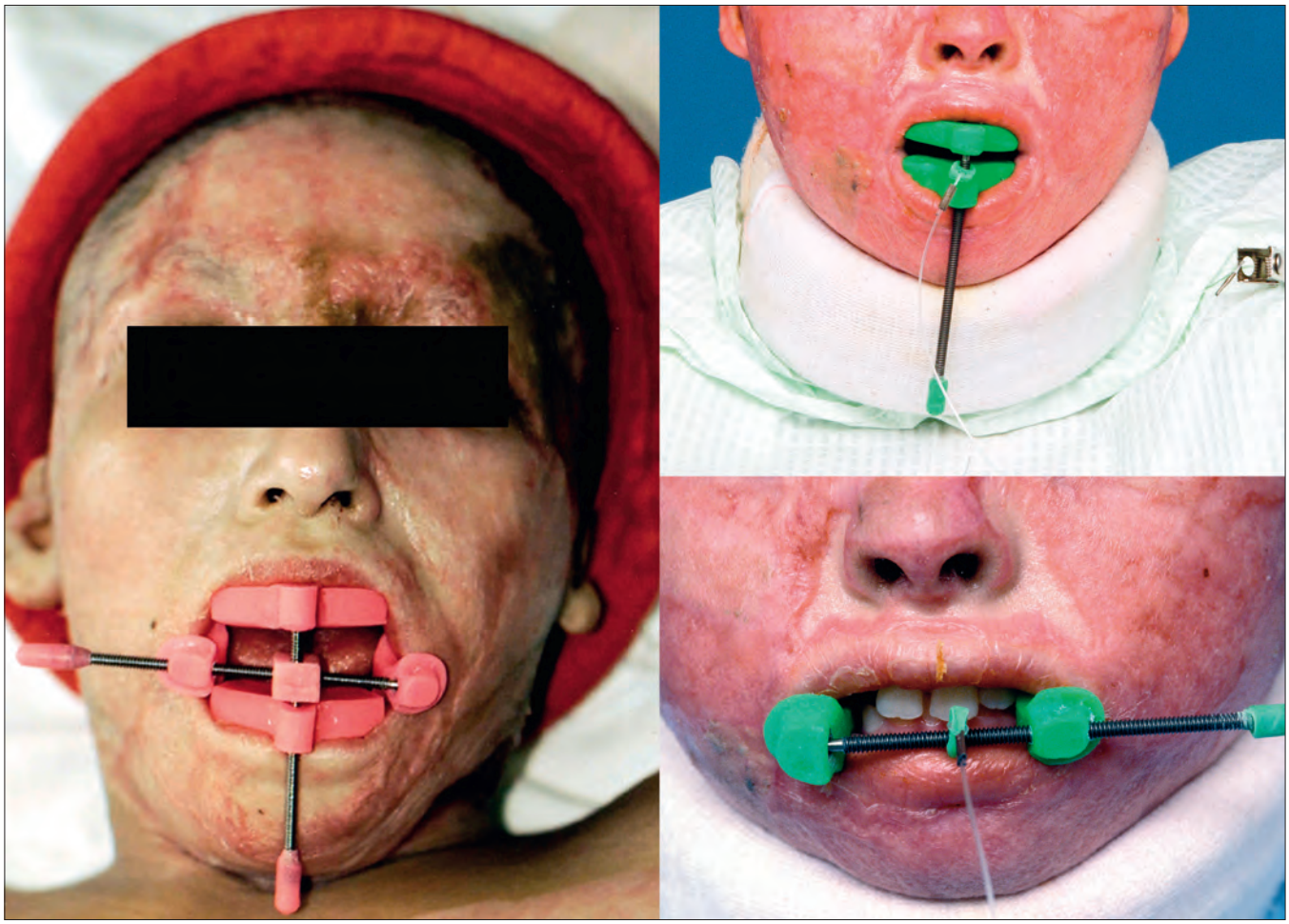

Fig. 47.3 Horizontal, vertical, and circumferential mouth-opening devices are utilized to correct oral microstomia.

Fig. 47.4 An anterior neck conformer helps prevent neck flexion contractures.

needs, a soft neck collar or a Watusi-type collar may also be fabricated as the patient's wounds heal and contractures or scars develop. The Watusi-type collar allows for isolated, direct pressure to a thicker scar band.[19,21,22] It has been observed that, in some cases, acute patients rotate or laterally flex their neck on one side, which may lead to a lateral neck contracture (torticollis). If the patient is to remain in bed for a while, a dynamic head strap mechanism may be fabricated to counteract the lateral neck contractile forces and bring the neck into the neutral position. For the prevention of torticollis, the therapist may fabricate a lateral neck splint that conforms to the patient's head, the lateral neck, and anterior/posterior shoulder (Fig. 47.5).

SPINE

Contracture resulting from unilateral or asymmetric burns of the neck, axilla, trunk, and groin will cause lateral curvature of the spine (scoliosis). The level and amplitude of curvature will vary with the site and severity of the contracture. In addition, pelvic obliquity accompanying asymmetric hip or knee flexion contracture will impose a lateral lumbar curve. As long as the patient is recumbent, lateral curvature can be prevented by maintaining straight

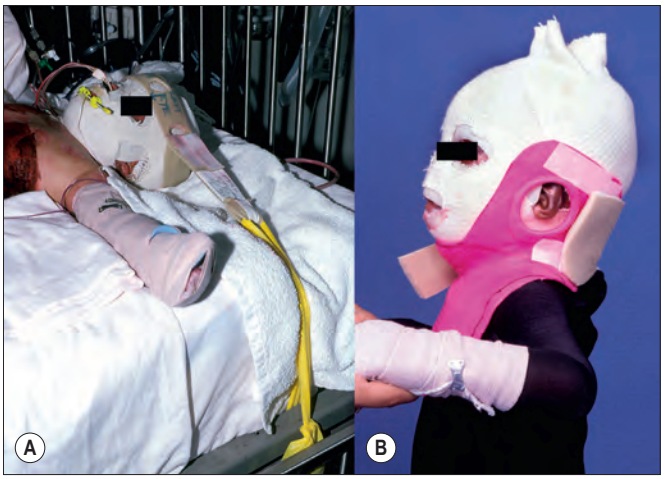

Fig. 47.5 **(A)** A dynamic head strap mechanism aids in positioning the neck in a neutral position during a prolonged ICU bed confinement. **(B)** A lateral neck splint is utilized to prevent lateral neck flexion contractures (torticollis).

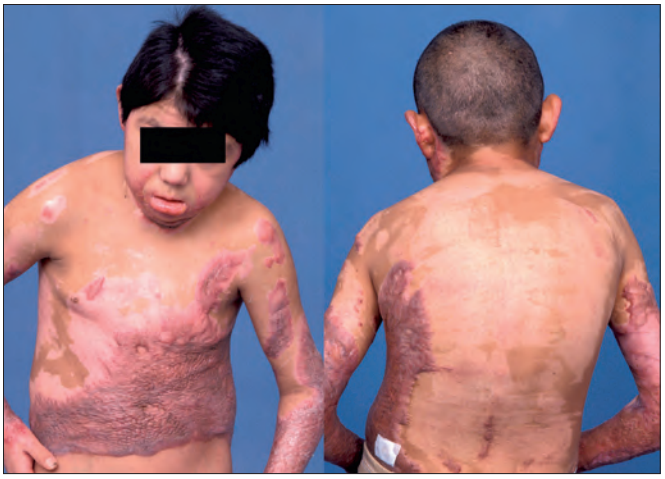

Fig. 47.6 Scoliosis resulting from a left chest, abdomen, and left lateral trunk injury.

alignment of the trunk and neck (Fig. 47.6). However, the curve is often insidious in onset and will not be recognized until the patient begins to walk. Trunk list observed early in the ambulation period can be simply a transient accommodation to pain and wound tightness, but a persistent list may herald the development of scoliosis. Other subtle signs of spinal curvature are asymmetry of shoulder levels, scapular asymmetry, asymmetry of dependent upper extremity alignment to the trunk, and asymmetry of pelvic rim levels. A spinal mobilization exercise program is established with the patient once a curvature is identified; however, once there is an established asymmetric contracture it is difficult by therapeutic means to stretch it out, so it is probably better to deal surgically with a deforming scar early than to permit even minor scoliosis to persist.

SHOULDER GIRDLE/AXILLA

Acutely the upper extremity positioning program focuses on reducing edema through elevation. Failure to reduce

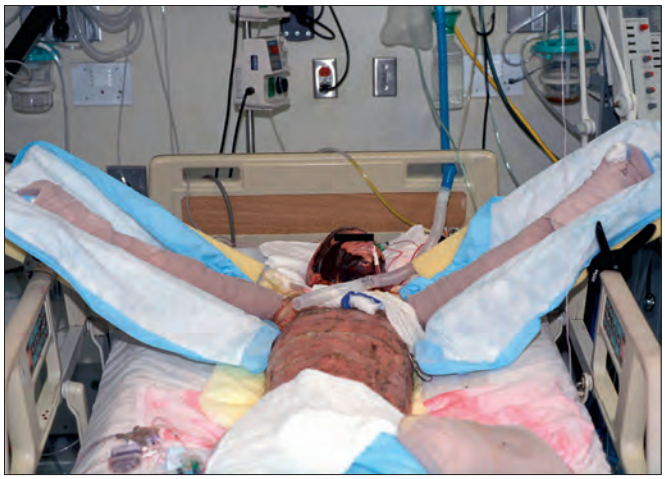

Fig. 47.7 Foam arm troughs are utilized for positioning the shoulders in bed.

edema in the first 48–72 hours can promote the development of a fixed deformity. Additionally, improper elevation techniques for the upper extremity may lead to soft-tissue calcification, increased bone density, and compressive neuropathies. The recommended position for the burned shoulder and axillary complex is 90 degrees abduction, 15–20 degrees horizontal adduction, and external rotation toward maximal. Abduction alone places the glenohumeral joint at risk for anterior subluxation, if the position is maintained for an extended period. Placement in horizontal adduction anatomically reduces the potential for tractioning of the brachial plexus or peripheral nerve compression. The glenohumeral joint is externally rotated in order to counteract anticipated deformities of internal rotation and adduction and to maintain balance of the soft tissues of the shoulder complex.

Positioning of the shoulder may be achieved with splints, silicone-filled pillows, bedside tables, foam arm troughs, metal abduction troughs, and thermoplastic slings suspended from a trapeze mechanism (Fig. 47.7).[23] Splinting of the shoulder joint becomes more intensive as scar maturation heightens the risk of contracture development. Airplane splints have been used for the resolution of axillary contractures and postoperatively to protect reconstructive procedures.[24–26] Upon closer inspection of the literature, a randomized controlled trial of adults with shoulder burn involvement compared splinting to no splinting with regard to functional outcomes and determined that shoulder splints did not improve clinical outcomes in the study population and that low adherence rates suggest splinting may be unacceptable to patients.[27] However, more recently, a pilot study of a newly designed multiaxis shoulder abduction splint concluded that the device resulted in a significant improvement in shoulder abduction angle compared to unsplinted patients.[28] The use of shoulder splints needs to be studied further to determine patient types, design principles, and timing of application.

In situations where deemed necessary, shoulder splints can be modified. To accommodate wound dressings and promote healing, a three-piece airplane splint may be fabricated (Fig. 47.8). Foam arm wedges may be substituted

Fig. 47.8 A three-piece airplane splint may be fabricated to accommodate wound dressings and promote healing while maintaining the shoulder abducted.

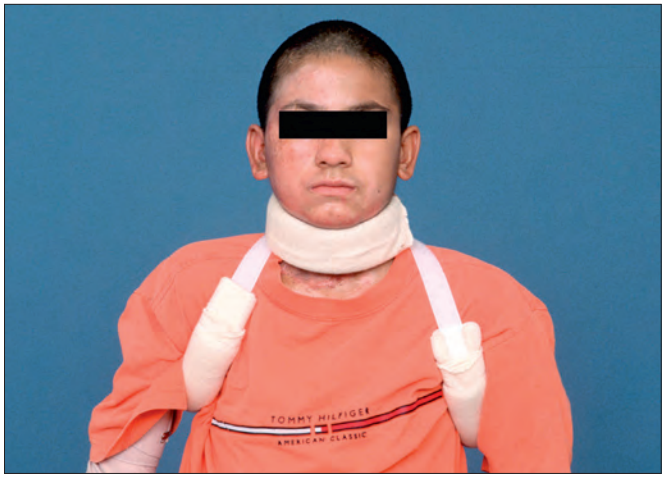

Fig. 47.9 A figure-of-eight axillary wrap provides a constant stretch of the axillary skin surfaces.

when the patient is in the bed postoperatively, when it is difficult to fabricate an airplane splint. Other adaptations may be required in the presence of amputations. Prefabricated airplane splints come equipped with mechanisms that allow for adjustments depending on available shoulder ROM.[19,20,22] A figure-of-eight axillary wrap may be utilized in conjunction with an airplane splint to provide compression for axillary contour and elongation of skin surfaces (Fig. 47.9). A descriptive study using the figure-of-eight sling after scar release and skin grafting indicated that the device is safe, comfortable, easy to use, and promotes compliant use by the patient; with at least as reliable results as the use of abduction splints.[29] For successful contracture management to the shoulder, the positioning program must be supplemented by exercise routines for ROM, strength, and endurance.

ELBOW/FOREARM

Acutely, elevation and extension is the desired position of the elbow. Severe burns involving the elbow may result in flexion contracture and threaten posterior exposure of the joint. Full extension is the protecting position for the elbow. If the joint is exposed posteriorly, extension may need to be rigidly maintained for several weeks. If the joint is not exposed, mobilization into increasing flexion range can begin very soon after the burn injury. The elbow is integral to the so-called delivery system for the hand, and elbow range to full or near-full flexion is more important for overall function than range to full or near-full extension.

Radial head rotation for pronation and supination is less often affected by the burn injury than is flexion and extension. The pronators and supinators are frequently injured in electrical accidents where bone heats, being a poor conductor, destroying the muscles closest to it. Forearm rotation is essential for accurate hand placement, and the rehabilitative program must address pronation and supination during functional tasks and skills training. Depending on the location and severity of the injury, the forearm may be positioned in neutral to slight supination. Static elbow splints may be soft or custom-fabricated of thermoplastic materials. An anterior elbow conformer may be fabricated over the burn dressing. Dynamic elbow extension or flexion splints may be utilized to provide prolonged, gentle, sustained stretch and aid in the correction of contractures.[30] Forearm dynamic pronation/supination splints may be custom-fabricated or obtained commercially for the correction of contractures.[19,20,22]

WRIST/HAND

A comprehensive team approach from initial evaluation through long-term follow-up is essential to maximize the functional outcomes for individuals with hand burns.[31] Treating therapists must have a thorough understanding of the effects of thermal injury on the anatomical structures of the wrist and hand. The presence of dorsal hand edema leads to intrinsic muscle ischemia and a resultant "intrinsic-minus" posture. The unsupported burned hand postures in wrist flexion, metacarpophalangeal (MCP) hyperextension, interphalangeal (IP) flexion, thumb adduction, and thumb IP flexion. The overall appearance is that of a claw deformity (Fig. 47.10A). Edema following a full-thickness burn to the dorsal hand imposes the positions of MCP hyperextension and IP flexion (Fig. 47.10B). Persistence of this position results in a claw hand deformity. The claw hand posture is primarily due to post-burn edema but may persist throughout the course of treatment due to scar contracture or in the presence of peripheral neuropathy. Among the digits, the second and fifth most easily drift into MCP hyperextension because each has a proper extensor tendon.

While superficial burns result in minor, transient edema, full-thickness injuries exhibit more severe and prolonged post-burn edema. Superficial hand burns should not be splinted in order to allow for frequent movement and the freedom to function independently.[2,3] In cases of severe thermal injury, it is important to monitor for signs and symptoms of vascular insufficiency or compartment syndrome. In treating the edematous burned hand, it is important to position the hand above the level of the heart at all times if it can be accomplished without compromising the neurovascular supply to the hand.[19,20,22]

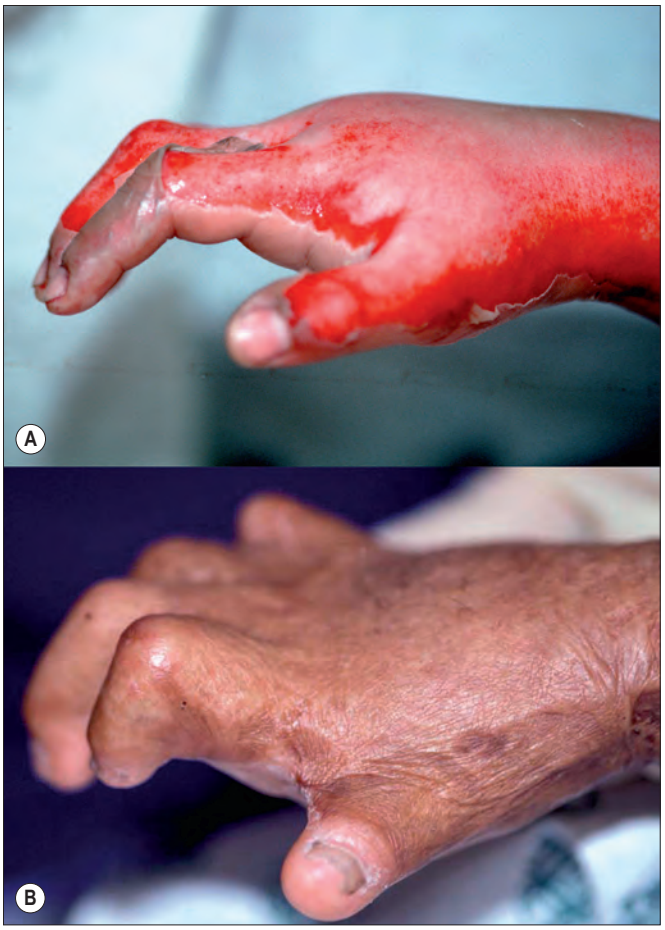

Fig. 47.10 **(A)** Edema following a full-thickness burn of the dorsum of the hand: imposed metacarpophalangeal extension and interphalangeal flexion. **(B)** The deformity resulting from the persistence of this position is that of a claw hand.

Fig. 47.11 The intrinsic plus position hand splint (burn hand splint) positions the hand appropriately to prevent contractures and preserve function.

Acute positioning of the wrist and hand after burn injury is for edema control; immobilization/protection of tendons, joint structures, and/or skin grafts; and optimal positioning to maintain soft-tissue lengths and functional abilities. Within the first 24–72 hours, it is recommended that the wrist be splinted into extension, allowing the MCP joints of digits one through five to fall into flexion due to the normal tenodesis action of the wrist and hand. Wrist extension is essential to control digital position and prevent a claw hand deformity. The recommended functional position of the wrist is from 0–30 degrees of extension.

The burned wrist and hand should be positioned to oppose impending wound contracture. A review of the burn literature indicates some disagreement regarding positioning of the wrist and hand. A consensus panel of burn rehabilitation experts discussed splinting of the MCP joints in at least 70 degrees of flexion at night.[2] Another group of burn experts went a little further and described the position of choice as being wrist extension, MCP flexion greater than 60 degrees, and IP joint extension.[3] A third group, including surgeons, described the desired position as 20–30 degrees of wrist extension, approximately 80 degrees of MCP flexion, IP extension, and thumb in maximum abduction.[32] The authors of this text previously recommended that the optimal position for the burned hand is wrist 0–30 degrees extension, 70–80 degrees MCP flexion and IP joints in full extension (although some burn centers may advocate a slight amount of IP flexion, deeming the position to be "safe"). The thumb should be positioned in a combination of palmar and radial abduction, with the MCP/IP joints slightly flexed. An example of a modification to the burn hand splint that would improve the protection of grafted areas through the use of a "roll bar" is described in the literature.[33] What is clear is the need for controlled studies to determine the appropriate body positions to reduce deformity risks and to determine the most effective methods for the use of splinting for maintaining ROM or contracture management. All the described positions resemble the "intrinsic-plus" position and can be achieved through fabrication/fitting of a burn hand splint by a rehabilitation therapist (Fig. 47.11). The burn hand splint positions the hand appropriately to minimize soft-tissue contractures and preserve functional mobility. Involvement of the extensor tendon apparatus should be assumed and protected until viability of the system is known.[34] Continuous splinting is recommended to manage edema, exposed tendons, peripheral neuropathies, and uncooperative/unresponsive patients.

In the intermediate phase, positioning and splinting are used to prevent/correct deformities and protect surgically reconstructed sites. Splints may be fabricated dorsal, volar, or on the medial/lateral aspects. Contractures are a major complication of hand burns because they affect one's ability to perform ADLs.[5] Joint contractures have also been found to negatively impact quality of life in burn survivors, especially with regard to physical function, role limitations, pain, and vitality.[35] Dorsal hand burns are prone to contract into MCP hyperextension, IP flexion, and thumb adduction and should be splinted into MCP flexion, IP extension, and thumb palmar abduction. The most common post-burn upper extremity contractures are wrist flexion, index finger MCP hyperextension, index finger proximal IP flexion, and small finger MCP hyperextension/proximal IP flexion.[36] The cupped palm deformity is functionally detrimental because

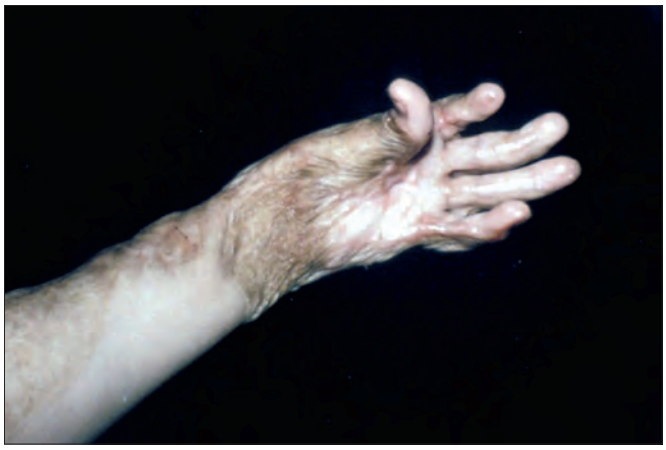

Fig. 47.12 The cupped palm deformity limits the hand's ability to grasp objects normally.

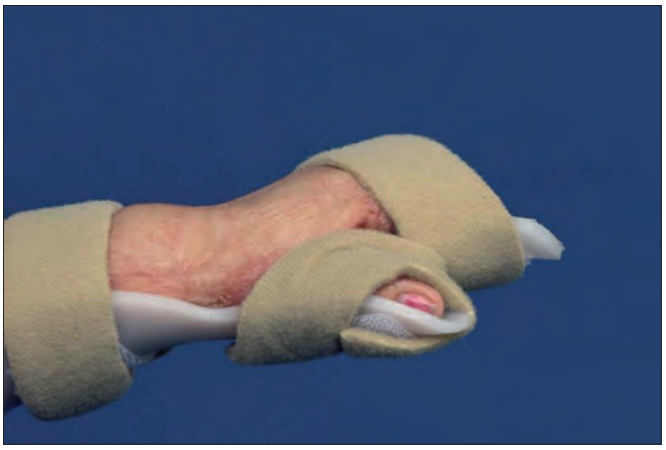

Fig. 47.13 An example of a palmar extension splint to stretch a palmar contracture.

it makes it impossible to smoothly reach around objects (Fig. 47.12).

Burns to the volar surface of the forearm will predispose the patient to wrist flexion contracture, whereas burns to the dorsal surface will likely result in a wrist extension contracture. If the wrist ROM becomes limited in a specific direction, splinting the wrist in the opposite direction is indicated. The fifth digit is occasionally pulled into extreme abduction and hyperextension by scar contracture, muscle imbalance, or ulnar neuropathy. The thumb may become similarly displaced into adduction and retroposition. It is important to remember that the likelihood for MCP joint problems exists throughout scar maturation. Palmar hand burns are prone to MCP flexion and thumb opposition contractures and should be splinted into palmar extension and thumb radial abduction.

Static positioning with custom thermoplastic splints can be relatively efficient to implement in the clinical setting; however, a review of the literature indicates that there is no strong evidence for the use of static splinting in preventing scar contractures.[37] More recently, a group of surgeons and therapists collaborated to look at serial splintage of the upper limb after burn injury and found that the preoperative use of splints may lead to lesser surgical interventions, and minor contractures may be completely corrected.[38]

Two common faults are seen in custom splints that are designed to gain MCP flexion and to position the thumb in MCP flexion/radial abduction. If the distal transverse fold of the splint is not proximal to the MCPs of digits 2–5, the splint will impede rather than favor MCP flexion. If the thumb component of the splint applies volar pressure rather than medial pressure, the MCP will extend and the first metacarpal will become correspondingly more adducted. The first MCP joint should be maintained in slight flexion, and pressure from the splint should be applied just to the medial surface. Any degree of first metacarpal adduction contracture increases the likelihood that the proximal phalanx will be pushed into hyperextension and eventually into subluxation.

In the case of circumferential hand burns, a palmar extension splint is fabricated to prevent flexion contractures and a cupping deformity of the palm (Fig. 47.13). The burn hand splint and an extension splint may be alternated. A

Fig. 47.14 The "sandwich" hand splint prevents proximal interphalangeal (PIP) flexion contractures.

"sandwich" splint may be fabricated that includes a burn hand splint with a dorsal shell over the IP joints to prevent flexion of the digits. All splints may be secured with elastic bandage or with Velcro strapping components (Fig. 47.14).[39] Individual gutter splints are used to prevent flexion contractures, to restrict boutonnière and mallet finger deformities, and to protect exposed extensor tendons until wound closure. Recently, a group of hand therapists has combined the use of digital gutter splints built into a compression garment to improve adherence to wear schedules in a pediatric population.[40] C-bar splints are used to prevent adduction contracture of the first web space. Figure-of-eight splints are fit to correct or restrict swan neck deformities.

Dynamic splints are utilized to provide low-load prolonged stretch to counteract contractile forces and are recommended for the correction of scar contractures.[37] Dynamic splinting of the hand will focus on MCP extension/flexion splints, IP flexion/extension splints, and thumb abduction and may include prefabricated or spring-loaded splints (Fig. 47.15).[41] Patients may require dynamic splinting to assist muscles weakened by peripheral neuropathy.

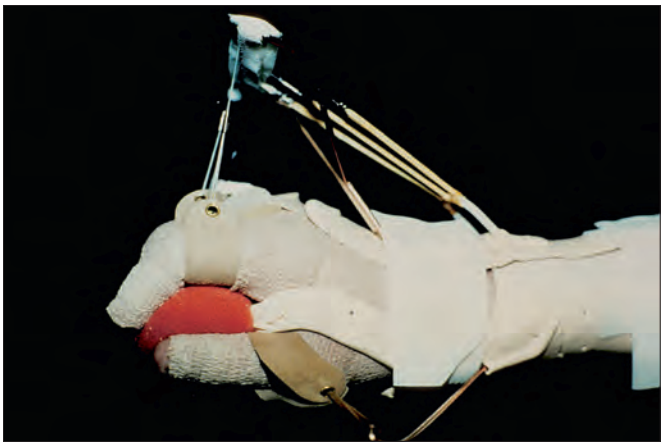

Fig. 47.15 A dynamic metacarpophalangeal (MCP) extension splint promotes functional use of the hand.

The therapist monitors dynamic splinting closely and makes frequent adjustments in order to provide effective tissue mobilization. Additionally, the fit of dynamic splints is checked frequently to ensure that the anatomical structures remain properly aligned.

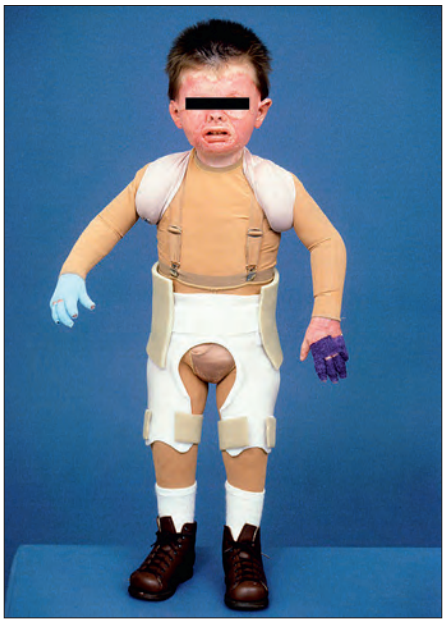

Fig. 47.16 An anterior hip spica splint is utilized to prevent anterior hip flexion contractures.

HIP

When anterior burns extend from the abdomen to the thigh, hip flexion is the position of comfort. If the hip is fixed in any degree of flexion, posture will be modified. Bilateral symmetric contractures impose increased lumbar lordosis, knee flexion, or both. Asymmetric contracture will cause pelvic obliquity and scoliosis. In adults and older children, thighs are more likely to be held in adduction than in abduction, whereas in preambulatory infants the secondary component of the contracture is abduction. Thus, for the hips, the preventive position is full extension, 0-degrees rotation, and symmetric abduction of 15–20 degrees. If elevation of the upper body is needed for edema reduction, then the entire frame of the bed is elevated with the use of wooden shock blocks placed at the head of the bed or the bed is placed in reverse Trendelenburg with support of a padded footboard. Soft mattresses should be avoided because they may promote hip flexion. Hip positioning is accomplished with the use of abduction pillows and other strapping mechanisms that eliminate hip rotation. If the patient wears bilateral foot splints, then connector bars may be utilized on the splints to bring about the desired bilateral hip positioning stated earlier. Hip flexion contractures may be serially corrected with an anterior hip spica or with a three-point hip extension splint (Fig. 47.16).[19,20,22] Subtle hip flexion contractures can be easily overlooked when the patient stands, there being only a slight increase in lumbar lordosis or forward or lateral shift of the trunk. If established hip flexion contractures are not surgically corrected, body posture is likely to be permanently altered with scoliosis or exaggerated lordosis.

KNEE

Burn injury to the anterior or posterior surface of the lower extremity that crosses over the knee joint may result in knee flexion. Deep anterior burns may expose the joint, occasionally destroying the patellar tendon. Deep posterior burns result in bridging scar formation. The appropriate position for the knee is full extension to be maintained by splint or, in severe cases, skeletal traction until there is efficient quadriceps function and the patient is ambulatory. Thereafter, night splints must be used until scar contracture is no longer a threat. Knee splints may include a posterior custom-made thermoplastic knee conformer or a soft knee immobilizer.

Persisting bilateral knee flexion contractures will impose hip flexion. Persisting unilateral contractures may impose pelvic obliquity and scoliosis. As with the hip, posture alteration may be so subtle as to be overlooked. Correction of even a slight contracture should be a surgical priority, as should elimination of a soft bridging scar band that does not prevent complete willful knee extension but causes the patient habitually to hold the knee in slight flexion.

FOOT/ANKLE

Ankle equinus is the most frequently occurring deformity involving the foot. Initially, it is related more to gravity and failure to support the foot at neutral at the talotibial joint than to the early effect of the burn. Loss of deep and superficial peroneal nerve function will compound the problem by encouraging the foot to drift into inversion as well as equinus because of loss of dorsiflexion and eversion motors. In the end, the total deformity for the unsupported foot may be ankle equinus, hindfoot inversion, and forefoot varus and equinus. Ankle equinus quickly becomes a resistant deformity so that, within a few days or even hours, the foot can no longer be positioned at 90 degrees of dorsiflexion in the neutral ankle position. Eventually the contractures of scar, muscle, and capsular structures combine to fix the deformity.

Equinus deformity and the attending inversion and forefoot varus can be prevented by accurate and unyielding support of the foot in neutral alignment or slight dorsiflexion. If the patient must be nursed prone, the feet must be allowed to fall free from the mattress. Static splinting, if not performed correctly by an experienced therapist, is often unsuccessful because of the patient's desire and tendency to plantarflex strongly, displacing the splint and leading to ulcers of the heel, malleoli, toes, and where the splint edges touch the skin. A stable footboard may be effective if the feet are kept securely and totally against it. For large burns and particularly for circumferential burns of the lower extremities, skeletal suspension incorporating calcaneal traction will support the foot at neutral if the traction pin is placed in the calcaneus well behind the axis of ankle motion. A balanced traction system demands that the knees be supported in flexion with tibial pins at the level of the tibial tubercle. Calcaneal pins will not prevent forefoot equinus. If traction must be employed for several weeks, proximal-pull dorsal pins in the first or first and second metatarsals may be required for support of the forefoot. Transmetatarsal pins are useful as well when calcaneal traction alone is not sufficient to correct equinus.

Minor established equinus deformity can be corrected with a standing and walking program. At the outset, graduated heel lifts may be used to accommodate to the deformity. If the patient must be bed-confined, skeletal traction through the calcaneus may be the quickest and most efficient way to correct the deformity. Traction is effective even if scar contracture contributes to the deformity. Serial corrective casts or posterior splints alone are useful mainly for minor contractures. For the treatment of circumferential foot/ankle burns, anterior foot splints are also fabricated and their application is alternated with the posterior foot splints in preventing plantar or dorsal foot contractures.[19,20,22] The Multi Podus System foot splints may be utilized for the positioning of the burned foot/ankle because they relieve heel pressure and prevent pressure ulcers (Fig. 47.17). For fixed, unyielding deformity, scar release combined with tendo-Achillis lengthening with or without posterior capsulotomy is a standard surgical procedure that yields inconsistent results. The correction achieved is often just to neutral or to slight dorsiflexion. The Ilizarov technique has been used with generally satisfactory immediate results in severe cases.[42] No matter how correction is achieved, if there are no dorsiflexion motors and if the range of ankle motion is only a few degrees, ankle fusion may in the end yield the best functional result.

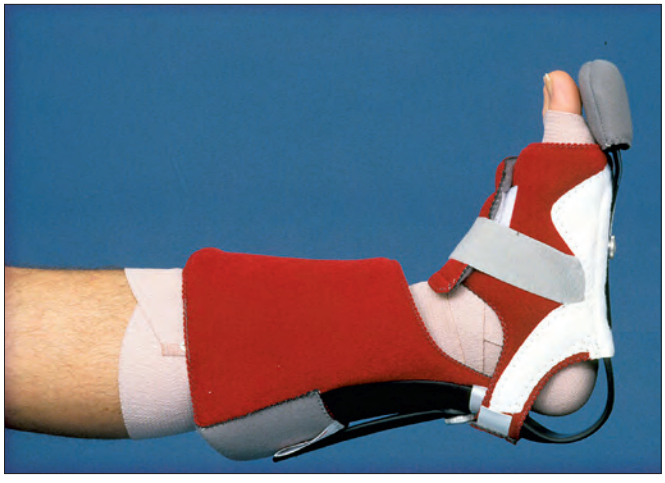

Fig. 47.17 The Multi Podus splint is utilized to position the burned foot appropriately and prevent heel and malleoli skin breakdown.

The most common intrinsic deformity of the foot is extreme extension of the toes due to dorsal scar contracture. This deformity is insidious in onset and is difficult to prevent because there is no type of nonskeletal splinting that will hold the toes flexed. In its extreme, the deformity includes dorsal metatarsophalangeal (MTP) subluxation, which may involve one or all toes depending on the location of the scar. The metatarsal heads become prominent on the plantar surface and walking may be painful. Correction of the deformity requires dorsal surgical release of the contracture, manual correction of the deformity, and, in severe cases, intrinsic or extrinsic pinning of the digit or digits in an overcorrected position (i.e., MTP and interphalangeal flexion). The deformity will commonly if not inevitably recur to some degree unless the patient, after the operation, is able to achieve active MTP flexion in all digits.

Dorsal scar contractures extending from leg to foot to toes may pull the foot into marked inversion if the scar is medial or into eversion if the scar is lateral. The fifth and first toes may be separately displaced by the same scar bands. These contractures must always be surgically corrected. Their persistence will lead to bone deformity in a growing child and will permanently adversely affect foot and ankle function. Even slight inversion, whether imposed by scar contracture or motor weakness, will increase pressure on the lateral border of the foot, leading to callus formation and a painful, inefficient gait. Occasionally the base of the fifth metatarsal is so offensive as to require partial surgical osteotomy.

When there is both anterior and posterior scar contracture, the talus will remain aligned with the calcaneus in a relatively plantar flexed position as the midfoot and forefoot are pulled into dorsiflexion. The result is so-called rocker bottom foot with the head of the talus being the principal weight-bearing feature. This deformity once established defies correction by usual surgical means because of the shortage of soft tissue and because vessels and nerves cannot be stretched to accommodate the corrected position. The Ilizarov technique may offer a partial solution to the problem. Removal of the head of the talus may give a reasonable weight-bearing surface. With chronic painful ulceration, amputation is the best treatment.[42]

Orthotic Treatment of the Lower Extremity

Multiple articles have been written about surgical interventions for burns to the feet in both adults and children.[43–46] The approach of the orthotist in treating the injured foot depends on the extent of the burn injury. Contracture deformities of the feet after burn injuries present a complex problem for all members of the burn rehabilitation team.[47] The options for management include orthopedic shoes with and without modifications, orthotic inserts, ankle–foot orthoses (AFOs), and heel lifts. Orthopedic shoes, which are the fundamental component of lower extremity orthotics, may be utilized with some modifications in correcting

deformities of the burned foot. Modifications of these shoes may include arch pads, molded foot thermoplastics, tongue pads, and metatarsal bars. The ideal shoes should distribute all forces to the foot appropriately, reduce pressure on sensitive or deformed structures, and encourage total surface weight-bearing along the plantar aspect of the foot. Inserts for plantar foot support, such as the University of California Biomechanical Laboratory (UCBL)-type, may be utilized as indicated.

During the preambulation stage, the patient may be fitted with those orthotic devices mentioned earlier; if properly utilized, they can position the ankle joint in a balanced position, assist in preventing or correcting plantar/dorsal contractures, and correct inversion/eversion of the foot.

Leg length discrepancies are seen frequently in the cases of severe lower-extremity burn injuries and should be addressed with a shoe lift. The ankle–foot complex is difficult to address, especially in the case of a severe thermal injury. In most cases, the resultant deformity is the equinovarus foot. Both conventional and thermoplastic systems may be designed to treat the equinovarus or equinovalgus foot. Such systems may include a metal AFO, polypropylene plastic posterior AFO (solid ankle or with an articulation), an AFO with stirrup attachment, or an AFO with stirrups and patellar tendon support. A dorsiflexion spring assist may be incorporated in the AFO to aid weak ankle motion. Different straps, such as a valgus correction strap, may be attached to the AFO for the correction of specific problems. Interface materials, such as silicone, Plastizote, and Aliplast, can be incorporated into an AFO to provide protection of the soft tissues, provide for total surface weight-bearing, and accommodate any anatomical anomalies that may be present (Fig. 47.18). In the event that a return of ROM is anticipated, an AFO could be fabricated that can be modified as the patient progresses. As described, the ankle joint is incorporated into the AFO; however, the device is left solid and articulated at a later date.

During more complicated cases, and depending on the anatomy and function of the lower extremities, a knee–ankle–foot orthosis, hip–knee–ankle–foot orthosis or a trunk–knee–ankle–foot orthosis may also be designed for the best functional outcome.[48]

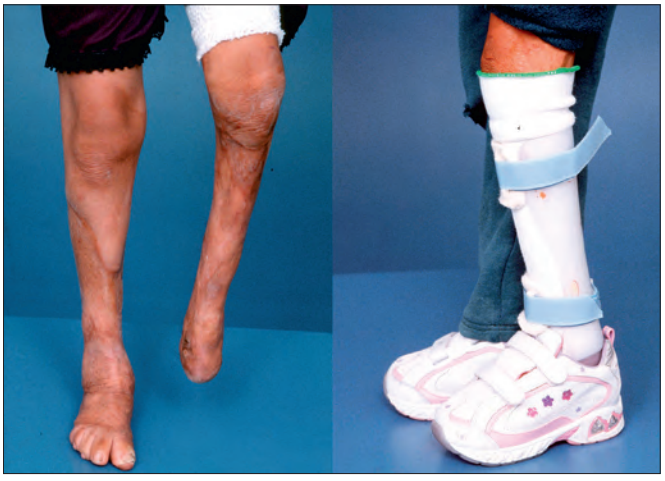

Fig. 47.18 Specialized materials may be required to accommodate anatomical anomalies. Standard ankle–foot orthoses can be fabricated utilizing silicone materials to accommodate excessive scarring and limb loss.

SERIAL CASTING

Multiple authors have identified serial casting as a treatment option for burn scar contracture management.[5,49–54] Casting has been used in patients with burns for postoperative immobilization to promote graft adherence and to minimize scar contracture during the remodeling phase of healing.[54] Circumferential casting after skin grafting to the lower extremity has been an effective means of providing protection to the grafted area.[55] Serial casting has been used successfully on outpatients with burns when active ROM is limited due to scar tissue formation.[52] Dewey, Richard, and Parry described serial casting as an alternative to the use of orthotic devices for contracture management in the presence of burn scars.[9]

The literature has several examples of casting being used as an anticontracture device for the hand,[56–61] wrist,[54,60] elbow,[54,62] axilla,[63,64] knee,[54] and ankle.[53,54] In a retrospective study published in 2000, Richard, Miller, Staley et al. compared patients treated with a multimodal approach of scar massage, therapeutic exercises, and pressure therapy to those treated with a progressive approach that included static or dynamic splints and serial casting; the authors found significantly fewer days were required to correct the burn scar contractures in the progressive treatment group.[50]

Casting works based on the biomechanical principle of stress relaxation in much the same way as a static splint design does.[9] Similar to static splinting, serial casting is a rehabilitation approach used to increase elongation of scar tissue.[2] The application of a series of casts provides a low-force, long-duration stress that can cause a permanent, plastic deformation of connective tissue.[51] The goal of serial casting is gradual realignment of the collagen in a parallel and lengthened state by constant circumferential pressure.[53] Prolonged, gentle, sustained stretch provided by the cast aids in tissue elongation for the correction of contractures (Fig. 47.19). Burn scar under constant traction shows collagen formation in parallel alignment along the forces of stress.[65] Low-intensity force with prolonged duration of stretching can be applied to connective tissue whether it is scarred, contracted, or surgically shortened.[66]

A review of the literature indicates that serial casting is typically used when the patient is noncompliant, does not tolerate splints, there is persistent ROM limitation, or a skin graft site requires protection or immobilization.[51,53,54] Serial casting can be a relatively simple, fast, and painless intervention and provides an alternative to complex splinting when patient compliance is an issue (e.g., in pediatric patients or patients with decreased arousal). Bennett, Helm, Purdue, and Hunt casted 35 patients with scar contractures at an average of 161 days after burn injury and found that all had significant improvements in ROM, which raises the question of why serial casting is so often considered a last resort.[54]

Additionally, clinicians may be hesitant to apply a cast because of open wounds, despite the fact that serial casting has been advocated for protection of involved sites after skin

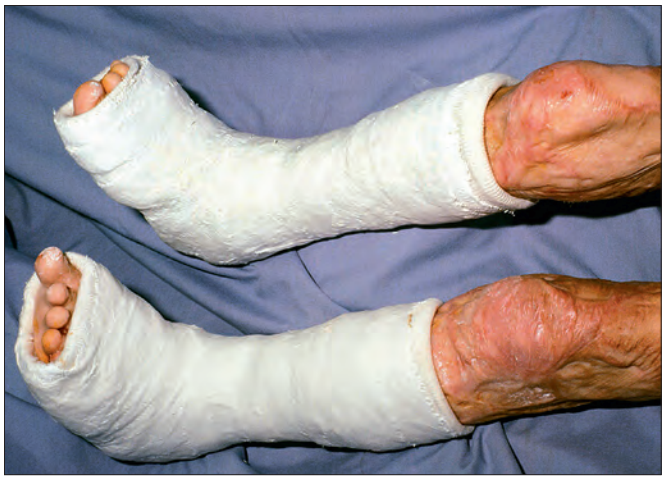

Fig. 47.19 Serial casting provides prolonged, gentle, sustained stretch and aids in tissue elongation and correction of contractures without pain.

grafting.[55] Ricks and Meagher evaluated cast application immediately after skin grafting in 36 patients with lower-extremity burns.[55] They found that the casted group had significantly fewer days from skin grafting to wound closure, a higher rate of graft adherence, and needed fewer surgical treatments for deficits in ROM. The use of serial casts is often advocated as a last-resort treatment when a patient does not respond to traditional therapy and is often used primarily in the long-term phase of recovery.[2]

The process of cast fabrication has been described for use in both the adult and pediatric patient populations.[51,55,56,59] A precasting assessment should include goniometric measurements, end-feel assessment of the involved joints to determine the structures involved, duration of limitation, skin or wound status, neurovascular status, functional needs, and cognition of all involved parties. The patient is educated on the position in which the cast will be applied, the expected duration of casting, and any restricted activities. Ridgway described the serial casting technique and sequence: (1) skin hygiene, (2) scar massage with moisturizer, (3) ROM exercises and assessment, (4) wound dressings, (5) application of a silicone insert, 6) extremity in figure-of-eight wrap or tubular bandage, (7) padding over bony prominences, and (8) one therapist to position and one therapist to fabricate cast.[53] Clinicians need to provide adequate pressure relief over bony prominences, however, to prevent skin breakdown. The clinician should only allow a minimal time lapse between cast removal and cast reapplication. Serial casting may be supplemented with static splinting of the adjacent joints.

Patients may require premedication and may also benefit from soft-tissue preconditioning (heating) for stretch prior to cast application. Precautions should be taken to ensure proper and evenly applied padding, including extra layers at the proximal and distal ends of the cast. The casting material should be rolled out and handled with an open hand as much as possible. Aggressive molding or overtight applications are to be avoided and can lead to compression neuropathies or vascular compromise. When cast materials harden, an exothermic reaction occurs causing the temperature within and beneath the cast material to rise, which leads to elevated temperatures and the risk of burn injuries. The greatest risk of thermal injury occurs when a thick cast using warm dip water is allowed to mature while resting on a pillow.[67] Excessively thick casts and a dip-water temperature of higher than 24°C should be avoided. Placing the limb on a pillow during the curing process of the cast puts the limb at risk for further injury and should be avoided.[68]

A variety of materials are available for the fabrication of casts. The most widely known would probably be plaster-of-Paris. Plaster is fast setting when reacting with lukewarm water. Plaster casts are inexpensive, strong, and easy to fabricate. However, they require longer drying times (24–48 hours), are prone to indentations and skin irritations, and are heavy. Other disadvantages of this technique include decreased water resistance and breakage if not constructed strongly enough. Plaster casts may be removed with a cast saw or moistened and removed with scissors.

Fiberglass casting material is an alternative to plaster-of-Paris. Fiberglass casting tape is fast setting when reacting with cool water. Fiberglass materials require a shorter drying time (15–30 minutes), are lightweight and durable, and offer resistance to dirt and water. Fiberglass casting methods are costlier than plaster. Because of fiberglass's abrasive properties, therapists must wear gloves when handling the materials during cast fabrication and removal. The patient's skin and clothing should be protected from contact with the fiberglass casting tape, as well as with fiberglass fibers during cast removal. Fiberglass casts require a cast saw for removal.

Recently, nonlatex polyester materials such as Delta-Cast have been utilized as alternatives to plaster and fiberglass. These materials, which resemble fiberglass, are very lightweight, flexible, and, because of their elastic properties, conform very well. These casts may be cut in a bivalve fashion so that they can be removed and reapplied after wound care, hygiene, and exercise.[69]

After cast fabrication is complete, the clinician should check the firmness of the cast, neurovascular status of the extremity, sharpness of cast edges, and any signs of the cast rubbing adjacent structures. When casting is completed, the patient should feel a gentle but not painful stretch. The first cast should be removed at approximately 24 hours; thereafter, depending on the patient's tolerance, it could be applied for up to 1 week at a time. In the literature, the reported frequency of cast change ranges from daily to every 10 days.[53,54,57,60,62,63] In cases of casting over open wounds, the cast should be removed every 1–2 days to avoid complications in wound healing.[53,55] The use of insert material for scar management under casts has been documented and found to be useful.[53] Serial casting is terminated when either normal ROM has been restored or no further functional gains are achieved.

According to a consensus summit of burn care professionals, the traditional thought processes regarding the use of serial casts with the burn patient need to be re-evaluated, casting regimens need to be standardized, and studies are needed to evaluate serial casting at various stages of burn recovery and the overall effectiveness of the modality for contracture management.[2]

Prosthetic Interventions

A prosthesis is a device used to replicate the function and appearance of a missing limb. Amputations among the burn patient population most often occur as a result of electrical insults but can also result from more severe thermal injuries as well. They have a significant physical and psychological consequence, which impacts quality of life.[70] Prosthetics are designed, fabricated, and fit by a certified prosthetist. Each device is individualized based on the needs of the patient. But, in general, the prosthesis should be comfortable to wear, easy to don/doff, lightweight, of durable construction, and be cosmetically appealing. The prosthetist and rehabilitation professional will consider the following when designing the prosthesis and its components: level of amputation, shape and contour of the residual limb, functional expectations, cognitive abilities, vocational requirements, hobbies/leisure pursuits, and financial resources. Standard prosthetic texts are useful in providing broad basic information and explanations of the many components available and their use.[71,72]

Patients who have sustained severe burns and subsequent amputations have complex, long-term impairments and face considerable functional deficits.

Severely burned patients tend to have sensorimotor limitations in the intact extremities that may affect their ability to utilize a prosthesis. Their limitations and strengths are important considerations when planning treatment. These patients may exhibit muscle weakness not usually seen at the same amputation levels in the nonburn patient. Areas of weakness should be noted and compensation, such as increasing joint stability through alignment or componentry, should be provided. Burned individuals may use their remaining functioning extremities differently than patients without total body involvement. Prosthetic rehabilitation should enhance adaptations and necessary compensatory methods. The challenge to the prosthetist is to design a device that is maximally useful to a person who may have multiple limitations. To be useful, a device must be as easy to use as possible. Simplicity often determines whether the device is successful or discarded.

Prostheses may be preparatory or definitive. Preparatory devices are those fitted while the residual limb is still maturing. A preparatory prosthesis is provided when reduction of stump volume is anticipated or when fitting over a bulky dressing is necessary. These devices are usually simple, passive devices that allow for early motion skills and weight-bearing through the affected limb. Some patients will continue to use their preparatory prosthesis for extended periods of time while other areas of the body are treated. Prior to definitive fitting, body weight, residual limb volume, and wear and use patterns should be stable in order to optimize the long-term result with the definitive prosthesis. The definitive prosthesis is fitted when the residual limb is fully mature. The use of a preparatory prosthesis is not mandatory, but the use of one will improve the fit and control of the definitive prosthesis and may, secondarily, reduce the amount of time needed for rehabilitation post-burn injury.

Prosthetic preparation in burn rehabilitation begins in the postsurgical phase. Early prosthetic treatment of an amputee includes splinting for the prevention of contracture. An upper extremity splint may extend past the distal end of the residual limb to match the length of the whole limb, thus assisting a patient in retaining the concept of length. Initially, therapists must address: promotion of wound healing; pain management, residual limb shaping, prevention of contractures, skin desensitization techniques (tapping, massage, scar mobilization, pressure application), edema control, and coping mechanisms for adjustment and grief. With early socket fitting, some skin problems will be encountered, but these are not usually of major significance. Silicone gel or urethane socket inserts have been used successfully for pressure relief to burn-scarred skin. As wound healing progresses, prosthetic training will begin to focus on care of the prosthetic device, don/doff methods, skin inspection routines, weight-bearing with the device, and progressive functional skills.

Just as upper extremities are different from lower extremities, so, too are upper- and lower-extremity prostheses. The minimum requirements for successful use of an upper-extremity prosthesis are trunk control to support an upright posture, sufficient upper body strength to selectively activate the control devices, and static and dynamic balance skills. The patient will need to be trained on specific body movements to develop control of the upper-extremity prosthesis. Glenohumeral flexion provides excellent power and reach for functional routines. It can be used to flex the elbow, activate the terminal device, and for activities away from the midline of the body. Scapular protraction is also trained for activation of the terminal device and facilitation of fine motor tasks at midline or close to the body. The other motions of glenohumeral depression/elevation, extension, and abduction are most frequently used to lock or unlock an elbow joint.

Different types of upper-extremity prostheses are available along a continuum from mostly passive or cosmetic to primarily functional. Most devices fall somewhere in the middle range between cosmesis and function. Cosmetic prostheses are difficult to keep clean, expensive, and ultimately sacrifice function for appearance. Functional prostheses fall into two categories. They can be designed to be body-powered (using cables) or externally powered (myoelectric or switch control). Body-powered prostheses are moderate in cost and weight, more durable, and offer higher sensory feedback. However, they require more gross limb movement and can be less cosmetically appealing. Externally powered prosthetic devices allow for more proximal function, greater strength for grasp/prehension, and improved cosmesis. Additionally, they may be heavy and expensive, offer less sensory feedback, and require more regular maintenance. Regardless of the type of prosthesis planned for, fitting of an upper-extremity body-powered prosthesis within 7–30 days correlates with higher acceptance and success rates.[73] Body-powered prostheses are most commonly used in burn rehabilitation, and Table 47.1 describes the components of upper-extremity prosthetic devices.[74,75]

The rehabilitation upper-extremity prosthetic goals should include stability of the shoulder girdle to allow prehension, overall ease of movement of the entire limb, energy-efficient use of the device, and the appearance of a normal upper extremity. Table 47.2 describes upper-extremity

Table 47.1 Prosthetic Components

Upper Extremity	Functions	Lower Extremity
Socket	Interface between prosthesis and residual limb Selective loading/pressure relief	Socket
Suspension	Holds prosthesis to residual limb Force transmission for function	Suspension
Control system: Usually movement of the shoulder or chest	Links movement of a body part to the prosthesis	Control system: Usually movement of the hip or knee
Interposed elbow joint	Performance of hand to midline Provides support during stance phase, smooth swing phase, and motion for sitting and kneeling	Interposed knee joint
Interposed wrist joint	Attaches socket to terminal device; orients terminal device in space	Shank (pylon)
Terminal device	Restores cosmetic appearance Replicates anatomic joints Replaces hand/ankle function Stable, weight-bearing surface Shock absorption	Prosthetic foot

Table 47.2 Types of Amputations and Prosthetic Needs

Types of Amputations		Prosthetic Needs
Upper extremity	Transphalangeal	Passive for cosmesis
	Transmetacarpal	Oppositional devices
	Transcarpal	Body-powered hand or hook
	Wrist disarticulation	Forearm socket, wrist component, and terminal device
	Transradial	
	Elbow disarticulation	Proximal arm socket, elbow hinge (passive, active, or externally powered), forearm lever arm, wrist component, and terminal device
	Transhumeral	
	Shoulder disarticulation	Harness system and transhumeral components
	Interscapulothoracic disarticulation	Harness system, shoulder socket and transhumeral components
Lower extremity	Transphalangeal	Toe-filler
	Toe disarticulation	Foot plate
	Ray amputation	Partial foot to tibial height prosthesis
	Transmetatarsal	
	Transtarsal	
	Syme	Socket to knee, low-profile foot
	Transtibial	Socket with foot and ankle
	Knee disarticulation	
	Transfemoral	Socket, knee joint, and ankle/foot complex
	Hip disarticulation	Socket is total contact shell, hip/knee joints, and ankle/foot complex
	Hemipelvectomy	

amputations by level and identifies the appropriate prosthetic device to address the patient's functional needs.[74,75]

The rehabilitation program for successful use of lower-extremity prosthetics begins with donning/doffing of the device, transfer skills, activities to build wearing tolerance, practice to reinforce balance reactions, and preambulation skills. Preparatory weight-bearing treatment for use of a lower-extremity prosthesis usually begins on a tilt table, progressing to standing and then ambulation in the parallel bars. The rehabilitation goals should address stability, ease of movement, energy efficiency, and the appearance of natural gait.[76] Table 47.1 outlines the common components of lower-extremity prostheses and their functions.

Lower-limb prosthetics require the following minimum requirements for successful use: upright trunk control, sufficient upper body strength, adequate lower-body stability and control, static and dynamic balance skills, and good postural alignment. Lower-extremity prosthetic fitting begins when the patient's wounds are well-healed and will tolerate pressure and weight-bearing. Lower-limb devices may be either preparatory or definitive. Table 47.2 details types of lower-extremity amputations by level and identifies the appropriate prosthetic and components.[74,75]

Two common sequelae of traumatic amputations are phantom sensation and phantom pain. *Phantom sensation* is the perceived sense that the amputated limb is still present. It is not typically characterized as painful by the patient. The patient may report feeling that the amputated limb has shrunk (telescoping). In contrast, *phantom pain* is the sensation of pain originating in the amputated part. Upon assessment, the pain may or may not be dermatomal in presentation. The patient may report constant burning, stinging, cramping, or a feeling of awkward positioning. Phantom pain is most intense acutely, gradually becomes intermittent, is worse at night, and is often exacerbated by stress/anxiety. From a therapy standpoint, phantom sensation may be managed by desensitization techniques, whereas phantom pain may be responsive to transcutaneous electrical nerve stimulation.

The overall process of prosthetic evaluation and fitting is described in Fig. 47.20. Satisfactory use of a prosthetic device in burn rehabilitation requires continuous dialogues among the patient, therapist, prosthetist, and surgeon. Return clinic visits should include consistent prosthetic re-evaluation. However, ultimately, the use of a prosthetic device depends largely on patient motivation.[74] Most prostheses can be expected to last at least 3–5 years with standard daily use. Children will need more frequent modifications or adjustments as they grow and develop.[77] In general, the simplest system that provides the most functional–cosmetic level is accepted by the amputee as the best choice.

Burn Scar Management

HISTORICAL REVIEW

The burn wound, like any other wound, heals by the formation of scar at the injured site to replace the destroyed tissues. Scar is defined as the fibrous tissue replacing normal tissues destroyed by injury or disease.[78] In the case of a burn injury, the scar, if not managed appropriately, has the potential of becoming thick and raised, resulting in scar hypertrophy. Hypertrophic scars are not cosmetically appealing, and, if they cross any joints, they may restrict movement and function. Pressure therapy for scar management is a very old and established component of a recovering burn patient's continuing rehabilitation program. Extensive historical notes on the earliest references to scarring are provided by Linares and colleagues, who attribute the first full medical description of scars to Petz in 1790.[18] They also state that the first medical reference to the use of pressure for treatment was written by Johnson in 1678 referring to the work of Ambroise Paré in the sixteenth century.[18] Other historical events noted by Linares et al. are the first known accounts of the use of pressure for treatment of children in 1859, use of elastic bandages in 1860, adhesive plaster for pressure in 1881, and use of traction to treat scars in 1902. Linares's review includes descriptions of Nason's work in 1942, in which he noted that ischemia produced by pressure arrests the overproduction of scar tissue, "where the imprint of the elastic of an undergarment or a belt may be seen—no keloid is present."[18] Another historical review by Ward[79] reveals that Blair in 1924 reported the positive influence of pressure on healing wounds. Nason's application of the "constant pressure" principle included developing a type of neck splint made of a piece of dental impression compound or a piece of heavy felt strapped tightly over the scar for 6–8 weeks and possibly longer. Later, various splints were developed utilizing pressure and immobilization.[80] In the 1960s, Silverstein and Larson observed the influence of pressure on fresh scars. Their observations led to the manufacture of custom pressure garments that revolutionized scar management in the 1970s and continue to be the most preferred method of managing scars to date.[18,79]

THE SCAR

As the burn wound closes, or after skin grafting operations take place, scars begin to form. Generally, the deeper the burn injury is, the higher the risk for the development of hypertrophic scars. Also, the longer a wound remains open, the higher the chances for hypertrophic scar formation.[80,81] As the wound begins the healing process, collagen fibers develop to bridge the wound surface, forming an immature (active) scar, which appears as a red, raised, and rigid mass.[82–85] Abston reported that pressure therapy while the scars were active led to flatter, softer, and more devascularized scars.[86] Burn scars may take up to 2 years or longer to mature. Factors contributing to the formation of hypertrophic scars may include wound infection, genetics, immunological factors, repeated harvesting of donor sites, altered ground substance, age, chronic inflammatory process, location of the injury, and tension.[87] Scar hypertrophy may be evident at 8–12 weeks after wound closure.[88]

SCAR ASSESSMENT

A thorough burn scar assessment should be carefully conducted by the burn therapist because the burn scar has serious implications on the final functional and cosmetic outcome at the completion of the rehabilitative process. Over the years, several scar assessment scales and individual scar assessment tools have been developed to quantify burn scars to determine the efficacy of scar management interventions. These scar assessment scales and tools are either objective (provide a quantitative measurement of the various scar characteristics) or subjective (provide an overview of the quality of the scar as measured by an observer). The Vancouver Burn Scar Assessment developed by Sullivan and colleagues is a subjective way of rating the burn scar pigmentation, vascularity, pliability, and height, and it is widely used among clinicians.[2,89] Despite the fact that the Vancouver Burn Scar Scale is a subjective scale, it continues to be the most frequently utilized burn scar assessment scale by researchers to date. Baryza and Nedelec have attempted to improve the Vancouver scale through the years, and they have somewhat succeeded in doing so.[90–92] Other scar scale assessments include the Patient and Observer Scar Assessment Scale (POSAS) and the Manchester Scar Scale (MSS). The majority of scar scale assessments available are thought to be subjective in nature and are criticized for their lack of validity and reliability. Hambleton and colleagues studied the thickness of scars with ultrasonic scanning. This method, which is completely noninvasive, allows for a comparison of the thickness of dermal tissue in the traumatized area with that in normal skin at regular intervals following initial healing.[93] Darvey et al. described a technique for the objective assessment of scars utilizing a video camera image on a computer and quantitatively analyzing the color of the scars using a custom-written computer program.[94] Esposito used a modified tonometer to measure skin tone, which correlates to skin pliability and tension.[95] Bartell and co-workers used the elastometer properties of normal versus injured skin. In his study, Bartell showed that scars, if left untreated, will show improvement over time.[96] Hosoda utilized laser flowmetry to determine the perfusion of hypertrophic scars versus nonhypertrophic scars.[97] Other studies suggest that laser Doppler flowmetry and monitoring of transcutaneous oxygen tension may in the future be ways of determining scar maturation.[98,99]

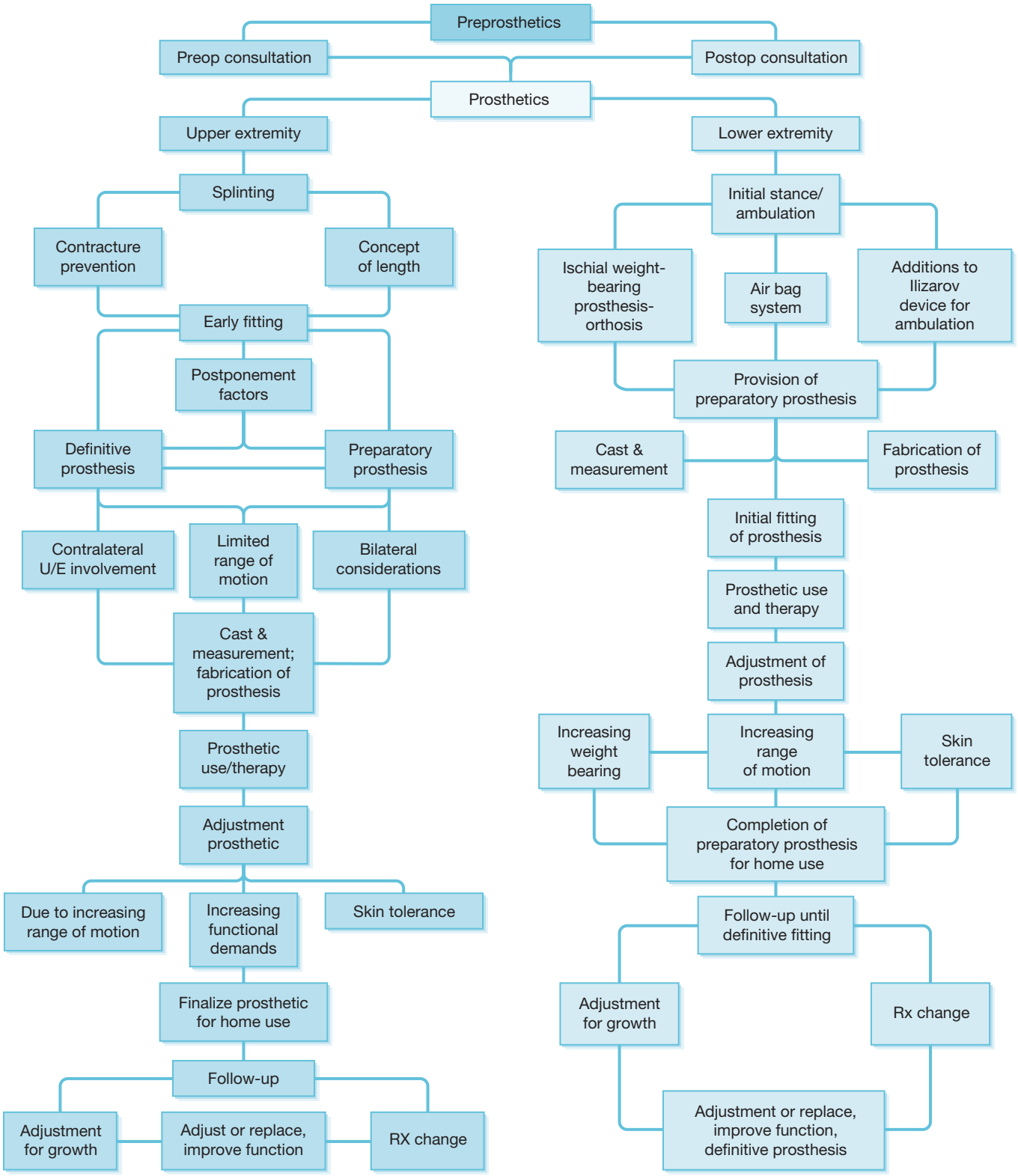

Fig. 47.20 Algorithm showing the process of prosthetic evaluation and fitting.

Fearmonti et al. have compared several scar assessments and individual scar measurement devices and have highlighted their insufficiencies and limitations.[100] A comprehensive, reliable, and valid burn scar assessment that is inclusive of all major scar characteristics relevant to burn rehabilitation has yet to be developed.[101] Individual scar characteristic assessment devices may, in some instances, show some reliability and validity; however, they are cost-prohibitive and impractical to use in the clinic on a daily basis.[102]

TREATMENT OF HYPERTROPHIC SCARS

To date, hypertrophic scars remain very problematic and difficult to manage. Even though the mechanism of scar maturation is not yet well understood, clinically, the accepted protocol to treat hypertrophic scars includes the use of pressure therapy, which should be instituted early on in the maturation process of the burn scar. Means of pressure therapy include pressure garments, inserts, and conforming orthotics. Once the skin has healed enough to withstand shearing, massage and heat modalities may be utilized as an adjunct in scar management. The use of pressure in effectively depressing scars was well documented by Silverstein and Larson in the 1970s; their observations and studies sparked the near-universal use of pressure garments. When an active scar is compressed, it blanches, which indicates decreased blood flow in the area.[88] Less blood leads to decreased oxygen in the tissues, which in turns leads to decreased collagen production, which brings a balance between collagen synthesis and collagen breakdown (lysis). When a balance in the production and breakdown of collagen is established, the resultant scar appears flatter.[103] Kealey et al. conducted a prospective randomized study to compare the efficacy of pressure garment therapy in patients with burns. Patients were randomly assigned to receive either pressure garment therapy or no pressure garment therapy. Assessment of the maturity of scar included use of the Vancouver Burn Scar Assessment Scale. The results on 113 patients studied in the follow-up revealed no significant differences between groups when age, body surface area burned, length of hospital stay, or time to wound maturation were compared.[104] In addition to this study, other studies have reported problems related to lack of adherence and discomfort, blistering, ulceration or scar breakdown, swelling of extremities, and skeletal and dental deformity due to excessive pressures, which often leads to cessation of treatment, significant side effects, and deformity.[88,104–109]

On the other hand, studies have also reported benefits of pressure garments.[110–112] The reader is referred to various recent excellent review articles on the efficacy or lack of efficacy of pressure garments in the management of hypertrophic burn scars.[113,114] The reason for the absence of unequivocal evidence is that garments must be worn continuously for a least 23 hours a day, making compliance or adherence difficult.[18,107,114] In addition, the optimal pressure that must be applied to the scar for treatment is not known.[107,115–117] Thus the studies and debates continue, and, at least until more evidence is gathered, pressure therapy with the familiar elastic garments is still prescribed. Patients and families would no doubt feel relieved if the data eventually show that pressure does not make a significant difference in long-term outcomes. However, it should be noted that the studies thus far include neither the examination of burns over joints nor do they include burns of the hands, neck, and face. In addition, none of the studies to date addresses the use of pressure in the form of splints, another source of discomfort and tension for burned children and their families.

None of the known studies has yet broached the face with an attempt to determine the efficacy of pressure versus no pressure. Facial pressure garments in children may pose problems due to interference with growth.[118,119] We recommend that these patients should be closely monitored for normal facial and dental development by physicians, including dental specialists. The elastic hood and underlying silicone face pad present special problems for patients, and some extreme challenges for the adults trying to assist a burned child or adolescent. The elastic mask and hood, covering head, face, and hair, effectively hides the identity of the person wearing it. It is perceived by children as sinister, associated with "bad men" or monsters, and most children who have worn this garment can relay stories of being ridiculed by strangers who did not know the purpose of the garment. Emotional expressiveness, usually apparent in facial movements, is hidden by the hood. More than one child has explained nonadherence with the prescribed wearing of the elastic mask with a statement similar to "I want my friends to see me laugh." A study by Groce et al. compared the elastic mask and hood with silicone pad to the transparent silicone face mask and found no significant differences between the amount of pressure applied by each to the forehead, cheeks, and chin.[120] Many children have expressed a preference for, and seem to wear more readily, the transparent mask. This study should make it easier for them to be granted their choice—an important event during a time when so much is happening to them outside of their control.

PRESSURE THERAPY

As long as the scars are active, they may be influenced by pressure therapy. However, not all burn scars require pressure. Patients with burn wounds that heal within 7–14 days do not need pressure therapy. Those patients whose wounds heal within 14–21 days are closely monitored for pressure therapy needs and may be generally advised to use pressure garments prophylactically. A wound that heals after 21 days will require the use of pressure garments.[103] The correct amount of pressure in suppressing the hypertrophic scar has not yet been determined. Pressure of as little as 10 mm Hg may be effective in remodeling the scar tissue over time. Pressures over 40 mm Hg, however, may be destructive to tissues and cause paresthesias.[88] Early use of pressure therapy may improve scar outcome and accelerate time to scar maturity.[121] The use of conforming thermoplastics along with elastic bandages may also be utilized as means of early pressure therapy.[122] Once the wounds are almost or completely closed, tubular elastic bandages such as Tubigrip may be utilized. These tubular bandages are offered in different sizes and accommodate all anatomical circumferences. Care should be taken in applying these tubular bandages so that the fragile skin or the freshly applied skin grafts do not shear or that the minimal dressing underneath is not disturbed. The burn therapist should be aware that these tubular bandages are materials made of a single elastic thread spiraling through the weave of the fabric, and disturbance of the continuous elastic by cutting holes into it will alter the pressure gradient provided by these materials. The tubular elastic bandages should be doubled over the skin surface area treated to provide adequate pressure.[123] Early pressure application over the hand and digits can be accomplished through the use of thin, elastic, and self-adherent wraps such as Coban (Fig. 47.21).

Fig. 47.21 A Coban wrap can be used to decrease edema and aid in the effective management of hand scar hypertrophy.

This form of pressure is excellent for adult and pediatric patients for controlling edema, and it aids in the early scar management of hands when the shearing forces of a glove cannot be tolerated. Small children are excellent candidates for Coban gloves versus a garment glove because of compliance issues, comprehension of instructions in assisting with the application of a custom glove, and difficulties in obtaining accurate measurements for a custom glove. Coban may be applied over the burn dressings or directly onto the healed digits. The burn therapist needs to be aware that if Coban is wrapped too tightly, it may deform the interosseous structures of the healing hand. However, if Coban is wrapped too loosely it may encourage swelling of the hands when used in combination with arm elastic garments. Coban strips are pre-cut approximately twice the length of the digits to be wrapped. Each strip is wrapped in a spiral fashion beginning at the nail bed of each digit, overlapping half of the Coban width and ending in the adjacent web space. Each fingertip needs to be exposed so that blood circulation can be monitored at all times. The Coban is stretched from 0% to 25% of the entire elasticity of each strip. Once all web spaces are covered, the rest of the hand is wrapped with Coban, extending approximately 1 inch past the wrist joint. No skin areas should be visible once the Coban glove is completed. If small hand areas remain uncovered, a small piece of Coban is stretched over the area and adheres to the rest of the Coban. When the glove is completed, the therapist should very superficially lubricate the entire glove with lotion to eliminate the adherent effect of the Coban and allow for the functional use of the hand. Coban should be removed on a daily basis by the therapist or caregiver. Removal of Coban should be done carefully by cutting off or unwrapping each digit individually to avoid disturbing any wound healing.

The use of prefabricated interim pressure garments is widely accepted and utilized in burn rehabilitation. These garments are available commercially from different companies, and they include pieces for the entire body. Interim garments, which are made of softer materials, introduce the burn patient to circumferential pressure and protect newly healed skin. Another reason for using these

Fig. 47.22 Custom-made pressure garments may be fabricated for the entire body.

garments prior to ordering custom-made garments is to allow for the patient's weight to stabilize (post-acute hospitalization) and any remaining edema to subside. In some cases where obtaining custom-made garments on regular intervals (approximately 12 weeks) is not an option, the recommendation should be that interim garments should be the choice for long-term pressure therapy. Once the patient's weight has stabilized, edema has subsided, and the skin is able to withstand some shearing (approximately 3–4 weeks post-wound closure), measurements are taken for the fabrication of custom-made pressure garments (Fig. 47.22). Today, several companies specialize in the fabrication of these garments. Clinically, custom therapeutic pressure for the prevention, control, and correction of scar hypertrophy averages 24–28 mm Hg, which is approximately equal and opposing to the capillary pressure (25 mm Hg). At this pressure level, many researchers believe that scars may be altered.[107] In order for pressure therapy to be effective, pressure garments need to be worn at all times, day and night. They should only be removed for bathing and on occasion during exercises should they interfere with movements. Each order is duplicated so one set of garments can be worn while the other is being washed. Today, pressure garment companies offer multiple colors of materials and, for the pediatric population, cartoon characters may be sewed on the garments to make them cosmetically appealing and improve patient compliance.[124,125] The burn therapist should choose a reputable company that provides excellent service and support for the patient and the therapist. The company's willingness and flexibility to manufacture nonstandard garments, availability of special options, cost, and turnaround time should be taken into

consideration when selecting the burn center's pressure garment provider.[126]

INSERTS

Inserts are widely utilized in burn rehabilitation as an adjunct to achieving effective pressure over certain anatomical locations where pressure garments do not provide adequate pressure. These locations include concave body areas such as the face, neck, antecubital fossae, sternum, palm of the hands, web spaces, upper back, and arches of the feet. These materials come commercially prefabricated or may be custom-made by the burn therapist. Inserts come in different forms, such as silicone/nonsilicone gels or gel sheets, elastomers, putties mixed with a silicone catalyst, skin care silastic pads, foam, and even in the form of hard thermoplastic materials contouring to different anatomical locations. The experienced burn therapist chooses the appropriate insert material best suited for the patient according to the stage of scar maturation and skin sensitivity. Generally, pressure therapy begins with a soft, thin, and elastic insert and progresses to a more rigid insert in depressing the more unyielding burn scar. Inserts need to be worn underneath pressure garments, starting with a few hours of application and progressing as tolerated toward a 23-hour application.[127] The inserts should extend approximately 5 mm beyond the scar margins and should be applied for several hours the first day then increased by 2-hour increments every other day until the patient is able to wear it for up to 23 hours per day.[128] They should be removed frequently for cleaning (warm water and soap), to avoid scar maceration and skin breakdown. Patients may be allergic to certain insert materials so the burn therapist may try different inserts until one is found to be best tolerated by the patient's skin. In cases of scar maceration, blisters, skin breakdown, contact dermatitis, a rash, or an allergic reaction, inserts should be removed immediately until healing occurs. Silicone, a polymer based on the element silicon, appears to be the trend in the treatment of hypertrophic scars. To date, the mechanism of how silicone affects the burn scar is not known. Clinically, silicone has been observed to depress the height of hypertrophic scars, prevent shrinking of fresh skin grafts (hard elastomer silicone pads vs. silicone gel pads), and increase the pliability of scars, thus allowing for increase in the ROM of affected joints. Silicone, being occlusive, may cause the collection of excessive moisture and cause skin maceration if not removed frequently for cleaning and drying. Its disadvantages are that it is very expensive and short-lived.[129–131] The therapist should look for silicone gel pads with a nonshearing protective medium on the nonskin surface in order for the gel to last longer. Also, buying larger gel pads and cutting them to fit the patient's need may be a cost-effective method for working with today's shrinking clinic budgets.

Other insert materials include liquid silicone elastomer, which when mixed with a catalyst forms a solid but elastic insert (Fig. 47.23). The experienced therapist is able to create custom inserts for difficult anatomical locations such as the face and web spaces using this technique. Prosthetic Foam is a liquid-based silicone elastomer which, when mixed with a catalyst, solidifies in the form of a very pliable foam insert that works best for the palm of the hands, where function needs to be preserved while pressure is applied. These foam inserts also work best for applying pressure to contour surfaces on the face (around the eyes, mouth, and nose) while protecting these sensitive areas from excess and rigid pressure. Elastomer putties such as Otoform K or Rolyan Ezemix form semi-rigid but still elastic inserts for different areas of the body where the scar can tolerate more pressure, such as in the web spaces to prevent syndactyly.[130]

Fig. 47.23 Silicone elastomer inserts for the dorsum of the hand and web spaces are utilized for the prevention of syndactyly and depression in scar tissue.

High-thermoplastic transparent masks were developed in 1968 by Padewski to be applied directly to the face to prevent, control, and reverse scar hypertrophy. These masks require the moulaging of the patient in creating a negative facial mold. A positive mold of the face is fabricated with the use of plaster. The patient's positive facial mold is then sculpted in an attempt to recreate the patient's nonburned face. A high thermoplastic material such as Uvex or W-Clear is then pulled over the positive mold to create the transparent face orthosis (Fig. 47.24A). Holes for the eyes, nose, and mouth are cut. The transparent face orthosis is worn with various harness systems designed to secure it to the face to address facial scar management.[132] The use of three-dimensional scanners can replace the traditional methods of face orthosis fabrication. Using a scanner greatly reduces patient anxiety by achieving the same accuracy as moulaging in a fraction of the time without physically touching the patient's face. The scan is sculpted on a computer and a positive tool is manufactured out of foam off-site. The positive tool is then sent to the facility for face orthosis fabrication. In the past, scanners were so large that facilities had to dedicate an entire room to their use; today, scanners are small enough to fit in a portable case and are run by laptops. These newer portable scanners give a therapist the freedom to scan patients in any setting in the hospital including intraoperatively. In cases of significant scar hypertrophy on the face, the positive mold is sculpted sequentially over a period of time to avoid excessive pressure over facial scar that could lead to skin breakdown. A silicone elastomer face mask may be created utilizing the existing positive facial mold and is worn under facial pressure garments

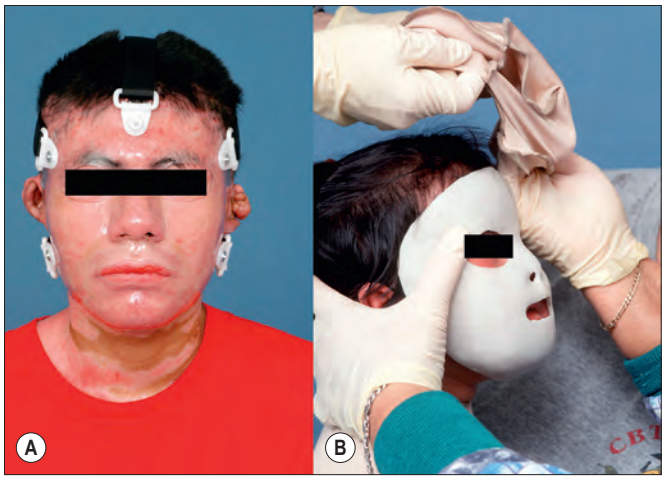

Fig. 47.24 (A) A Uvex clear face mask or **(B)** a silicon elastomer face mask provides pressure to the face to prevent scar hypertrophy and preserve facial features.

(Fig. 47.24B). The use of the clear and silastic masks is preferred over the use of just a facial garment because these masks provide conforming pressure around facial openings (eyes, nose, and mouth). Frequently, the burn therapist manufactures the clear orthosis to be worn during the day and the silastic mask along with the facial garment to be worn at night.[17,18,133,134]

BURN SCAR MASSAGE

Once the burn scars have matured enough to tolerate shearing forces, massage may be incorporated into the scar management regimen. Scar massage is an effective modality for maintaining joint mobility in the case of contractures. It aids in softening or remodeling the scar tissues by freeing adhering fibrous bands, allowing the scars to become more elastic and stretchy, thus improving joint mobility. Initially, the therapist may utilize a nonfrictional massage applying mostly stationary pressure to skin blanching and mobilizing the skin surface without friction. Utilization of lubricants during this massage technique should be avoided. As the skin begins to tolerate frictional massage, the scar tissue is manipulated in circular, parallel, and perpendicular motions, using a lubricant and mobilizing the skin to blanch when performing the desired technique.[135,136] Clinically, scar massage is found to alleviate itching and is utilized for desensitization purposes. An electrical massager with a heat attachment may be used along with lubrication because heat and massage in combination may increase scar pliability. Massage should be performed at least twice daily; the recommendation is three to five times daily for 5–10 minutes on each treated body surface. The burn therapist should frequently assess the skin condition to avoid further injuries. The patient and/or family are instructed on home massage techniques, and electrical massagers may be issued for home use. To decrease the effects of scar tissue, a burn therapist must utilize all available options to achieve a functional outcome. Therapeutic heat is the most common modality used in burn scar management. Application of heat may permit easier elongation of scar tissue through increased extensibility of connective tissue.[137] Heat relaxes tissues and makes them pliable in preparation for mobilization. Heat modalities may include hot packs, paraffin wax, fluidotherapy, and ultrasound. Even though the use of therapeutic heat as an adjunct to rehabilitation is well-documented, therapeutic heat modalities are infrequently utilized in burn rehabilitation.[138,139]

Caution should be used in the application of heat modalities on patients who have sustained a burn injury. Patients may not be able to tolerate heat over areas of healed or grafted burns due to hypersensitivity. Conversely, patients with diminished sensation are unable to determine if the temperature is appropriate and are at risk for further injury. Although caution needs to be taken, the use of therapeutic heat in burn patients can provide an effective method for increasing burn scar extensibility.

The use of passive stretch in conjunction with therapeutic heat greatly increases the effectiveness of the treatment. Studies have shown that the use of therapeutic heat during a slow load prolonged stretch is an effective method for attaining rapid and lasting increases in ROM when compared to low load prolonged stretch alone.[140] Warren et al. reported that low loads for prolonged periods of time were found to produce significantly greater residual length in rat tail tendon, especially at elevated temperatures.[141]

Hot packs can provide superficial heat to burn scars and assist with stretching contractures. Common treatments in burn rehabilitation include using hot packs alone before treatment or in conjunction with therapeutic exercise such as active ROM or prolonged stretch. Because of the shallow depth of heat penetration, hot packs may have little effect on deeper layers of scar tissue.[137]

Ultrasound has been used by rehabilitation therapists to increase temperatures deep within the tissue. Reported benefits of ultrasound in the treatment of burn scar include increased extensibility of collagen tissue, increased blood flow, and elevation of pain thresholds.[137] Application of topical therapeutic ultrasound to scar tissue has been reported to produce a tissue temperature rise that leads to an increase in the extensibility of collagen.[142] The combination of ultrasound and passive stretch was found to further increase tissue elongation.[137] Paraffin is an effective heat modality used most commonly for the hands or feet. Heated paraffin encourages collagen extensibility and may also be beneficial because of the softening of the scar by the mineral oil in the paraffin.[137] The use of passive stretch in conjunction with paraffin has been shown to increase joint ROM and was found to make patients' skin noticeably softer and more pliable after use.[143] Similar to other heating modalities, paraffin has been found to increase ROM in conjunction with stretching compared to stretching alone.[144]

Burn scar management is a complicated and lengthy process, and, for it to be successfully completed, the patient and caregivers should be committed to follow the therapist's recommendations. Extensive training should take place addressing the use and care of pressure garments, inserts, lubrication, and other therapeutic scar management procedures to be performed by patients and their caregivers. Lubricants that do not contain perfume and other skin irritants should be selected and applied (at least 2–3 times daily) to the healing skin. Lubricants with a sun protection

factor (SPF) of at least 15 are recommended.[145] Written instructions with pictures and diagrams along with videos addressing scar management should accompany the patient home on discharge from the hospital. Follow-up visits to the burn or rehabilitation clinic for the assessment of overall recovery, including garments, inserts, and other home therapeutic interventions, are needed so that the patient may successfully complete his or her burn rehabilitation during the first two years after the injury. The therapist's knowledge, creativity, and continuing research in improving the currently existing scar management techniques may be the key to positive outcomes in pressure therapy.

THERAPEUTIC EXERCISE

Burns often result in devastating injuries that severely affect a person's ability to perform functional activities through severe deconditioning, ROM limitations, weakness, and fatigue.[146,147] Therapeutic exercise is one of the central interventions used by physical and occupational therapists to combat the multitude of problems associated with burn injuries. Therapeutic exercise is defined as scientific supervision of bodily movement with or without apparatus, for the purpose of restoring normal function to diseased or injured tissues.[148] The use of therapeutic exercise in conjunction with a comprehensive rehabilitation plan helps to prevent deforming contractures and to maintain strength in both involved and uninvolved extremities.[149]

Even though painful and extensive therapy is required during the long rehabilitation process, the results are for the most part dependent on the patients' and families' understanding, involvement, and dedication to the treatment.[138]

The goals of therapeutic exercise in burn rehabilitation are to:

- reduce the effects of edema and immobilization,
- maintain functional joint motion and muscle strength,
- stretch the scar tissue,
- return the patient to optimal level of function.

Exercise prescription is an ongoing process that is altered according to the patient's medical status and changing needs.[150] In the conservative treatment of burn wounds, a vigorous physical therapy program is instituted immediately so as to maintain function.[151] Postoperatively, exercises involving autografted skin over joints are usually discontinued for 4–5 days. Escharotomies, fasciotomies, heterografts, and synthetic dressings are not contraindications for exercise.[152] Early mobilization to decrease edema, proper exercise techniques, and accurate documentation of function are more important than the type of wound closure.[151]

One of the most common and clinically significant complications after severe burn injuries is burn scar contractures that lead to decreased ROM and joint deformities.[147] Scar contracture and joint mobility limitations are the result of the shortening of immature connective tissue. Therapy aims to prevent deformity and the subsequent limitation of movement. In circumferential burns, both the flexor and extensor surfaces are at risk of contracture. Therapeutic exercise in conjunction with splinting should promote agonist and antagonist movements around those joints to maintain mobility.[153] Treatments are tailored to each individual patient, with independent living being the ultimate goal throughout the rehabilitation continuum.

Therapeutic exercise begins immediately following the burn injury. For a patient being treated conservatively, movement helps maintain strength and ROM and aids in circulation and healing. Exercise is initially painful, and the very first repetition is often the most difficult. Discomfort is due to stretching skin that has lost its natural lubricating mechanism and has become dry and tight. Movement itself decreases pain. Each subsequent repetition will be easier as the skin stretches and the muscle pumping action of active movement helps resolve edema, thus significantly reducing pain.

To show the progression of exercise throughout a patient's stay after a burn injury, exercise will be discussed in terms of the rehabilitation phases described by Richard.[154]

Exercise During the Acute Rehabilitation Phase

The acute rehabilitation phase is defined as the time from admission until about the time that a patient's wounds are 50% closed or skin grafting for wound closure has begun.[154] Early therapeutic intervention on the burn unit has long-term implications for restoration of function.[146] Early initiation of burn rehabilitation with an emphasis on several factors including early ambulation and a focus on preventing joint contracture through stretching exercise has been shown to be effective in reducing contractures.[155]

During the early part of the acute rehabilitation phase, the exercise goals are resolution of edema, maintenance of joint mobility, and prevention of respiratory complications, which can often be performed without interfering with life-saving measures.[150]

During this phase, patients spend long periods in bed due either to their medical status or postoperative immobilization after skin grafting. Results of patient immobilization due to burn injury include decreased cardiovascular fitness, disuse osteoporosis, increased risk of thromboemboli, pulmonary complications, decubiti, and muscle atrophy.[150] Due to the patient's medical status during the acute rehabilitation phase, the patient may not be able to tolerate vigorous exercise. It is therefore recommended that exercise programs focus on increased frequency of treatment sessions that are shorter in duration.

Active ROM exercises are significant in the reduction of edema in the extremities and can begin within 24–72 hours after burn injury.[150] Active ROM exercise is performed independently by a patient. This is the form of exercise most recommended because it stretches healing skin and provides strength-inducing benefits. Frequent exercise performed actively (with voluntary muscle contribution) by a patient promotes the greatest increase in movement. Active ROM exercises are vital during burn rehabilitation to counteract the effects of prolonged bed rest and muscle atrophy, as well as to maintain ROM and prevent contractures. The best exercise for a joint affected by burns is complete active ROM.[149] Active ROM more adequately addresses the patient's functional physiological and psychological needs than does passive ROM.[156] Although active ROM may be a superior form of exercise for a burn patient, its use during the acute burn phase may be somewhat limited. Medical status and intubation, as well as fear and anxiety may all make active ROM exercises difficult to carry out.

If a patient can actively participate in movement but cannot move actively through his or her full ROM, active-assistive ROM is appropriate. Active-assistive ROM exercises utilize the same principles as active ROM, but a patient is assisted by an outside force (therapist or assistive device) to achieve the full ROM. A patient will achieve improvements in strength and ROM, but not equal to those provided by active exercise. Therapists should use their judgment in letting the patient perform as much of the exercise as possible actively and only assisting when needed.

While active range may be the most beneficial, it can be difficult to initiate after admission due to the patient's medical status and level of responsiveness. Critically ill, septic, and heavily medicated patients are often unable to cooperate in active exercises.[150] In these conditions, passive exercise is used to maintain ROM, assess joint motion, and elongate tissue.[157] Passive ROM exercises are an important factor in preventing contractures and maintaining ROM when a patient cannot or does not willing actively move through his or her available ROM. Although passive ROM requires less energy expenditure, it does not fulfill as many of the patient's needs as active exercise.[156] The use of a continuous passive motion (CPM) device has been documented to be an effective modality for improving joint ROM.[152] Rehabilitation advances have shown CPM treatment to be a viable option because of its benefits to soft-tissue remodeling, joint nutrition, wound healing, and venous dynamics.[158,159] Care must be taken when applying CPM devices to reduce risk of shearing against skin.

Early exercise activity is beneficial in shortening the acute care hospitalization stay post burn injury, with studies currently being researched further. Strengthening exercises are of great importance throughout the continuum of burn rehabilitation to combat muscle atrophy and can begin during the acute rehabilitation phase. Resistive exercises are used to maintain or increase strength, ROM, proprioception, and coordination.[160,161] Due to the patient's level of consciousness and comprehension during the acute rehabilitation phase, strengthening exercises may be difficult to institute and should start with simple exercises progressing as the patient's status improves. Isometric exercises are beneficial to maintain muscle strength when a patient is on bed rest and are comfortable for the patient to perform while requiring a minimal amount of energy expenditure.[157] The benefit of isometric exercise is that the patient will not "forget" how to contract the muscle, a common phenomenon occurring with periods of prolonged immobilization. Isometric exercise also helps in maintaining muscle strength. Manual resistance can also be applied gently by the therapist as the patient contracts his muscles and attempts motion against the resistance, or the patient is asked to maintain a position and then resistance is applied.[150]

Another important aspect of a patient's recovery is the ability to ambulate. Ambulation can begin as soon as possible after admission as long as the patient is medically stable.[160] Severe weakness, impaired motor control, decreased cognitive status, pain, and risk of graft shearing are all factors that can make ambulation a difficult task.[162] An Unna boot may be applied at time of skin grafting to the lower extremity and contribute to early patient ambulation. The Unna boot is a bandage impregnated with calamine lotion and zinc oxide which, when applied over the grafted lower extremity (six layers), hardens to a semi-rigid dressing resembling a plaster cast. This cast-like total contact dressing provides uniform support to the fresh skin graft and facilitates early ambulation. An Unna boot may be applied for up to 7 days post-grafting, though it could be removed earlier for inspection of the skin graft. If removed, a new Unna boot needs to be fabricated depending on the burn center's lower-extremity postoperative immobilization protocol.[163]

Primary goals of ambulation include maintaining lower-extremity ROM, reducing the risk of thrombophlebitis, preventing decubiti, providing mild cardiovascular conditioning, and maintaining or increasing strength and endurance.[150] Ambulation exercises may also help increase appetite. In addition, ambulatory patients have fewer problems with lower-extremity contractures and physical endurance.[152]

All wounds must have the proper dressings applied prior to ambulation. Lower-extremity burn wounds should be wrapped with elastic bandages in order to facilitate capillary support. Wrapping that incorporates the figure-of-eight pattern has been reported to provide better pressure than the spiral wrap, perhaps due to increased vascular support.[164]

As with other exercise, proper positioning facilitates proper gait.[153] The patient who has been allowed to assume a position of comfort will have difficulty extending the hips and knees during ambulation. The ankle may be tight, limiting plantigrade position when in the upright position. If the joints are in normal alignment, the amount of pain and energy needed to mobilize these joints are greatly reduced.

In the past, it was common practice to have patients placed on bed rest for long periods of time after autograft application to the lower extremities, approximately 5–10 days after autograft application.[165–167] More recently, however, several studies have shown the benefits of earlier postoperative ambulation.[166,168–171]

The proposed benefits of early ambulation include decrease in the incidence of pulmonary embolism, deep vein thrombosis, and joint stiffness, as well as a shorter hospital length of stay.[168] Other benefits include maintaining strength and endurance, increased independence, a decrease in fear, and fewer complaints of pain.[170]

In preparing for ambulation, therapists may use a tilt table with patients who lack the capacity to stand and mobilize their lower extremities (Fig. 47.25).[162,164,172,173] Tilt tables provided passive weight-bearing with no active muscle contraction needed. Tilt tables provide gradual weight-bearing through the lower extremities and are also an effective treatment for orthostatic hypotension.[162] However, therapists should keep in mind that a tilt table represents a mostly passive introduction of gravity to the body and does not promote proper alignment of the musculoskeletal system. Creative efforts and aggressive techniques are sometimes necessary to encourage ambulation in patients who first appear incapable or unprepared to begin erect weight-bearing exercise.

Patients tend to perform much better when given an achievable goal, such as walking a specific distance or to a certain place. Children do well when provided with a desired incentive such as an age-appropriate activity or a game.

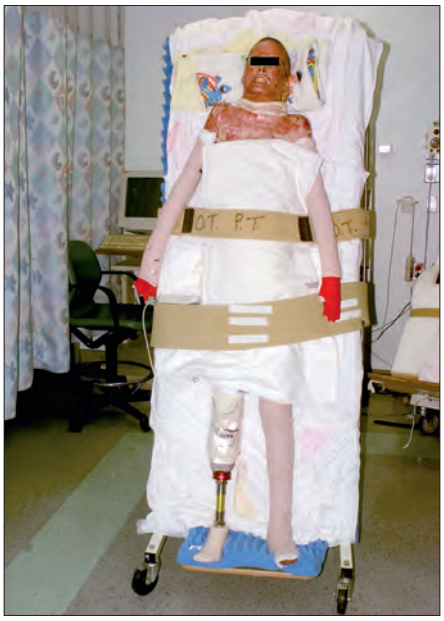

Fig. 47.25 The tilt table may be utilized prior to ambulation for those patients who may have difficulty assuming the upright position.

Frequent rest periods may be necessary secondary to decreased endurance levels or pain.

Exercise During the Intermediate Rehabilitation Phase

The intermediate phase is the time surrounding closure of the wound and extending up until the time of complete wound closure.[154] The prevention of functional impairments becomes the focus of therapeutic exercise as patients begin to achieve wound coverage. The goals of exercise during this timeframe include the stretching of healing skin, maintaining full joint ROM, preserving motor skill coordination, promoting functional independence, and maintaining strength and endurance to minimize muscle atrophy.[150,174]

As wounds close, scar formation begins, which leads to contractures that limit ROM and impede function, which makes exercise even more important. As a patient's medical status continues to improve and operations become less frequent, more time can be allotted to spend in rehabilitation. Increased alertness and improved medical status also lead to increased involvement of the patient in rehabilitation. As the patient advances medically, the therapeutic course should become more challenging.

While purely passive ROM should be utilized less during the intermediate phase of rehabilitation due to the patient's increased ability to move actively, it still serves an important purpose. Passive ROM provides an opportunity to assess joint movement and determine if the patient can attain as much movement actively as the therapist can passively.[160]

Another form of passive movement that can be utilized by a rehabilitation therapist is the sustained stretch. Sustained stretch becomes an important intervention as the formation of burn scars leads to contractures.

Sustained stretching exercises are performed with a slow, prolonged force. Gentle, sustained stretch is more effective than multiple repetitive movements in gaining length of burned tissues. Slow sustained stretch is considered to be one of the most effective methods to combat the strong destructive forces that lead to contracture formation.[175] Connective tissue has the characteristic of plastic elongation under constant tension. Therefore, correction of contractures around joints can be accomplished most effectively by the application of prolonged stretching to the shortened connective tissues.[176] When applying a sustained stretch, two factors may be considered when applying pressure to an extremity: blanching of the scar tissue and the patient's response.[160] While this is an effective treatment for ROM limitations, it can be uncomfortable or painful for patients. It is important to impart enough force on the affected extremity to produce plastic elongation without causing trauma to the tissues or to the patient.

Strengthening exercises move from manual resistance toward the use of weights and resistive tubing. Areas to be concentrated on should include areas of weakness found during strength assessments as well as muscles opposing scar tissue contractures.[157]

Concerning ambulation, it is important that the therapist set daily goals for the patient to achieve and to encourage the patient to walk farther while providing the least amount of support needed. As the patient begins to ambulate more, it is important that the rehabilitation therapist frequently assesses the patient's gait. Any gait deviations must be identified and corrected before they become lasting habits.

As patients begin to ambulate farther with less assistance, they become more confident in their abilities. Increased independence provides the patient with a sense of functional independence.[156]

Long-Term Rehabilitation Phase

The long-term phase occupies the timeframe from wound closure or discharge from the acute hospital setting until such time as the patient has received maximal benefit from rehabilitation services.[154]

As patients near discharge from the acute hospital setting, they will be given more responsibility over their exercise program. As patients progress, they will be expected to perform beyond their daily rehabilitation treatment sessions. Patient compliance with home exercise programs is vital to increasing functional independence.

During the long-term rehabilitation phase, patients should progress to independently ambulating community distances. Gait pattern should be refined to become more efficient without any gait deviations. If the patient is able to progress further, rehabilitation therapists can challenge the patient by having him or her ambulate on uneven surfaces, navigate around various obstacles, and climb stairs. It is important that the patient be able to ambulate in normal surroundings, not just in the confines of the rehabilitation department.

Most burn rehabilitation programs emphasize functional gains and prevention of contractures, with only modest attention to aerobic conditioning.[177] If ROM is lacking, the therapist's priority should be to treat the limitation in motion rather than strengthening the patient because

normal healthy muscle is unable to generate the force required to elongate burn scar tissue.[157]

The Role of Exercise Physiology in Burn Rehabilitation

EXERCISE FOR THE OUTPATIENT

This section describes the methodology used in designing an exercise training program for persons with severe burns who have been discharged from the hospital. Exercise training is defined here as "a planned, structured and repetitive body movement done to improve or maintain one or more components of physical fitness."[178,179] The evidence for the use of exercise in the outpatient setting and the methodology presented here are based primarily on the outpatient exercise program implemented in severely burned children at Shriners Hospitals for Children in Galveston, Texas, and in some severely burned adults.[180] This exercise program is supplemented by physical and occupational therapy. The program has proved beneficial in children 7–18 years of age.[180,181] In addition, the effects of a music- and movement-based exercise program on children younger than 7 years of age has been assessed in a small study also performed at Shriners Hospitals for Children in Galveston. The effects include increases in as well as maintenance of ROM in children who participated in a movement and music program versus those who did not.[182] The principles in designing an exercise program for children and adults with severe burns is based largely on guidelines offered to healthy, nonburned children and adults (Fig. 47.26).[178,179,183–186]

EXERCISE EVALUATION

It is important to perform an initial evaluation of risk factors and/or symptoms for various chronic conditions concomitant to the burn. These include pre-existing conditions such as chronic cardiovascular, pulmonary, and metabolic diseases. The objective of the exercise evaluations is to obtain information to optimize safety during exercise testing and training and also to develop a sound and effective exercise rehabilitation program.

Health screening before exercise evaluation should begin with the collection of subjective data. This should include evaluation of exercise or sports interests, objectives, level of activity prior to burn, functional limitations (e.g., loss of digits, lower-body bilateral amputee), and other pertinent information. To our knowledge, there are no burn-specific physical activity questionnaires. However, simple questionnaires for assessing pre-burn physical activity exist and can be modified to fit a specific given population.[187–189] This evaluation can consist of muscle strength, cardiopulmonary status, and muscle/joint flexibility testing. The information gathered during the subjective and objective evaluations can then be used to design a structured exercise program or plan to be carried out at home or at an exercise facility. Finally, a plan to periodically re-evaluate subjective and objective data and the exercise program itself should be incorporated.

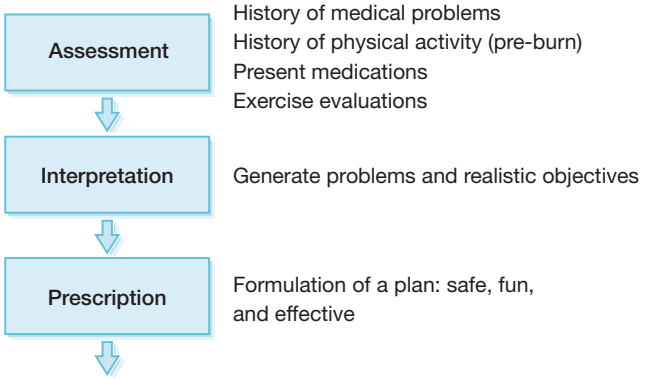

Fig. 47.26 Basic diagram depicting various components involved in the design of an exercise program.

Subjective Data

A patient's limitations or problems should be characterized. Obtaining a history of pre-burn physical activity or habits, present medical complaints, symptoms, and limitations is crucial to develop a sound exercise program. Symptoms or limitations that may affect exercise tolerance may include pain during ambulation, weakness in ambulation, itching, joint contractures, amputations, shortness of breath, or easy fatigability. In addition, the therapist should note present medications and the possible effects of these. Following the evaluation of subjective data, an exercise evaluation to gather objective data on the patient's exercise or physical capacity should be performed.

Objective Data

Assessment of objective data includes age, height and weight, percent TBSA burn, and percent full-thickness burn. Variables before, during, and after a cardiopulmonary exercise test (CPET) should be obtained if possible. These include heart rate, blood pressure, Borg's rated perceived exertion (RPE), basic electrocardiogram (ECG), and spirometry.[190,191] However, if a CPET is not possible, an effective exercise program can still be designed. Assessment of upper and lower body muscle strength should also be done. This includes assessment of peak strength levels (if possible), as well as determining the loads or weights that will be used during the resistive component of the exercise program. The assessment of peak muscle strength can be accomplished during knee or elbow extension but can also be accomplished during a handgrip.[180,192,193] These tests involve peak-to-maximal efforts, and good communication between patient and tester must exist. In addition, a certain level of developmental mental maturity must exist in order for many of these objective data to be maximally helpful. We recommend a chronological age of 7 years or older, although children as young as 3–4 have also been tested successfully.[194] Finally, major muscle/joint flexibility should be assessed using measures such as sit-and-reach or

goniometry for ROM. Other types of tests may include neuromuscular tests such as gait analysis, balance time, or reaction time. Finally, assessment of functional performance can also be done, such as sit-and-stand scores, timed walk or jog, and/or lifting. The results of these evaluations will be used to identify major problem areas, write an exercise prescription, design the exercise program, and assess progress during and after it.

EXERCISE TESTING

The objectives for exercise testing involve many factors. The primary objectives during cardiopulmonary testing are to evaluate physical work capacity and cardiorespiratory or aerobic fitness, observe cardiorespiratory and metabolic responses, establish bases for an appropriate exercise prescription, and assess changes in fitness due to exercise training. The primary objectives during muscular function testing include measuring muscle strength (absolute and relative to body weight), measuring antagonist-to-agonist muscle ratios, assessing changes in body composition (lean mass, fat mass, and bone density), and providing a basis for the progressive resistance exercise prescription. Exercise testing should be conducted prior to the start of any exercise rehabilitation program and again at the end to evaluate its efficacy. Sometimes if the program is of long duration, a mid-point evaluation can be done.

Peak Oxygen Consumption or Aerobic Exercise Capacity. All patients should undergo a standardized exercise test to objectively evaluate peak aerobic exercise capacity. We use the treadmill exercise test and the modified Bruce treadmill protocol. Note that other treadmill protocols, such as the "ramp protocol," can also be used.[195,196] In addition, if it is not possible for the patient to be tested on a treadmill, a cycle ergometer or arm ergometer can also be used to evaluate or assess physical conditioning before starting exercise rehabilitation or a training program. In addition, estimation of aerobic capacity is also possible with exercise field tests such as the Cooper 12-minute test or the 1.5-mile run test. Heart rate can be easily obtained with monitors. Oxygen consumption (VO_2) should be measured if possible, but requires more expensive equipment that can perform continuous breath-by-breath analysis of inspired and expired gases, flow, and volume. For the Bruce protocol, speed and grade begin at 1.7 mph and 0%, respectively. Thereafter, the speed and level of incline are increased every 3 minutes. Patients are constantly encouraged to complete 3-minute stages, and the test is terminated when peak volitional effort is achieved. Additional variables that can be collected during the test include blood pressure, Borg's RPE,[197,198] basic ECG, and spirometry. The peak VO_2 and peak heart rate, together with resting values, can then be used to establish or guide the intensity at which patients will exercise during the program.

Strength Measurements. Isokinetic dynamometry strength testing should be performed to assess muscle function and to later evaluate progress. If using the Biodex Isokinetic dynamometer, the test can be done on the dominant leg extensors and/or the leg with burns. We recommend testing at various angular velocities, such as 150 degrees/s, 90 degrees/s, or 180 degrees/s. The patient is seated and his position stabilized with a restraining strap over the mid-thigh, pelvis, and trunk. All patients should be familiarized with the equipment before the actual test starts. We recommend that the procedure first be demonstrated by the person administering the test. Second, the test procedure is explained to the patient, and then the patient is allowed to practice the actual movement during three submaximal repetitions without load as warm-up. Third, after the three submaximal warm-up repetitions, 10 maximum voluntary muscle contractions (full extension and flexion) can be performed consecutively without rest in between. The amount of repetitions and the number of repetition sets can be varied. For example, we recommend 10 repetitions and two sets, with a 2-minute rest interval between sets. Values of peak torque, total work, and average power are calculated by the Biodex software system, and progress of muscle function can be monitored.

Three-Repetition Maximum Test (3RM)

Typically, before starting a resistive training program, it is useful to determine a safe and effective load for patients to use during workouts. To determine the amount of weight or load that can be used as a baseline or starting load, the repetition maximum (RM) method can be used. We recommend the three-repetition maximum load (3RM), which is determined as follows. After an instruction period on correct weight-lifting technique, the patient warms up with a lever arm and bar (or wooden dowel) and is allowed to become familiar with the movement. After this, the patient lifts a weight that allows successful completion of four repetitions. If the fourth repetition is achieved successfully and with correct technique, a 1-minute resting period is allowed. After the resting period, a progressively increased amount of weight or load is lifted at least four times. If the patient lifts a weight that allows successful completion of three repetitions, with the fourth repetition not being volitionally possible due to fatigue or inability to maintain correct technique, the test is terminated and the amount of weight lifted from the successful set is recorded as the patient's individual 3RM. We recommend the order of exercises to be from exercises that involve large muscle groups to ones that involve smaller muscle groups: bench press, leg press, shoulder press, leg extension, biceps curl, leg curl, and triceps curl. Another alternative is to bypass the 3RM test and use 8–12RM method or 15RM method. These methods are typically easier to implement in children.

Body Composition Measurement

Patients with severe burns lose a significant amount of lean body mass (LBM). Therefore assessment of LBM should be made. Additionally, assessment of bone mass and fat mass should be made. We assess body composition using dual-energy X-ray absorptiometry (DXA). DXA with pediatric software can measure the attenuation of two X-ray beams; one high energy, the other low energy. These measurements are then compared with standard models of thickness used for bone and soft tissue. Subsequently, the calculated soft tissue is separated into LBM and fat mass. This is a great measurement to also assess the progress of the program and, if applicable, nutritional interventions. However, the DXA machine is expensive. It is not known if other methods to measure body composition, such as underwater

weighing or bio-impedance, are applicable to patients with burns because of the presence of hypertrophic burn scars.

When to Implement an Exercise Program

Traditionally, a 12-week exercise training program has been implemented immediately after discharge.[199] However, we have also reported improvements in function and psychosocial health when the 12-week exercise program is implemented at the 6-month post burn time point.[200]

Recently we have started a small pilot study to add aerobic exercise to standard physical therapy and occupational therapy. The aerobic exercise is quantitative because it incorporates the use of an arm ergometer in which the revolutions per minute and the load in watts can be adjusted.

COMPONENTS OF AN EXERCISE PROGRAM

An exercise program typically consists of a warm-up phase, an endurance phase, recreational activities (optional), and a cool-down phase. While aerobic training activities should be done 3–5 days per week, complementary flexibility and resistance exercises may be performed at a lower frequency (2–3 days per week).[201] Flexibility exercises can be included as part of the warm-up or cool-down, or be done at a separate time. Resistive training is often performed on alternate days to aerobic training; however, both types of activities can be combined into the same workout session. Typically the warm-up period will be of approximately 5–10 minutes, though it can be longer. This will be followed by a stimulus or endurance phase of 20–60 minutes and a cool-down period of approximately 5–10 minutes. Aerobic and resistance training should be prescribed in specific terms of frequency, intensity, duration, and mode of exercise. Each of these terms will be discussed in greater detail later. An optional recreational game may occasionally substitute the endurance phase. However, because of potential difficulties in setting an appropriate intensity for an appropriate length of time, it is suggested that recreational activities be done to complement the endurance phase. If a recreational activity is added to the endurance phase, then shortening the endurance phase should be carefully considered, although maintaining a minimum of 20 minutes.

Warm-Up Stage

Prior to the endurance phase, a variety of very light exercises or low-intensity calisthenics should be done to improve the transition from rest to the endurance phase of the exercise session. The emphasis at the onset of an exercise session is to gradually increase the level of activity until the proper intensity is reached to begin the endurance phase. Stretching exercises to increase the ROM of the joints involved in the activity were previously included in the warm-up. However, recently, evidence has been introduced to contraindicate the inclusion of stretching during the warm-up period.[202,203]

In fact, evidence suggests that a pre-exercise warm-up that consists of only light aerobic exercise to increase body temperature is adequate for increasing flexibility before an exercise session.[179] For example, patients might walk moderately fast during the endurance phase, but might conclude the warm-up period with slow, easy walking. However, a moderate walk (e.g., 3.5 mph) can be a warm-up for a patient who jogs at 5.5 mph during the endurance phase. Heart rate may be monitored or assessed if needed to ensure that the warm-up activity is not too strenuous.

Endurance Stage

The endurance phase develops cardiorespiratory or aerobic fitness and includes 20–60 minutes of continuous or intermittent (minimum of 10-minute bouts accumulated throughout the day) aerobic activity. Duration depends on the intensity of the activity; thus moderate-intensity activity should be conducted over a longer period of time (≥30 minutes), and, conversely, individuals training at higher levels of intensity (i.e., vigorous exercise) should train for at least 20 minutes.[201] The most effective exercises for the endurance phase employ large muscle groups in activities that are rhythmic or dynamic in nature. Sports such as soccer, basketball, or tennis also have aerobic conditioning potential if a sufficient amount of time for inducing aerobic improvement is achieved (minimum of 20 minutes total). On the other hand, activities like golf and bowling are unlikely to elicit a cardiovascular training effect, but are enjoyable and may yield health-related, as well as psychosocial, benefits.

Recreational Activities

The inclusion of enjoyable recreational activities during (or immediately after) the endurance phase often enhances compliance with the exercise program. Game rules may need to be modified to accommodate skill level requirements and competition, and to ensure safety. The outcome of the game (winning or losing) should be of lesser importance than the safety, participation, and enjoyment of the patient. It is important to remember that recreational activities complement the endurance phase and should not consistently replace it. Recreational activities may also promote development or improvements in psychosocial health by increasing the patient's amount of social interaction.

Cool-Down Stage

At the end of the activity session, about 2–5 minutes of cool-down activities—slow walking and stretching exercises—are recommended to gradually return heart rate and blood pressure to normal levels. This period includes exercises of diminishing intensities: slower walking or jogging, calisthenics, and stretching exercises. This part of the exercise session is important in reducing the chance of a hypotensive episode after the exercise session, as well as other cardiovascular complications.

Exercise Prescription

Some basic exercise physiology principles should be kept in mind when designing an exercise program for burned patients. Two such principles are *progressive overload* and *specificity principles*. The progressive overload principle refers to the observation that a body system must be exercised at a level above that to which it is presently accustomed in order for a training effect to occur.[178] The system

or tissue gradually adapts to this overload. The typical variables that comprise overload include the intensity, duration, and frequency (days per week) of exercise. The principle of specificity refers to the concept that the training effect is specific to the muscle fibers involved in the activity. Specificity also refers to types of training used in a very specific manner to produce a very specific adaptation or outcome. If a muscle is engaged in endurance-type exercise, the primary adaptations are in capillary and mitochondrial numbers, which increase the aerobic capacity of the muscle. These principles are applicable to burned patients; however, it must be noted that a high intensity of exercise is not needed to achieve health-related benefits. On the other hand, to achieve athletic performance or competitive-related goals, moderate to high levels of intensity will be required. Another consideration that should be kept in mind when designing an exercise program is the patient's age. Prepubescent children are very different in their physiological and mental response to exercise training than are postpubescent children. Older adults also have different health and physical problems than younger adults. It is for these reasons that medical exams as well as exercise evaluations are strongly recommended prior to starting an exercise program. It is beyond the scope of this chapter to address these differences and/or problems. However, general guidelines for both children and adults are offered, and the reader should seek additional information for population-specific recommendations or position stands on exercise and physical activity from associations such as the American College of Sports Medicine (http://www.acsm.org/publications/positionStands.htm), the American Academy of Pediatrics (http://www.aap.org/), the American Medical Association (http://www.ama-assn.org/), or the American Heart Association (http://www.americanheart.org/).

AEROBIC TRAINING

Intensity

To improve aerobic fitness, generally the intensity of exercise should be between 65% and 95% of the peak heart rate or between 45% and 85% of the heart rate reserve (HRR).[204] The heart rate reserve is the difference between peak heart rate obtained during a CPET and resting heart rate. The range of heart rate values associated with the exercise intensity needed to induce an improvement in cardiovascular fitness is termed the "target heart rate zone."

The peak heart rate (HR_{peak}) is obtained from the CPET. However, when this is not possible, one simple method to estimate HR_{peak} is to use the formula (220 minus age).[178] This formula may not be applicable to young children, so we recommend that, in children, rated perceived exertion (RPE; see later discussion), together with the heart rate obtained during a maximal exercise capacity test, be used.

The RPE scale can also be used as a guideline in setting the intensity of exercise.[197] The RPE is a valuable and reliable indicator of both exercise tolerance and intensity. This method of monitoring exercise intensity is useful when it is impossible to obtain an HR_{peak} or if patients are on medications that affect heart rate, such as β-blockers. There are currently two RPE scales that are commonly used: the original or category scale, which rates exercise intensity on a scale of 6–20, and the revised or category-ratio scale of 0–10. It is reported that the category-ratio scale uses terminology better understood by the subject, thereby providing the tester with more valid information. It has been found that an aerobic training effect and the threshold for the start of anaerobic training are achieved at a rating of "somewhat hard" to "hard," which approximates a rating of 12–16 on the category scale or 4–5 on the category-ratio scale.[205] Finally, if a patient cannot use the heart rate method or the RPE method, the "Talk Test" can also be used as a highly consistent method to set and monitor intensity of exercise.[206]

The "Talk Test," or the point at which speech first becomes difficult, approximates exercise intensity almost exactly equivalent to the ventilatory threshold. The patient is advised to exercise at an intensity at which speech is comfortable. When speech becomes uncomfortable, one can assume, based on previous studies, that exercise intensity is consistently above ventilatory threshold or above the desired intensity of exercise needed for general improvements in fitness.[206] It must be noted that when setting the exercise intensity, safety and effectiveness are linked. An appropriate intensity should also be well suited to result in a long-term, active lifestyle.

Duration

The duration of an aerobic exercise session is closely linked to the intensity of the activity (i.e., a longer duration of low-intensity exercise can be accomplished than of high-intensity exercise). In general, the duration of exercise for burned patients once discharged should be from 5 to 20 minutes in the first week. This will depend on the patient's functional status and also pain tolerance.

If the patient tolerates up to 20 minutes, then this duration is appropriate. The objective should be 20–60 minutes of aerobic activity. This can be accomplished continuously or intermittently throughout the day, with a minimum of 10-minute bouts. Typically a duration of 20–30 minutes at between 40% and 50% and up to 85% of HRR (excluding time for warm-up and cool-down) should induce health and fitness improvements.[201,207]

In burned patients with extremely low aerobic capacity or endurance, four to six 5-minute bouts with rest periods between bouts will provide benefits. The duration of the exercise sessions (or bouts) can be progressively increased over time. However, as mentioned earlier, a high intensity of exercise or a very long duration of exercise is not needed to achieve health-related benefits, particularly during the initial stages of outpatient exercise rehabilitation.

Frequency

It is reported that deconditioned persons may improve cardiorespiratory fitness with only twice-weekly exercise.[201] However, it is generally agreed that optimal training frequency appears to be achieved with 3–5 workouts per week. The additional benefits of more frequent training appear to be minimal, whereas the incidence of lower-extremity injuries increases abruptly. For those exercising at 60–80% HRR, an exercise frequency of 3 days per week is sufficient to improve or maintain VO_{2peak}. When exercising at the lower end of the intensity continuum, exercising more than 3 days per week is not deleterious. Patients with extremely

low functional capacities may benefit from multiple short (5 days per week) exercise sessions. Clearly the number of exercise sessions per week will vary depending on the patient's limitations, but also on the patient's and caregiver's lifestyles.

Mode

The most important consideration in choosing the mode of exercise for the endurance phase of the sessions is to engage large muscle groups in activities that are rhythmic or dynamic. The greatest improvements in aerobic fitness result when exercise involves the use of large muscle groups over appropriate periods of time (Fig. 47.27). The mode of exercises includes treadmill walking/running, rowing, or cycling. If no treadmill is available, then walking or jogging at a track or field is appropriate. Swimming is also an appropriate mode of exercise, although closure of burn wounds should be ensured to minimize wound infection or the contamination of others. Endurance games are also appropriate modes of exercise.

Progression of Exercise

We recommend starting slowly and safely progressing in duration and intensity, but also in transitioning from early activities to activities that are more difficult to perform. This method of progression decreases the potential for inducing excessive muscle soreness that might cause new injuries or aggravate old ones. The emphasis on slow to moderate walking as the primary activity early in the fitness program is consistent with this recommendation, and the participant must be educated to not move too quickly into more demanding activities. For example, if the individual can walk about 1–2 miles without fatigue, then the progression to a walk-jog or jogging program is a reasonable recommendation.

The recommended rate of progression in an exercise conditioning program depends on functional capacity, medical and health status, pain tolerance, location of burns, age, individual activity preferences and goals, and an individual's tolerance to the current level of training. For burned patients, the endurance aspect of the exercise prescription can be divided into three stages of progression: initial, improvement, and maintenance.[179]

Initial Conditioning Stage. The initial stage should include light and moderate muscular endurance activities (e.g., 40–60% of HRR). These exercises typically have a low potential for injury and induce minimal muscle soreness

Fig. 47.27 Aerobic training should incorporate the use of large muscle groups over appropriate time periods.

and pain. Exercise adherence may be compromised if the level or intensity of exercises in the program is initiated too aggressively. The amount of time spent in this stage varies depending on the individual's adaptation to the exercise program. We recommend at least 4 weeks of initial conditioning. The duration of the exercise session during the initial stage may begin with approximately 15–20 minutes and progress up to 30 minutes, at least three times per week. Deconditioned individuals should be allowed more time for adaptation at each stage of conditioning. The age of the individual should also be taken into account when progressions are recommended because adaptation to conditioning likely takes longer in older individuals, but also in extremely debilitated individuals.[201]

Improvement Stage. The goal of the improvement stage of training is to provide a progressive increase in the overall exercise stimulus, which will allow for significant improvements in aerobic fitness. The improvement stage of the exercise-conditioning program differs from the initial stage in that the participant is progressed at a more rapid rate. This stage is reported to usually last from 4 to 5 months, during which intensity is progressively increased within the upper half of the target range of 50–85% of HRR. However, our experience in a 12-week training program in children 7–18 years of age indicates that after 3–4 weeks of initial conditioning, some patients are able to start the improvement stage. In this stage, duration may be increased consistently every 2–3 weeks until participants are able to exercise at a moderate to vigorous intensity for 20–30 minutes continuously. During this stage, interval training may also be beneficial, provided the total time engaged in moderate to vigorous exercise is at least 20 minutes.

Maintenance Stage. The goal of this stage of training is the long-term maintenance of the cardiopulmonary fitness level developed during the improvement stage. This stage of the exercise program may begin at any time the participant has reached previously agreed objectives. During this stage, the individual may no longer be interested in continually increasing the conditioning stimulus. Also, in this stage, further improvement may be none to minimal, but continuing the same workout routine enables individuals to maintain their fitness levels, as well as develop the healthy exercise habit. At this point, it is suggested that program goals be re-examined and new goals or objectives set.

RESISTIVE TRAINING

Strength is defined as the ability to produce force, and the ability to produce force over an extended period of time is referred to as *muscular endurance*. Both muscle strength and endurance affect ADLs because it requires a percentage of an individual's muscular capacity to perform these everyday tasks. Severe burns result in extensive and prolonged loss of muscle mass; therefore resistance training, which increases LBM, should be part of an exercise rehabilitation program for burned individuals.[180]

Just as when designing the aerobic portion of an exercise program, the resistive training portion of an exercise program follows similar principles of training. Both the overload principle and specificity principle are applicable. Strict rules of proper technique and safety must be observed to reduce potential for injury or accidents. A normal breathing pattern should be maintained, with breath-holding avoided. Breath-holding during lifting can induce excessive increases in blood pressure that, in individuals with hypertension, diabetes, or other medical risks, can be dangerous.

Similarly to the aerobic exercise program, testing or evaluation of muscle function precedes the resistive exercise program. This helps individuals identify problem areas (areas in need of required improvement), set goals, and track progress. In addition, muscle strength tests have value in determining back-to-work status.[208] Some of these tests involve peak to maximal muscular efforts. These tests can be done on weight machines or using dumbbells.

Typically, these tests are done at 100% of one-repetition maximum (1RM), but can also be done at 3RM. For extremely deconditioned individuals or for very young children, modification of these guidelines can involve testing using 3RM up to 12RM if needed. An important point to remember is that safety of the individual is crucial. Therefore, correct technique during all testing and training must be observed. The order of exercises or muscles tested is also important. It is recommended that large muscle groups are tested first and alternate between upper body and lower body. For example, a 3RM test may be done in the following order of exercises: bench press, leg press (or squats), shoulder press, leg extension, biceps curl, leg curl, and triceps curl. The 3RM load can be determined as follows. After an instruction period on correct weight-lifting technique, the patient warms up with a lever arm and bar (or wooden dowel) and is allowed to become familiar with the movement. After this, the patient lifts a weight that allows successful completion of four repetitions. If the fourth repetition is achieved successfully and with correct technique, a 1-minute resting period is allowed. After the resting period, a progressively increased amount of weight or load is lifted at least four times. If the patient lifts a weight that allows successful completion of three repetitions, with the fourth repetition not being volitionally possible, because of fatigue or inability to maintain correct technique, the test is terminated and the amount of weight lifted from the successful set is recorded as the individual 3RM. This weight is then used to determine the amount of weight or load that will be used during the first 1–2 weeks (of, e.g., a 12-week program) as a baseline load.

Exercise Type

There are many resistance training exercises. However, these can be divided into core exercises and assistance exercises. *Core exercises* recruit one or more large muscle groups (e.g., chest, shoulder, and back). *Assistance exercises* typically recruit smaller muscle groups such as biceps, triceps, and calves. A good program should typically involve both types of exercises.

Training Frequency

The number of days to train varies according to the individual's training status. For severely burned individuals, we recommend 2–3 days per week of resistance training.

Type of Contraction

Resistance exercise programs or exercises that emphasize accentuated lengthening or contractions (eccentric) are not recommended for severely burned individuals. These types of contractions have a high potential for acute delayed onset of muscle soreness while having similar outcomes to concentric or isometric muscle contractions. The muscle soreness, if severe enough, has the potential to discourage further participation in exercise activities. The movements during weight-lifting should be rhythmic and done at moderate repetition and duration.

Amount of Load Lifted

Commonly, a certain percentage of the 1RM or 3RM is used as a guideline for choosing a training load. The amount of load lifted can be as much as 100% of 1RM or as little as lifting no load. We recommend initially, during the first week of training, allowing the individual to become familiar with the exercise equipment and to be instructed on proper weight-lifting techniques. Initially, the weight or load the subjects will lift should be set at 50–60% of their individual 3RM for 12–15 repetitions for the first 1–2 weeks. Thereafter, the load lifted can be increased to 70–75% (8–10 repetitions) of their individual 3RM and continued for weeks 2 or 3, to week 6. After this, the training intensity can be increased to 75–85% (8–12 repetitions) of the 3RM and implemented from weeks 7–12 or longer. Note that these guidelines provide an estimate of training load and have some limitations.[185] Another method of determining training load is to perform multiple RMs based on the number of repetitions planned for the specific exercise. For example, if 8 repetitions were desired for biceps curl, then one would test the individual by having him or her perform 8RM testing sets.

Number of Repetitions

It is believed that muscle strength and endurance can be obtained simultaneously by performing a specific number of repetitions within a certain range (e.g., 6–10 repetitions). The number of repetitions will depend on load lifted (% of 1RM) and on the objective or goals set at the start of the exercise program. We recommend 8–12 repetitions done at moderate to high intensity to improve both muscle strength and endurance.[180]

Number of Sets

There are very limited data in children as to whether three sets or one set is required to increase muscle strength. Much of the adult-based literature supports similar responses in muscle strength, muscle endurance, and hypertrophy for single- and multiple-set resistance training programs.[201,209–212] Finally, it is important to stress two points: (1) the difference in strength gains is typically more pronounced in trained individuals, and (2) both single and multiple training increases strength. The first point is usually not the case with burned patients, and the second point stresses the fact that an increase in strength is expected with resistance training compared to the standard of care in burned individuals.

Exercise Order

There are many methods of ordering resistance exercises. One of these is to arrange core exercises, then assistance exercises.[212] Another method is to arrange large muscle groups and then small muscle groups.[213–215] Yet another method, which allows the individual to recover more fully between exercises, is to alternate upper-body with lower-body exercises. This is especially well-suited for deconditioned or untrained individuals.[213,214] For example, in severely burned children, we have successfully implemented the following order of resistive exercises: bench press, leg press or squats, shoulder press, leg extension, biceps curl, leg curl, triceps curl, and toe raises. These exercises can be done on variable resistance machines or free weights.[180] Free weights, bands, or variable resistance machines are appropriate for burned individuals wishing to participate in an exercise program (Fig. 47.28).

Rest Periods

As a general rule, it is important to allow enough time between exercises to perform the next exercise in proper form. The rest period also varies depending on the individual's training status and specific training objectives.

Progressive Overload

In order for improvements to continue over time, it is important to carefully monitor and chart the individual's workouts or loads lifted. Progressive overload can be applied in a variety of ways, such as increasing the weight lifted, increasing repetitions while keeping load constant, or decreasing rest periods. A conservative method termed the "2-for-2 rule" is suggested. This rule states that "if an individual can perform two or more repetitions above his or her assigned repetitions goal in the last set, for two consecutive workouts for a specific exercise, then weight or load should be added to that specific exercise for the next training session."[215] For example, say that the assigned number of sets and repetitions is three sets of 8–12 reps in the chest press machine and the individual can perform 12 reps in all three sets after several workout sessions (the specific number of sessions depends on many factors). If the individual is able to complete 12 reps in the third set (i.e., the last set) for two consecutive workout sessions, then, in the following training session, the load for that exercise should be increased. The amount of weight (load) that should be added depends on factors such as the physical condition of the individual (strong or weak) and the body area (upper body or lower body). In general, an increase of 1–2 kg for a less trained, weaker individual is suggested for upper-body exercises, while an increment of 2–4 kg is suggested for lower-body exercises.[185]

Example of an Exercise Program

An example of our exercise rehabilitation program is described here (Table 47.3). The results of this program are published.[17,133,134] This program has been successfully implemented at discharge from hospital, but also at 6 months post-burn.

Fig. 47.28 Resistance training consists of exercises with free weights or variable resistance machines.

Table 47.3 Brief Description of the Shriners Hospitals for Children—Galveston Hospital Outpatient Exercise Rehabilitation Program

AEROBIC WORKOUT	
Intensity	70–85% of each individual's previously determined individual peak aerobic capacity. However, heart rate and rated perceived exertion are obtained at regular intervals during aerobic exercise
Duration	20–40 min
Frequency	3–5 days per week
Mode	Aerobic exercise on treadmills, cycle ergometers, arm ergometers, rowing machines, and outdoor activities such as soccer or kickball
RESISTANCE WORKOUT	
Exercise type	Upper and lower body of core and assistance exercises
Amount of load lifted and number of repetitions	The weight or load-lifted set at approximately 50–60% of each individual 3RM and lifted for 4–10 repetitions for three sets. During the 2nd week, the lifting load increased to 70–75% (3 sets, 4–10 repetitions) of their individual 3RM and continued for weeks 2–6. After this, training intensity is increased to 80–85% (3 sets, 8–12 repetitions) of the 3RM and implemented from weeks 7–12
Frequency	2–3 days per week; alternating days of work with days of recovery
Number of sets	2–3 sets
Exercise order	Bench press, leg press or squats, shoulder press, biceps curl, leg curl, triceps curl, toe raises, and abdominals
Type of exercises	Eight basic resistance exercises done using variable-resistance machines or free weights: 4 for upper body, 3 for lower body, and abdominals
Rest period	A rest interval of approximately 1 min between sets

Note: Each exercise training session consists of resistance and aerobic exercises, with aerobic exercise preceding resistance exercise. This outpatient exercise program should be supplemented with outpatient physical and occupational home therapy or home activities.

IMPORTANT CONSIDERATIONS

- The ultimate goal of an exercise rehabilitation program should be to improve physical function. However, the means by which this is achieved are also important. An exercise program should be challenging, effective, but also must be safe and fun. It should also promote lifelong healthy habits. This will maximize compliance with the exercise program.
- The American College of Sports Medicine (ACSM) has an extensive list of absolute and relative contraindications to exercise and exercise testing that should be carefully considered when designing an exercise program for adults or children. These contraindications will also pertain to individuals with severe burns.
- Individual goals should be established early in the exercise program. Whenever possible, they should be developed by the participant with the guidance of an exercise professional. The goals or objectives must be realistic, and an intrinsic or extrinsic rewards system should be implemented at that time.
- It is recommended that exercise professionals work together with an occupational and/or physical therapist to avoid duplication of services, as well as to identify areas in need of special attention.
- Based on our clinical experience with children and adolescent patients, individuals with severe burns should participate, as soon as possible after hospital discharge, in a structured exercise program. This program should be supervised and, if possible, conducted in the presence of a trained professional. However, if this is not possible, the exercise program, with some common sense guidelines, should offer a choice for safe and effective participation.
- For adults, a careful medical and exercise evaluation should be conducted prior to starting an exercise program. Cardiovascular or pulmonary problems, as well as other conditions such as diabetes, must be identified prior to starting an exercise program to avoid potential fatal or near-fatal complications.
- It is important to get the burned individual started with an exercise program or a more active lifestyle as soon as possible, but it is never too late to get started regardless of the time post-burn.
- When beginning the exercise program, it is better to start slowly and build up gradually than to start too fast and risk injury.
- For children, avoid using very intense or maximal (1RM) resistance training or testing. Gradual progression is of utmost importance to avoid injury and to promote exercise adherence.
- The individual should listen to his or her body. During and after workouts, the individual (and supervisor) should be alert to signs of a potential health problem as a result of overexertion. Signs may include pain, shortness of breath, dizziness, or nausea.
- Be flexible and allow individuals to be flexible. Do not rigidly stick to a schedule if the patient does not feel up to it. If he or she is overly tired or under the weather, take a day or two off.
- Monitor the individual's progress. Reassess fitness every 6 weeks. You may notice that you need to increase the amount of time you exercise in order to continue improving (if part of the original goals).
- The exercise professional or individual should keep an exercise diary or logbook to help chart progress.
- If the patient loses motivation, try setting new goals or try a new activity (or activities). Sometimes bringing a friend or family member into the program may help in motivation. Incorporate variety into the exercise routine.
- Finally, work on conveying to the patient or client that a fun and safe exercise program can result in maintenance of lifelong physical as well as psychosocial healthy habits (Fig. 47.29).

Patient and Caregiver Education

When patients are being discharged from an acute hospital stay, it is vital that they leave with an individualized home exercise program. Splinting and positioning, ADL performance, scar control measures, and psychosocial issues should also be addressed. This program can then be advanced to allow for progression during the phases that the burned individual goes through in what may be in excess of a 2-year recovery period. During follow up visits, the patient's progress is assessed and adjustments to the home exercise program are made as indicated. This detailed knowledge of the patient's status will allow the burn team to coordinate care so that recommendations can be followed through. Providing the patients with a checklist is a valuable tool to enable him or her to assume some control of the rehabilitation process, track progress, and encourage continuation of the program. Many patients and their caregivers are often overwhelmed by the rehabilitation program. It takes an extraordinary amount of time and energy to plan and participate in a home exercise/instruction program. Continuous communication among the patient, caregiver, and the burn team will ease the patient's transition into recovery.

One way of helping patients with the exercise program is to establish communication with a community-based exercise center, such as a commercial or hospital-based facility. Often, direct and constant communication between a burn hospital's rehabilitation department, exercise physiologists and/or physician, and a community-based exercise facility (i.e., personal trainer) will maximize the potential for adherence to and efficacy of such home exercise programs by adding supervision and structure.

Conclusion

The rehabilitation of burn patients, although challenging, can be rewarding to all involved in their care. Continuous evaluation of the interventions provided will ensure each patient's maximum functional outcome. Experience, education, and research will produce therapeutic interventions that will optimize each patient's recovery. Ultimately, the goal of the rehabilitation team is to provide the patient with the means for a productive life.

Fig. 47.29 Overall long-term burn rehabilitation should result in lifelong physical as well as psychosocial healthy habits and improvements in quality of life.

Complete references available online at www.expertconsult.inkling.com

Further Reading

American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription*. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2009.

Borg G, Hassmen P, Langerstrom M. Perceived exertion related to heart rate and blood lactate during arm and leg exercise. *Eur J Appl Physiol Occup Physiol*. 1987;56(6):679-685.

Kisner C, Colby LA. *Therapeutic Exercise: Foundations and Techniques*. 5th ed. Philadelphia: FA Davis; 2007.

Mackin EJ, Callahan AD, Skirven TM, et al, eds. *Rehabilitation of the Hand and Upper Extremity*. 5th ed. St Louis, MO: CV Mosby; 2002.

Noble BJ, Borg GA, Jacobs I, et al. A category-ration perceived exertion scale: relationship to blood and muscle lactates and heart rate. *Med Sci Sports Exerc*. 1983;15(6):523-528.

Randall L, Braddom MD. *Physical Medicine and Rehabilitation*. 4th ed. Philadelphia: Saunders; 2007.

Roberts L, Alvarado MI, McElroy K, et al. Longitudinal hand grip and pinch strength recovery in the child with burns. *J Burn Care Rehabil*. 1993;14(1):99-101.

References

1. Yohannon SK, Ronda-Velez Y, Henriquez DA, et al. Burn survivors' perceptions of rehabilitation. *Burns*. 2012;38(8):1151-1156.
2. Richard RL, Barzya MJ, Carr JA, et al. Burn rehabilitation and research: proceedings of a consensus summit. *J Burn Care Res*. 2009;30:543-573.
3. Moore ML, Dewey WS, Richard RL. Rehabilitation of the burned hand. *Hand Clin*. 2009;25:529-541.
4. Parry IS, Esselman PC. Clinical competencies for burn rehabilitation therapists. *J Burn Care Res*. 2011;32:458-467.
5. Schneider JC, Holavanahali R, Helm P. Contractures in burn injury: defining the problem. *J Burn Care Res*. 2006;27:508-514.
6. Holavanahalli RK, Helm PA, Kowalske KJ. Long-term outcomes in patients surviving large burns: the musculoskeletal system. *J Burn Care Res*. 2015 May 28.
7. Fess EE, Philips CA. *Hand Splinting: Principles and Methods*. 2nd ed. St Louis, MO: CV Mosby; 1987:125-254.
8. Richard RL, Ward RS. Splinting strategies and controversies. *J Burn Care Rehabil*. 2005;26:392-396.
9. Dewey WS, Richard RL, Parry IS. Positioning, splinting, and contracture management. *Phys Med Rehabil Clin N Am*. 2011;22:229-247.
10. Harries CA, Pegg SP. Foam ear protectors for burned ears. *J Burn Care Rehabil*. 1989;10:183-184.
11. Wust KJ. A modified dynamic mouth splint for burn patients. *J Burn Care Res*. 2006;27:86-92.
12. Ridgway CL, Warden GD. Evaluation of a vertical mouth stretching orthosis: two case reports. *J Burn Care Rehabil*. 1995;16(1):74-78.
13. Taylor LB, Walker J. A review of selected microstomia prevention appliances. *Pediatr Dent*. 1997;19:413-418.
14. Heinle JA, Kealey GP, Cram AE, et al. The microstomia prevention appliance: 14 years of clinical experience. *J Burn Care Rehabil*. 1988;9(1):90-91.
15. Maragakis GM, Tempone MG. Microstomia following facial burns. *J Clin Pediatr Dent*. 1999;23:69-73.
16. Sykes L. Scar traction appliance for a patient with microstomia: a clinical report. *J Prosthet Dent*. 1996;76(1):464-465.
17. Rivers EA, Strate RG, Salem LD. The transparent face mask. *Am J Occup Ther*. 1979;33:108-113.
18. Linares HA, Larson DL, Willis-Galstraun B. Historical notes on the use of pressure in the treatment of hypertrophic scar and keloids. *Burns*. 1993;19(1):17-21.
19. Malick MH, Carr JA. *Manual on Management of the Burned Patient, Including Splinting, Mold and Pressure Techniques*. Pittsburgh: Harmarville Rehabilitation Center; 1982.
20. Leman CJ. Splints and accessories following burn reconstruction. *Clin Plast Surg*. 1992;19(3):721-731.
21. Walters CJ. *Splinting the Burn Patient*. Laurel, MD: RAMSCO; 1987.
22. Richard R, Stalay M. *Burn Care and Rehabilitation Principles and Practice*. Philadelphia: FA Davis; 1994:242-323.
23. Godleski M, Holden MS, Luby D, et al. *J Burn Care Res*. 2014;35(6):e379-e386.
24. Manigandan C, Gupta AK, Venugopal K, et al. A multi-purpose, self-adjustable aeroplane splint for splinting of axillary burns. *Burns*. 2003;29:276-279.
25. Manigandan C, Bedford E, Ninan S, et al. Adjustable aesthetic aeroplane splint for axillary burn contractures. *Burns*. 2004;31:502-504.
26. Vehmeyer-Heeman M, Lommers B, Van den Kerckhove E, et al. Axillary burns: extended grafting and early splinting prevents contractures. *J Burn Care Rehabil*. 2005;26:539-542.
27. Kolmus AM, Holland AE, Byrne MJ, et al. The effects of splinting in shoulder function in adult burns. *Burns*. 2012;38:638-644.
28. Jang KU, Choi JS, Mun JH, et al. *Clin Rehabil*. 2015;29:439-446.
29. Obaidullah, Ullah H, Aslam M. Figure-of-8 sling for prevention of recurrent axillary contracture after release and skin grafting. *Burns*. 2005;31:283-289.
30. Richard RL. Use of the Dynasplint to correct elbow flexion contracture: a case report. *J Burn Care Rehabil*. 1986;7:151-152.
31. Kowalske KJ. Hand burns. *Phys Med Rehabil Clin N Am*. 2011;22:249-250.
32. Kamolz LP, Kitzinger HB, Karle B, et al. The treatment of hand burns. *Burns*. 2009;35:327-337.
33. Kaine EC, Fidler P, Schulz J, et al. "Roll bar" for protective posture splint limits potential trauma to dorsal hand grafts. *J Burn Care Res*. 2008;29:204-207.
34. Howell J. Management of the burned hand. In: Richard R, Staley M, eds. *Burn Care and Rehabilitation: Principles and Practice*. Philadelphia: FA Davis; 1994:531-575.
35. Leblebici B, Adam M, Bagis S, et al. Quality of life after burn injury: the impact of joint contracture. *J Burn Care Res*. 2006;27:864-868.
36. Schneider J, Holavanahalli R, Helm P, et al. Contractures in burn injury part II: investigating joints of the hand. *J Burn Care Res*. 2008;29(4):606-613.
37. Schouten HJ, Nieuwenhuis MK, van Zuijlen PP. A review on static splinting therapy to prevent burn scar contracture: do clinical and experimental data warrant its clinical application. *Burns*. 2012;38:19-25.
38. Puri V, Khare N, Venkateshwaran N, et al. Serial splintage: preoperative treatment of upper limb contracture. *Burns*. 2013;39:1096-1100.
39. Ward RS, Schnebly WA, Kravitz M, et al. Have you tried the sandwich splint? A method of preventing hand deformities in children. *J Burn Care Rehabil*. 1989;10:83-85.
40. Sudhakar G, Le Blanc M. Alternate splint for flexion contracture in children with burns. *J Hand Ther*. 2011;24:277-279.
41. Manigandan C, Sureshkumar K, Rachel R, et al. Dynamic joint-aligned PIP and DIP corrective-flexion/extension orthosis for post-burn finger contractures. *Burns*. 2005;31:787-788.
42. Calhoun JH, Evans EB, Herndon DN. Techniques for the management of burn contractures with the Ilizarov fixator. *Clin Orthop Relat Res*. 1993;280:117-124.
43. Shakirov BM. Evaluation of different surgical techniques used for correction of post-burn contracture of the foot and ankle. *Ann Burns Fire Disasters*. 2010;23:137-143.
44. Shakirov BM. Deep foot burns: effects of early excision and grafting. *Burns*. 2011;37:1435-1438.
45. Hur G-Y, Rhee B-J, Ko J-H, et al. Correction of postburn equinus deformity. *Ann Plast Surg*. 2013;70:276-279.
46. Chang JB, Kung TA, Levi B, et al. Surgical management of burn flexion and extension contractures of the toes. *J Burn Care Res*. 2014;35:93-101.
47. Shakirov BM. Foot postburn bent contracture deformities. *Burns*. 2007;33:1054-1058.
48. O'Sullivan SB, Schmitz TJ. Orthotic assessment and management. In: *Physical Rehabilitation Assessment and Treatment*. 3rd ed. Philadelphia: FA Davis; 1994:655-684.
49. Esselman PC, Thombs BD, Magyar-Russell G, et al. Burn rehabilitation: state of the science. *Am J Phys Med Rehabil*. 2006;85:383-413.
50. Richard R, Miller S, Staley M. Multimodal versus progressive treatment techniques to correct burn scar contractures. *J Burn Care Rehabil*. 2000;21:506-512.
51. Staley M, Serghiou M. Casting guideline, tips, and techniques: proceedings from the 1997 American Burn Association PT/OT casting workshop. *J Burn Care Rehabil*. 1998;19:254-260.
52. Johnson J, Silverberg R. Serial casting of the lower extremity to correct contractures during the acute phase of burn care. *Phys Ther*. 1995;75(4):262-266.
53. Ridgway CL, Daughtery MB, Warden GD. Serial casting as a technique to correct burn scar contractures: a case report. *J Burn Care Rehabil*. 1991;12:67-72.
54. Bennett GB, Helm P, Purdue GF, et al. Serial casting: a method for treating burn contractures. *J Burn Care Rehabil*. 1989;10:543-545.
55. Ricks NR, Meagher DP. The benefits of plaster casting for lower-extremity burns after grafting in children. *J Burn Care Rehabil*. 1992;13:465-468.
56. Flesch P. Casting the young and the restless. *Proc Am Burn Assoc*. 1985;17:120.
57. Harris LD, Hatler B, Adams S, et al. Serial casting and its efficacy in the treatment of the burned hand. *Proc Am Burn Assoc*. 1993;25:129.
58. Torres-Gray D, Johnson J, Greenspan B, et al. The fabrication and use of the removable digit casts to improve range of motion at the proximal interphalangeal joint. *Proc Am Burn Assoc*. 1993;25:217.
59. Jackson RD. The MCP block cast with flexion glove: an alternative method over traditional splinting. *J Burn Care Rehabil*. 1997;18:S175.
60. Walker K, Serghiou M, Duplantis C, et al. Serial casting with silicone for volar hand/wrist contractures. *J Burn Care Rehabil*. 1997;18:S173.
61. Knutsen AC, Franzen B, Solem LD. Early serial casting for palmar burns to prevent contractures. Presented at the annual meeting of the American Burn Association, 2006, Las Vegas, NV.

62. Cattanach LB, Rivers E, Solem L, et al. Achieving optimal elbow extension using the serial, "fall-out" elbow cast. *Proc Am Burn Assoc*. 1990;22:138.
63. Kirby J, Facchine SL, Slater H, et al. Serial casting for axilla contractures. *Proc Am Burn Assoc*. 1992;24:11.
64. Doughterty ME, Tran K, Warden G. Retrospective review of axilla serial casting. Presented at the annual meeting of the American Burn Association, 2003, Miami Beach, FL.
65. Larson D, Abston S, Evans EB, et al. Techniques for decreasing scar formation and contractures in the burned patient. *J Trauma*. 1971;11:807-823.
66. Sapega A, Zuedenfeld T, Moyer R, et al. Biophysical factors in range of motion exercise. *Phys Sportsmed*. 1981;9(12):57-65.
67. Hutchinson MJ, Hutchinson MR. Factors contributing to the temperature beneath plaster or fiberglass cast material. *J Orthop Surg Res* [serial online]. 2008;3:10.
68. Halanski MA, Halanski AD, Oza A, et al. Thermal injury with contemporary cast-application techniques and methods to circumvent morbidity. *J Bone Joint Surg Am*. 2007;89:2369-2377.
69. Dougherty. Focused Rigidity Casting (FRC): another option for positioning the burn patient. Abstract. Proceedings of The American Burn Association. Vancouver, British Columbia; 2004.
70. Soto CA, Albornoz CR, Peña V, et al. Prognostic factors for amputation in severe burn patients. *Burns*. 2013;39(1):126-129.
71. Bowker JH. Michael JWM, ed. *Atlas of Limb Prosthetics: Surgical Prosthetic and Rehabilitation Principles*. St Louis, MO: CV Mosby; 1992.
72. Murray C, ed. *Amputation, Prosthesis, Use, and Phantom Limb Pain: An Interdisciplinary Perspective*. New York, NY: Springer; 2010.
73. Malone JM, Fleming LL, Roberson J. Immediate, early, and late postsurgical management of upper-limb amputation. *J Rehabil Res Dev*. 1984;21(1):33-41.
74. Kelly BM, Pangilinan PH, Rodriguez GM, et al. Upper limb prosthetics. http://emedicine.medscape.com/article/317234–overview; updated.
75. Hanger, Inc. *Prosthetics & Orthotics: Physician's Desk Reference*. Austin, TX: Hanger; 2007:88-113.
76. Cole MJ, Durham S, Ewins D. An evaluation of patient perceptions to the value of the gait laboratory as part of the rehabilitation of primary lower limb amputees. *Prosthet Orthot Int*. 2008;32(1): 12-22.
77. Marulanda GA, Henderson ER, Palumbo BT, et al. Use of extendable prostheses: a limb-salvaging alternative for patients with malignant bone tumors. *Expert Rev Med Devices*. 2008;5(4):467-474.
78. Stedman TL, ed. *Stedman's Medical Dictionary*. 23rd ed. Baltimore, MD: Williams and Wilkins; 1976.
79. Ward RS. Pressure therapy for the control of hypertrophic scar formation after burn injury, a history and review. *J Burn Care Rehabil*. 1991;12(3):257-262.
80. Linares HA. Hypertrophic healing: controversies and etiopathogenic review. In: Carvajal HF, Parks DH, eds. *Burns in Children: Pediatric Burn Management*. Chicago: Yearbook Medical; 1988:305-323.
81. Shakespeare PG, Renterghem L. Some observations on the surface structure of collagen in hypertrophic scars. *Burns*. 1985; 11(175):180.
82. Hayakawa T, Hino M, Fuyamada H, et al. Lysyl oxidase activity in human normal skins and post-burn scars. *Clin Chim Acta*. 1976;7:245-250.
83. Hayakawa T, Hino M, Fuyamada H, et al. Prolyl hydroxylase activity in human normal skins and post-burn scars. *Clin Chim Acta*. 1977;75:137-142.
84. Hayakawa T, Hashimoto Y, Myokei Y, et al. Changes in type of collagen during the development of human post-burn hypertrophic scars. *Clin Chim Acta*. 1979;93:119-125.
85. Hayakawa T, Hashimoto Y, Myokei Y, et al. The effects of skin grafts on the ratio of collagen types in human post-burn wound tissues. *Connect Tissue Res*. 1982;9:249-252.
86. Abston S, Boswick JA. Scar reaction after thermal injury and prevention of scars and contractures. In: *The Art and Science of Burn Care*. Rockville: Aspen; 1987:360-361.
87. Staley M, Richard R. *Burn Care and Rehabilitation Principles and Practice*. Philadelphia: FA Davis; 1994:380-418.
88. Reid WH, Evans JH, Naismith RS, et al. Hypertrophic scarring and pressure therapy. *Burns*. 1987;13(suppl):S29.
89. Sullivan T, Smith J, Kermode J, et al. Rating the burn scar. *J Burn Care Rehabil*. 1990;11:256-260.
90. Baryza MJ, Bryza GA. The Vancouver scar scale: an administration tool and its interrater reliability. *J Burn Care Rehabil*. 1995;16(5):535-538.
91. Nedelec B, Shankowsky HA, Tredget EEJ. Burn rating the resolving hypertrophic scar: comparison of the Vancouver scar scale and scar volume. *J Burn Care Rehabil*. 2000;21(3):205-212.
92. Nedelec B, Correa JA, Rachelska G, et al. Quantitative measurement of hypertrophic scar: interrater reliability and concurrent validity. *J Burn Care Res*. 2008;29(3):501-511.
93. Hambleton J, Shakespeare PG, Pratt BJ. The progress of hypertrophic scars monitored by ultrasound measurements of thickness. *Burns*. 1992;18(4):301-307.
94. Darvey RB, Sprod RT, Neild TO. Computerized colour: a technique for the assessment of burn scar hypertrophy. A preliminary report. *Burns*. 1999;25(3):207-213.
95. Esposito G, Ziccardi P, Scioli M, et al. The use of a modified tonometer in burn scar therapy. *J Burn Care Rehabil*. 1990;11:86-90.
96. Bartell TH, Monafo WW, Mustoe TA. A new instrument for serial measurement of elasticity in hypertrophic scar. *J Burn Care Rehabil*. 1988;9:657-660.
97. Hosoda G, Holloway GA, Heimback DM. Laser Doppler flowmetry for the early detection of hypertrophic burn scars. *J Burn Care Rehabil*. 1986;7:490-497.
98. Berry RB, Tan OT, Cooke ED, et al. Transcutaneous oxygen tension as an index of maturity in hypertrophic scars treated by compression. *Br J Plast Surg*. 1985;38:163-173.
99. Bray R, Forrester K, Leonard C, et al. Laser Doppler imaging of burn scars: a comparison of wavelength and scanning methods. *Burns*. 2003;29:199-206.
100. Fearmonti R, Bond J, Erdmann D, et al. A review of scar scales and scar measuring devices. *Eplasty*. 2010;10:e43.
101. Nguyen TA, Feldstein SI, Shumaker PR, et al. A review of scar assessment scales. *Semin Cutan Med Surg*. 2015;34:28-36.
102. Forbes-Duchart L, Cooper J, Nedelec B, et al. Burn therapists' opinion on the application and essential characteristics of a burn scar outcome measure. *J Burn Care Res*. 2009;30(5):792-800.
103. McDonald WS, Deitch EA. Hypertrophic skin grafts in burn patients: a prospective analysis of variables. *J Trauma*. 1987;27:147-150.
104. Kealey GP, Jensen KL, Laubenthal KN, et al. Prospective randomized comparison of two types of pressure therapy garments. *J Burn Care Rehabil*. 1990;11:334-336.
105. Hubbard M, Masters IB, Williams GR, et al. Severe obstructive sleep apnoea secondary to pressure garments used in the treatment of hypertrophic burn scars. *Eur Respir J*. 2000;16:1205-1207.
106. Sawada Y. A method of recording and objective assessment of hypertrophic burn scars. *Burns*. 1994;20:76-78.
107. Cheng JC, Evans JH, Leung KS, et al. Pressure therapy in the treatment of post-burn hypertrophic scar – a critical look into its usefulness and fallacies by pressure monitoring. *Burns Incl Therm Inj*. 1984;10:154-163.
108. Leung KS, Cheng JC, Ma GF, et al. Complications of pressure therapy for post-burn hypertrophic scars. Biomechanical analysis based on 5 patients. *Burns Incl Therm Inj*. 1984;10:434-438.
109. Stewart R, Bhagwanjee AM, Mbakaza Y, et al. Pressure garment adherence in adult patients with burn injuries: an analysis of patient and clinician perceptions. *Am J Occup Ther*. 2000;54:598-606.
110. Perkins K, Davey RB, Wallis K. Current materials and techniques used in burn scar management program. *Burns Incl Therm Inj*. 1987;13:406-410.
111. Staley MJ, Richard RL. Use of pressure to treat hypertrophic burn scars. *Adv Wound Care (New Rochelle)*. 1997;10:44-46.
112. Van den Kerckhove E, Stappaerts K, Fieuws S, et al. The assessment of erythema and thickness on burn related scars during pressure garment therapy as a preventative measure for hypertrophic scarring. *Burns*. 2005;31:696-702.
113. Macintyre L, Baird M. Pressure garments for use in the treatment of hypertrophic scars – a review of the problems associated with their use. *Burns*. 2006;32:10-15.
114. Puzey G. The use of pressure garments on hypertrophic scars. *J Tissue Viability*. 2002;12:11-15.
115. Giele HP, Liddiard K, Currie K, et al. Direct measurement of cutaneous pressures generated by pressure garments. *Burns*. 1997; 23:137-141.
116. Larson DL, Abston S, Willis B, et al. Contracture and scar formation in the burn patient. *Clin Plast Surg*. 1974;1:653-656.

117. Robertson JC, Hodgson B, Druett JE, et al. Pressure therapy for hypertrophic scarring: preliminary communication. *J R Soc Med*. 1980;73:348-354.
118. Fricke NB, Omnell ML, Dutcher KA, et al. Skeletal and dental disturbances after facial burns and pressure garments use: a 4 year follow-up. *J Burn Care Rehabil*. 1999;20:239-249.
119. Fricke NB, Omnell ML, Dutcher KA, et al. Skeletal and dental disturbances in children after facial burns and pressure garments. *J Burn Care Rehabil*. 1996;17:338-345.
120. Groce A, Meyers-Paal R, Herndon DH, et al. Are your thoughts of facial pressure transparent? *J Burn Care Rehabil*. 1999;20:478-481.
121. Parry I, Sen S, Palmieri T, et al. Nonsurgical scar management of the face: does early versus late intervention affect outcome? *J Burn Care Res*. 2013;34:569-575.
122. Engrav LH, et al. Do splinting and pressure devices damage new grafts? *J Burn Care Rehabil*. 1983;4:107-108.
123. Rose MP, Deitch GA. The effective use of a tubular compression bandage, Tubigrip, for burn scar therapy in the growing child. *J Burn Care Rehabil*. 1983;4:197-201.
124. Thompson R, Summers S, Rampey-Dobbs R, et al. Color pressure garments vs traditional beige pressure garments: perceptions from the public. *J Burn Care Rehabil*. 1992;13:590-596.
125. Ripper S, Renneberg B, Landmann C, et al. Adherence to pressure garment therapy in adult burn patients. *Burns*. 2009;35:657-664.
126. Ward RS. Reasons for the selection of burn-scar-support suppliers by burn centers in the United States: a survey. *J Burn Care Rehabil*. 1993;14(3):360-367.
127. Steinstraesser L, Flak E, Witte B, et al. Pressure garment therapy alone and in combination with silicone for the prevention of hypertrophic scarring: randomized controlled trial with intraindividual comparison. *Plast Reconstr Surg*. 2011;128:306e-313e.
128. Nedelec B, Carter A, Forbes L, et al. Practice Guidelines for the application of Nonsilicone or silicone gels and gel sheets after burn injury. *J Burn Care Res*. 2015;36:345-374.
129. Van den Kerchove E, Boechx W, Kochreyt A. Silicone patches as a supplement for pressure therapy to control hypertrophic scarring. *J Burn Care Rehabil*. 1991;12(4):361-369.
130. McNee S. The use of silicone gel in the control of hypertrophic scarring. *Physiotherapy*. 1990;76:194-197.
131. Quinn KJ. Silicone gel in scar treatment. *Burns*. 1987;13:533-540.
132. Parry I, Hanley C, Niszczak J, et al. Harnessing the transparent face orthosis for facial scar management: a comparison of methods. *Burns*. 2013;39:950-956.
133. Derwin-Baruch L. UVA therapists meet the challenge of scar management. OT Week. 1993;April 15:15–17.
134. Gallagher J, Goldfarb W, Slater H, et al. Survey of treatment modalities for the prevention and treatment of hypertrophic burn scars. *J Burn Care Rehabil*. 1990;11(2):118-120.
135. Parry I, Icaza I, Valaderes S, et al. Defining massage techniques used for burn scars. *J Burn Care Res*. 2016; Video Gallery. http://journalss.lww.com/burncareresearch/pages/videogallery.aspx?videold=5&autoPlay=false.
136. Niszczak J, Forbes L, Serghiou M. Burn rehabilitation. In: Maitin IB, ed. *Current Diagnosis and Treatment Physical Medicine and Rehabilitation*. New York: McGraw Hill; 2015.
137. Ward RS. The use of physical agents in burn care. In: Richard RL, Staley MJ, eds. *Burn Care and Rehabilitation Principles and Practice*. Philadelphia: FA Davis; 1994:419-446.
138. Miles WK, Grigsby de Linde L. Remodeling of scar tissue in the burned hand. In: Hunter JM, Schneider LH, Mackin EJ, et al, eds. *Rehabilitation of the Hand*. Vol. II. 4th ed. St Louis, MO: CV Mosby; 1995:1267-1294.
139. Wood EC. *Beard's Massage: Principles and Techniques*. 2nd ed. Philadelphia: WB Saunders; 1974:48-59.
140. Lentell G, Hetherington T, Eagan J, et al. The use of thermal agents to influence the effectiveness of low-load prolonged stretch. *J Orthop Sports Phys Ther*. 1992;15:200-207.
141. Warren CG, Lehmann JF, Koblanski JN. Heat and stretch procedures: an evaluation using rat tail tendon. *Arch Phys Med Rehabil*. 1976;57:122-126.
142. Ward RS, Hayes-Lundy C, Reddy R, et al. Evaluation of topical therapeutic ultrasound to improve response to physical therapy and lessen scar contracture after burn injury. *J Burn Care Rehabil*. 1994;15:74-79.
143. Head M, Helm P. Paraffin and sustained stretching in treatment of burn contractures. *Burns*. 1977;4:136-139.
144. Kowalske K, Holavanahalli R, Hynan O'Toole D, et al. A randomized-controlled study of the effectiveness of paraffin and sustained stretch in treatment of burn contractures. *J Burn Care Rehabil*. 2003;24:S67.
145. Huruitz S. The sun and sunscreen protection: recommendations for children. *J Dermatol Surg Oncol*. 1988;14(6):657-660.
146. Helm P, Herndon DN, deLatteur B. Restoration of function. *J Burn Care Res*. 2007;28:611-614.
147. Esselman PC. Burn rehabilitation: an overview. *Arch Phys Med Rehabil*. 2007;88(12 suppl 2):S3-S6.
148. Thomas CL. *Taber's Cyclopedic Medical Dictionary*. Philadelphia: FA Davis; 1985:1719.
149. Braddom RL, Boe L, Floers L, et al. The physical treatment and rehabilitation of burn patients. In: Hummel RP, ed. *Clinical Burn Therapy*. Boston: John Wright-PSG; 1982:279-299.
150. Nothdurft D, Smith PS, LeMaster JE. Exercise and treatment modalities. In: Fisher SV, Helm PA, eds. *Comprehensive Rehabilitation of Burns*. Baltimore, MD: Williams & Wilkins; 1984:122.
151. Johnson CL. The role of physical therapy. In: Boswick JA, ed. *The Art and Science of Burn Care*. Rockville: Aspen; 1987:304.
152. Robson MC, Smith DJ, VanderZee AJ, et al. Making the burned hand functional. *Clin Plast Surg*. 1992;19(3):663-671.
153. Fisher SV, Helm PA. Rehabilitation of the patient with burns. In: DeLisa JA, Gans BM, Walsh NE, et al, eds. *Rehabilitation Medicine Principles and Practice*. 2nd ed. Philadelphia: JB Lippincott; 1993:[ch 53].
154. Richard RL, Hedman TL, Quick CD, et al. A clarion to recommit and reaffirm burn rehabilitation. *J Burn Care Res*. 2008;29:425-432.
155. Okhovatian F, Zoubine N. A comparison between two burn rehabilitation protocols. *Burns*. 2007;33:429-434.
156. Kozerefski PM. Exercise and ambulation in the burn patient. In: DiGregorio VR, ed. *Rehabilitation of the Burn Patient*. New York: Churchill Livingstone; 1984:55-73.
157. Humphry CN, Richard RL, Staley MJ. Soft tissue management and exercise. In: Richard RL, Staley MJ, eds. *Burn Care and Rehabilitation: Principles and Practice*. Philadelphia: FA Davis; 1994:324-359.
158. Salter RB, Hamilton HW, Wedge JH, et al. Clinical application of basic research on continuous passive motion for disorders and injuries of synovial joints: a preliminary report. *J Orthop Res*. 1983;1(3):325-342.
159. Lynch JA. Continuous passive motion: a prophylaxis for deep vein thrombosis following total knee replacement. *Orthop Trans*. 1984;8(3):400.
160. Wright PC. Fundamentals of acute burn care and physical therapy management. *Phys Ther*. 1984;64:1217-1231.
161. Nedelec B, Parry I, Acharya H, et al. Practice Guidelines for cardiovascular fitness and strengthening exercise prescription after burn injury. *J Burn Care Res*. 2015 Aug 17;[Epub ahead of print].
162. Trees D, Ketelsen CA, Hobbs JA. Use of a modified tilt table for preambulation strength training as an adjunct to burn rehabilitation: a case series. *J Burn Care Rehabil*. 2003;24:97-103.
163. Harnar T, Engrav L, Marvin J, et al. Dr Paul Unna's boot and early ambulation after skin grafting of the leg. *Plast Reconstr Surg*. 1982;69:359-360.
164. Harden NG, Luster SH. Rehabilitation considerations in the care of the acute burn patient. *Crit Care Nurs Clin North Am*. 1991; 3(2):245-253.
165. Goldberg N, Stadler P, Kaplan M. Occupational therapy: splinting, positioning, and exercise. In: DiGregorio VR, ed. *Rehabilitation of the Burn Patient*. New York: Churchill Livingstone; 1984:33-54.
166. Schmitt MA, French L, Kalil ET. How soon is safe? Ambulation of the patient with burns after lower-extremity skin grafting. *J Burn Care Rehabil*. 1991;12:33-37.
167. Heimbach DM, Engrav LH. *Surgical Management of the Burn Wound*. New York: Raven Press; 1984:83-98.
168. Smith TO. When should patients begin ambulating following lower limb split skin graft surgery? A systematic review. *Physiotherapy*. 2006;92:135-145.
169. Cox GW, Griswold JA. Outpatient skin grafting of extremity burn wounds with the use of Unna boot compression dressings. *J Burn Care Rehabil*. 1993;14:455-457.
170. Burnsworth B, Krob MJ, Langer-Schnepp M. Immediate ambulation of patients with lower-extremity grafts. *J Burn Care Rehabil*. 1992;13:89-92.
171. Wallenberg L. Effect of early mobilisation after skin grafting to lower limbs. *Scand J Plast Reconstr Surg Hand Surg*. 1999;33:411-413.

172. Pessina MA, Ellis SM. Burn management. Rehabilitation. *Nurs Clin North Am*. 1997;32(2):365-374.
173. Chang AT, Boots R, Hodges PW, et al. Standing with assistance of a tilt table in intensive care: a survey of Australian physiotherapy practice. *Aust J Physiother*. 2004;50(1):51-54.
174. Melchert-McKearnan K, Deitz J, Engel J, White O. Children with burn injuries: purposeful activity versus rote exercise. *Am J Occup Ther*. 2000;54(4):381-390.
175. Blassingame WM, Bennett GB, Helm PA, et al. Range of motion of the shoulder performed while patient is anesthetized. *J Burn Care Rehabil*. 1989;10:539-542.
176. Kottke FJ, Pauley DL, Rudolph AP. The rationale for prolonged stretching for correction of shortening of connective tissue. *Arch Phys Med Rehabil*. 1966;47:345-352.
177. DeLateur BJ, Ober MS, Bresnick MG, et al. Randomized, controlled trial of an augmented exercise protocol in the prevention of deconditioning among burn survivors: a preliminary analysis. *J Burn Care Res*. 2006;27:S118.
178. Franklin BA. General principles of exercise prescription. In: *ACSM's Guidelines for Exercise Testing and Prescription*. Philadelphia: Lippincott Williams & Wilkins; 2006.
179. Wallace J, Kaminsky LA. Principles of cardiorespiratory endurance programming. In: *ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription*. Philadelphia: Lippincott Williams & Wilkins; 2006:336-349.
180. Suman OE, Spies RJ, Celis MM, et al. Effects of a 12-wk resistance exercise program on skeletal muscle strength in children with burn injuries. *J Appl Physiol*. 2001;91(3):1168-1175.
181. Suman OE, Mlcak RP, Herndon DN. Effect of exercise training on pulmonary function in children with thermal injury. *J Burn Care Rehabil*. 2002;23(4):288-293, discussion 287.
182. Neugebauer CT, Serghiou M, Herndon DN, et al. Effects of a 12–week rehabilitation program with music and exercise groups on range of motion in young children with severe burns. *J Burn Care Res*. 2008;29(6):939-948.
183. American Academy of Pediatrics. Strength training by children and adolescents. *Pediatrics*. 2001;107(6):1470-1472.
184. America Academy of Pediatrics Committee on Sports Medicine. Risks in distance running for children. *Pediatrics*. 1990;86(5):799-800.
185. Baechle TR, Earle RW, Wathen D, et al. Resistance training in essentials of strength training and conditioning. National Strength and Conditioning Association. *Hong Kong: Human Kinetics*; 2000:395–425.
186. Adams RB, Tribble GC, Tafel AC, et al. Cardiovascular rehabilitation of patients with burns. *J Burn Care Rehabil*. 1990;11(3):246-255.
187. Canadian Society for Exercise Physiology. Physical Activity Readiness Questionnaire (Par-Q) and You. Gloucester, ON: Canadian Society for Exercise Physiology; 1994:1–2.
188. Sallis JF, Strikmiller PK, Harsha DW, et al. Validation of interviewer- and self-administered physical activity checklists for fifth grade students. *Med Sci Sports Exerc*. 1996;28(7):840-851.
189. Kriska AM, Caspersen CJ. Introduction to a collection of physical activity questionnaires. *Med Sci Sports Exerc*. 1997;29(6 suppl):S5-S9.
190. Noble BJ, Borg GA, Jacobs I, et al. A category-ration perceived exertion scale: relationship to blood and muscle lactates and heart rate. *Med Sci Sports Exerc*. 1983;15(6):523-528.
191. Borg G. *Borg's Perceived Exertion and Pain Scales*. Champaign: Human Kinetics; 1998.
192. Cucuzzo NA, Ferrando A, Herndon DN. The effects of exercise programming vs traditional outpatient therapy in the rehabilitation of severely burned children. *J Burn Care Rehabil*. 2001;22(3):2120-2124.
193. Roberts L, Alvarado MI, McElroy K, et al. Longitudinal hand grip and pinch strength recovery in the child with burns. *J Burn Care Rehabil*. 1993;14(1):99-101.
194. Rowland TW. Aerobic exercise testing protocols. In: Rowland TW, ed. *Pediatric Laboratory Exercise Testing: Clinical Guidelines*. Champaign: Human Kinetics; 1993:19-42.
195. Myers J, Bellin D. Ramp exercise protocols for clinical and cardiopulmonary exercise testing. *Sports Med*. 2000;30:23-29.
196. Myers J, Buchanan N, Walsh D, et al. Comparison of the ramp versus standard exercise protocols. *J Am Coll Cardiol*. 1991;17:1334-1342.
197. Borg G, Hassmen P, Langerstrom M. Perceived exertion related to heart rate and blood lactate during arm and leg exercise. *Eur J Appl Physiol Occup Physiol*. 1987;56(6):679-685.
198. Borg GA. Perceived exertion. *Exerc Sport Sci Rev*. 1974;2:131-153.
199. Hardee JP, Porter C, Sidossis LS, et al. Early rehabilitative exercise training in the recovery from pediatric burn. *Med Sci Sports Exerc*. 2014;46(9):1710-1716.
200. Porter C, Hardee JP, Herndon DN, et al. The role of exercise in the rehabilitation of patients with severe burns. *Exerc Sport Sci Rev*. 2015;43(1):34-40.
201. American College of Sports Medicine Position Stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Med Sci Sports Exerc*. 1998;30(6):975-991.
202. Kokkonen J, Nelson AG, Cornwell A. Acute muscle stretching inhibits maximal strength performance. *Res Q Exerc Sport*. 1998;69(4):411-415.
203. Behm DG, Button DC, Butt JC. Factors affecting force loss with prolonged stretching. *Can J Appl Physiol*. 2000;3:261-272.
204. Howley ET. Type of activity: resistance, aerobic and leisure versus occupational physical activity. *Med Sci Sports Exerc*. 2001;33(6 suppl):S364-S369, discussion S419-S420.
205. Foster C, Florhaug JA, Franklin J, et al. A new approach to monitoring exercise training. *J Strength Cond Res*. 2001;15(1):109-115.
206. Persinger R, Foster C, Gibson M, et al. Consistency of the talk test for exercise prescription. *Med Sci Sports Exerc*. 2004;36(9):1632-1636.
207. Welsch MA, Pollock ML, Brechue WF, et al. Using the exercise test to develop the exercise prescription in health and disease. *Prim Care*. 1994;21(3):589-609.
208. Cronan T, Hammond J, Ward CG. The value of isokinetic exercise and testing in burn rehabilitation and determination of back-to-work status. *J Burn Care Rehabil*. 1990;11(3):224-227.
209. Stone MH, Fleck SJ, Triplett NT, et al. Health- and performance-related potential of resistance training. *Sports Med*. 1991;11(4):210-231.
210. Carpinelli RN, Otto RM. Strength training. Single versus multiple sets. *Sports Med*. 1998;26(2):73-84.
211. Faigenbaum AD, Pollock ML. Prescription for resistance training in health and disease. *Med Sci Sports Exerc*. 1999;31:38-45.
212. Stone MH, Wilson GD. Resistive training and selected effects. *Med Clin North Am*. 1985;69(1):109-122.
213. Pauletto B. Choice and order of exercise. *NSCA J*. 1986;8(2):71-73.
214. Fleck SJ, Kraemer WJ. *Designing Resistance Training Programs*. Champaign: Human Kinetics; 1997.
215. Baechle TR, Groves BR. *Weight Training: Steps to Success*. Champaign: Human Kinetics; 1998.

48 Musculoskeletal Changes Secondary to Thermal Burns

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Acknowledgment

This chapter was originally written by E. Burke Evans, MD. He passed away in May 2012. We are indebted to his knowledge of burn care. Care was taken to preserve as much of his original material while adding new information.

Introduction

Burn injuries have a tendency, even as they heal, to create musculoskeletal deformity. In addition, the protracted burn illness that accompanies severe burns may result in other skeletal changes. Box 48.1 presents a classification of musculoskeletal changes secondary to burns; from this, the most commonly occurring and clinically significant alterations have been selected for discussion.

Changes Confined to Bone

OSTEOPOROSIS

Osteoporosis is the most frequently occurring postburn change involving bone. Klein et al.'s ongoing studies suggest that, among persons with serious burns, reduction of bone mass density is pervasive.[2] Stated causes of osteoporosis in thermal burns are bed confinement, immobilization, hyperemia,[3] reflex vasomotor phenomena,[4] and adrenocortical hyperactivity.[5] In Chapter 26 of this book, Klein reviews the effects of burn injury on bone metabolism.[2,6] Klein et al.[9] noted very limited bone formation after a severe burn. Other endocrine changes that lead to loss of bone after burns have been described by Dolecek et al.[10] This coupled with the relatively high resorption leads to osteopenia postburn. Endogenous corticosteroid production is likely responsible for the decreased bone formation, and inflammatory cytokines are responsible for the bone resorption. In this section, only what is clinically apparent is discussed.

The more extensive the burn and the greater the number of complications, the longer the patient may be confined to bed and relatively immobile. The onset of osteoporosis is accelerated, and its intensity is more marked in the burn illness that features a hypermetabolic state. Klein et al. found that osteoblasts and probably osteocytes underwent apoptosis in response to the glucocorticoid stress hormones. The overall effect of burn is catabolic, and muscle wasting is also noted. If a single extremity of an otherwise normal person is immobilized for a long period of time because of local trauma, as with a fracture, loss of bone density can be easily seen on plain radiographs. So, with burns isolated to the extremities, the bones of affected extremities become osteoporotic, and in persons with generalized burns, the bones of deeply burned extremities may show more profound mineral loss than is observed in nonburned extremities or in the axial skeleton (Fig. 48.1). This tendency for more osteoporosis in severe burns was also noted by Pandit et al.,[11] who found that 56% of postburn patients had radiographic evidence of osteopenia. Van der Wiel et al.[7] found in an X-ray absorptiometry study of 16 adults with fractures of one tibia that there was eventual loss of bone mineral density in the contralateral femur and in the lumbar spine but to a lesser degree than in the ipsilateral femur. These findings, although not strictly analogous to those observed in burns, nevertheless point to the occurrence of generalized osteoporosis in other trauma states and the difference in loss of bone density relative to local factors. In fractures or in burns, impaired mobility and local hyperemia could account for this difference.

Another characteristic of the osteoporosis of burns that seems to set it apart is its persistence, not just until restoration of the anabolic state but also for months and years after the burn has healed (Fig. 48.2). This phenomenon may be most clearly observed in patients who have survived 90% burns, but Klein et al. record less than normal bone among even moderately burned children as long as 17 months after injury.[2] Muscle atrophy or the failure or inability of the person to return to the preburn level of physical activity may account in part for this protracted state of reduced bone mineralization.

There is no way to prevent osteoporosis in a patient whose burn is of such severity as to require an extended period of bed confinement. Methods of medical treatment described by Klein[12] and Rousseau et al.[13] include anabolic hormones, bisphosphonates, and cholecalciferol. Cholecalciferol was noted to have a positive effect on muscle health but little effect on bone. The advance of bone atrophy can at least be favorably modified even among patients with large burns if mobilization and active exercise are initiated soon after the burn. The bones of the axial skeleton, the pelvis, and the lower extremities are most efficiently stressed by weight bearing. Thus, standing is a priority measure, and it is common practice now to walk patients to tolerance before permanent wound cover. Muscle contraction alone may help forestall bone atrophy, and bone is better stressed if the contraction is resisted. Isometric muscle contraction is possible from even extensively burned patients and is important for bone stress and for maintaining muscle tone and muscle. Passive motion has no effect on bone and thus does not figure in the prevention of osteoporosis. Other preventive measures, such as closure of the wound and maintenance of nutrition, are routine in critical burn care. Treatment of established osteoporosis involves the more aggressive use of measures for prevention. There are no

Box 48.1 Classification of Musculoskeletal Changes Secondary to Burns

Alterations limited to bone

- Osteoporosis
- Periosteal new bone formation[1]
- Irregular ossification[1]
- Diaphyseal exostosis[1]
- Acromutilation of fingers[2]
- Pathological fracture
- Osteomyelitis
- Necrosis and tangential sequestration

Alterations involving pericapsular structures

- Pericapsular calcification
- Heterotopic paraarticular ossification
- Osteophyte formation

Alterations involving the joint proper

- Dislocation
- Chondrolysis[3]
- Septic arthritis
- Spontaneous dissolution[4-6]
- Ankylosis

Alterations involving muscles and tendons

- Desiccation of tendons[7]
- Fibrosis of muscles[8]

Alterations secondary to soft tissue

- Muscle and joint contractures
- Malposition of joints
- Scoliosis

Soft tissue injury

- Compartment syndrome
- Nerve injury

Abnormalities of growth

- Acceleration and retardation
- Destruction of growth plates

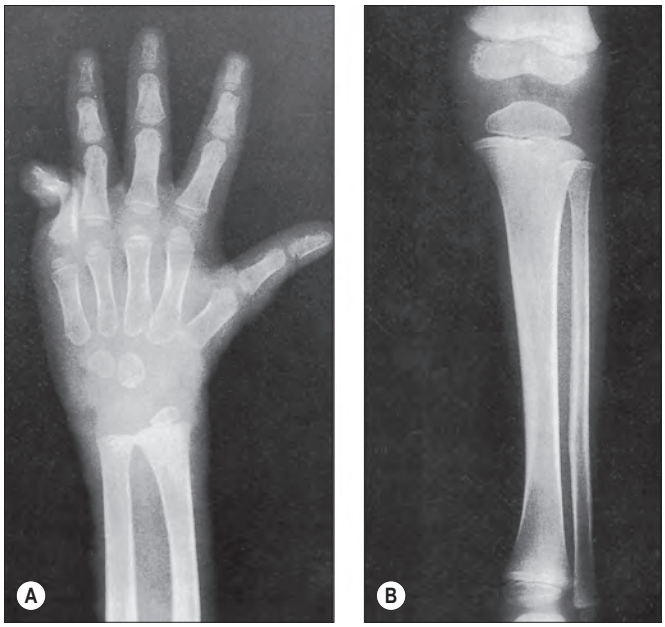

Fig. 48.1 (A) At 6 months after injury, there is the coarsened trabeculation of marked osteoporosis of bones of the left hand and forearm of a 4-year-old boy whose 70% full-thickness burn involved the head, chest, and both upper extremities. **(B)** A radiograph of the left tibia and fibula obtained on the same date as that of the hand shows minimal atrophy.

long-term comparative studies, however, that persuasively measure the effectiveness of exercise, diet, medication, or modality in the treatment of osteoporosis in any state. Thus, osteoporosis can be lessened by active muscle contraction and weight bearing. Medical treatments that show promise include anabolic hormones, bisphosphonates, and possibly cholecalciferol.

OSTEOMYELITIS

In burns, bones can become infected by exposure of bone by the burn, by an open fracture accompanying the burn, by extension of infection from a septic joint, by introduction of organisms along traction pins or internal fracture fixation devices, or by bloodborne organisms of bacteremia. Considering the apparent risk for seriously burned patients to develop osteomyelitis, it is surprising that it does not occur more regularly. Clinically significant osteomyelitis in burned patients is uncommon. Antibiotics given for the general state may prevent seeding of the bone or may repress any small focus of bone infection.

The cortex of long bones is a good barrier to surface organisms. Even exposure of cortex will have little adverse effect if the blood supply of the bone remains intact. Prolonged exposure will kill the outer layer of the cortex, which will in time sequestrate, separating at a well-defined fissure between dead and living bone. With minor or moderate exposure, the bone will usually survive long enough for bordering granulation tissue to cover it. For large defects, it may be useful to drill closely spaced holes through the exposed cortex so as to encourage buds of granulation tissue to emerge from the still vascular medullary canal. Another way to encourage granulation tissue formation over exposed bone is with superficial decortication with an osteotome or burr to expose the capillaries of the inner cortex.[14] With these practices, there is little risk for infecting the bone. It may be that there is sufficient centripetal pressure to discourage the invasion of organisms when the holes are fresh and that the holes are rapidly sealed by blood clot and advancing tissue. There are no reports of deep bone infection related to cortex drilling.

With open fractures at the site of a major soft tissue burn wound, bone infection is probably inevitable. These infections can often remain localized to the fracture site and not involve the rest of the bone. Local debridement and stabilization of the soft tissue wound are all that are required for treatment. Dowling et al. reported osteomyelitis of the tibia related to an open bimalleolar fracture in an extensively burned extremity.[8] English and Carmichael[15] showed three cases of osteomyelitis out of 28 fractures, and all were found in open fractures. On the other hand, osteomyelitis developed in neither of the two open fractures reported

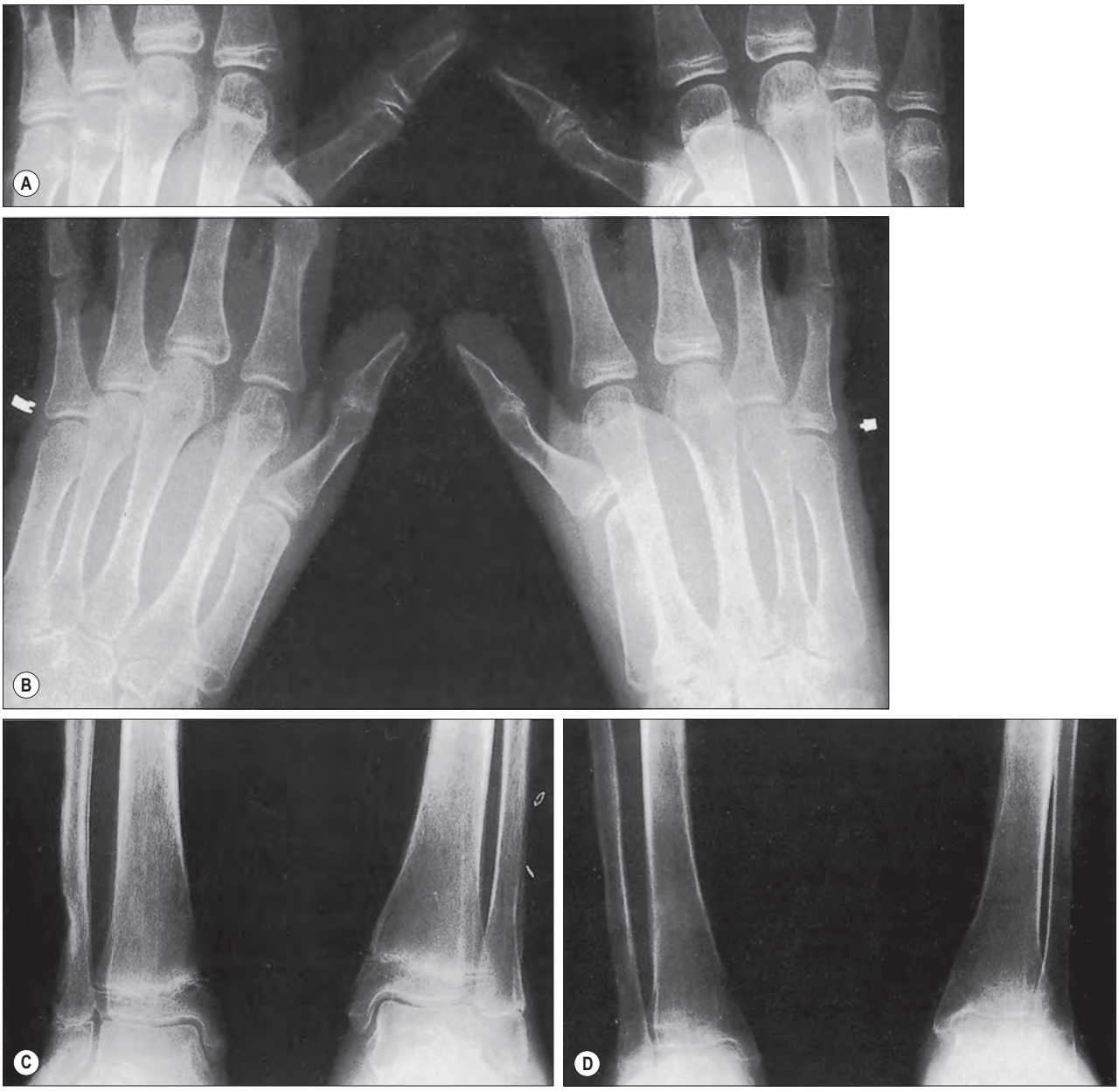

Fig. 48.2 **(A)** Advanced osteoporosis in the hands of a 14-year-old boy 9 months after a 100% total body surface area burn. All growth plates are open. **(B)** At 24 months after injury, osteoporosis persists, and there is irregular closure of the metacarpal and phalangeal growth plates. **(C)** At 8 months after injury, the growth plates of the distal tibiae and fibulae remain open. **(D)** At 24 months after injury, the distal growth plates of the tibiae and fibulae are closed. Other major growth plates remain open. Osteoporosis is unchanged.

separately by Choctaw et al.[16] and Wang et al.[17] We treated three patients in whom open fractures of the femur complicated thigh burns. Each case required aggressive and repeated debridement. One fracture was treated in traction, and the other two were treated with external fixators. In one of the patients, who was admitted 8 months after acute burn, there was established osteomyelitis of the femur in relation to the exposed fracture. Osteomyelitis did not develop in either of the other patients; in the end, all three had sound femurs.

When traction pins are directed through burned skin for the treatment of fractures or for suspension of a burned extremity, the factors favoring development of infection along the pin track and the formation of cigarette sequestra are:

- The introduction or migration of organisms from the burn wound
- Thermal necrosis during introduction of the pins
- Linear pressure of the traction pin
- Prolonged traction
- Excessive movement of the extremity leading to loosening of the pin
- Sealing of the skin of the pin sites.

For traction or suspension, pins may be inserted through acutely burned skin, through eschar, through granulation

tissue, or later through ischemic burn scar, which may be colonized with uncommon and antibiotic-resistant organisms. No amount of local cleaning is likely to sterilize the surface through which the pin must pass, yet it seems that organisms in sufficient numbers to colonize and infect are rarely introduced in this manner.

Local low-grade infections usually resolve when pins are removed if the pin sites are vigorously curetted of granulation tissue. In one case in which a four-pin custom external fixator was used in the treatment of an open infection of the elbow, diffuse osteomyelitis of the humerus and radius resulted. The infection was controlled with antibiotics and without surgery after the pins were removed. This case was included in Barret et al.'s report of skeletal pinning in 41 severely burned children.[18] In experience with the Ilizarov system for correction of skeletal deformity in burns, one patient developed a pin track infection of such severity as to require removal of the pin, curettage, and intravenous antibiotics for control of meticillin-resistant *Staphylococcus* spp.[19] In an ongoing yet unpublished study, we treated nine patients with open joints in external fixation for an average of 7.1 weeks, and none of them developed pin tract infections or osteomyelitis. The open joints were treated in joint-spanning external fixators. Most patients had multiple failed skin grafting procedures before fixator placement. The fixators were thought to have decreased the need for additional skin grafting.

Hematogenous osteomyelitis and that caused by spread from an infected joint are rare. There is no report of the occurrence of either entity in association with burns. If bone infection of this sort were be recognized, effective treatment would depend on the identification of the offending organisms for organism-specific antibiotic regimens.

FRACTURES

Pathological fractures were at one time common in burn management because of the practice of delayed excision of eschar and of keeping patients in bed until wounds were completely covered. During that time, fractures occurred because of bone collapse when patients first stood or walked or when stiff joints were manipulated (Fig. 48.3).[20] The bones most commonly affected were the femur at its distal metaphysis and the tibia at its proximal one. The only treatment required was support of the extremity until the fracture consolidated, usually in 4–6 weeks. Children were more often affected than adults, and the fractures usually compressed one cortex, producing an angular deformity that rapidly corrected with growth. Klein et al.'s study[2] strongly suggests that fractures occur more frequently in burned children than in a matched normal population even months after the acute burn. Now, however, in acute burn management, the most frequently seen fractures are those occurring at the time of, or in association with, the burn injury. Falls or violent trauma account for many of the fractures, and the sites are those common to the causes, bearing no relation to the burn itself.

Although fractures complicate burn treatment and occasionally delay mobilization of patients, their management need not be complex. Fractures in extremities not burned can be treated by manipulative reduction and cast immobilization, by open reduction and fixation, with an external fixator, or with skeletal traction (Fig. 48.4). Fractures in extremities with first-degree or superficial second-degree burns can be managed in the same way. Deep second- and third-degree burns present a different problem only with respect to the early bacterial colonization of third-degree burns and the degradation of deep second-degree burns to full-thickness burns that will in turn become colonized. There is a precious window of time when fractures requiring open reduction and internal fixation (ORIF) can be definitively treated without increased risk for infecting the bone; however, fracture reduction and stabilization are so important in the functional management of a severely burned patient that the risk for bone infection should be acknowledged and shouldered at any postburn stage. English and Carmichael[15] showed that if fractures were treated with open reductions within the first 48 hours postburn, the risk of infection is minimal. Therefore, early stabilization is encouraged in the first 48 hours before the risk of infection increases. Skeletal traction is used infrequently today. The disadvantages of skeletal traction are the confinement to bed and the imposed relatively fixed position of the affected extremity. External fixators make it possible to align and stabilize fractures in burned extremities without open operation and provide mobility to the patient. Brooker's extensive favorable experience supports this concept.[21] With both skeletal traction and external fixation, there is an added risk for bone infection because of the path from surface to bone provided by the pins. Pin tract infections can be minimized by scrupulous pin site care and by removal and replacement of any loosening pins. Frye and Luterman

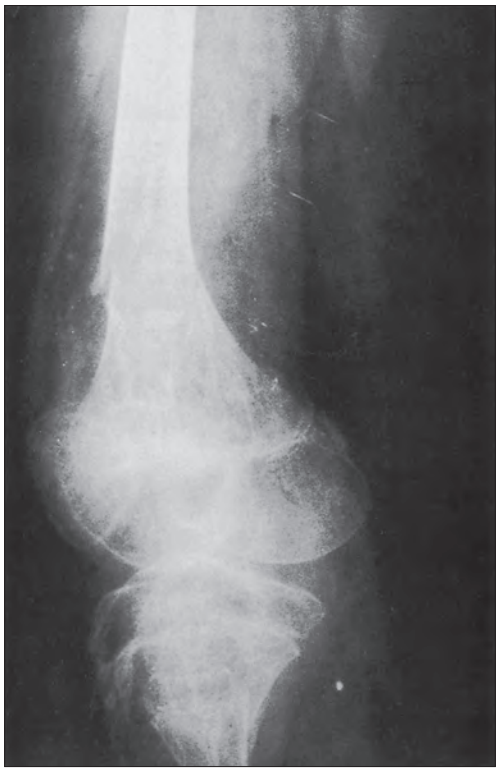

Fig. 48.3 Pathological fracture of the osteoporotic femur of a 9-year-old girl sustained on the first day she stood after 5 weeks of confinement for a 40% total body surface area burn.

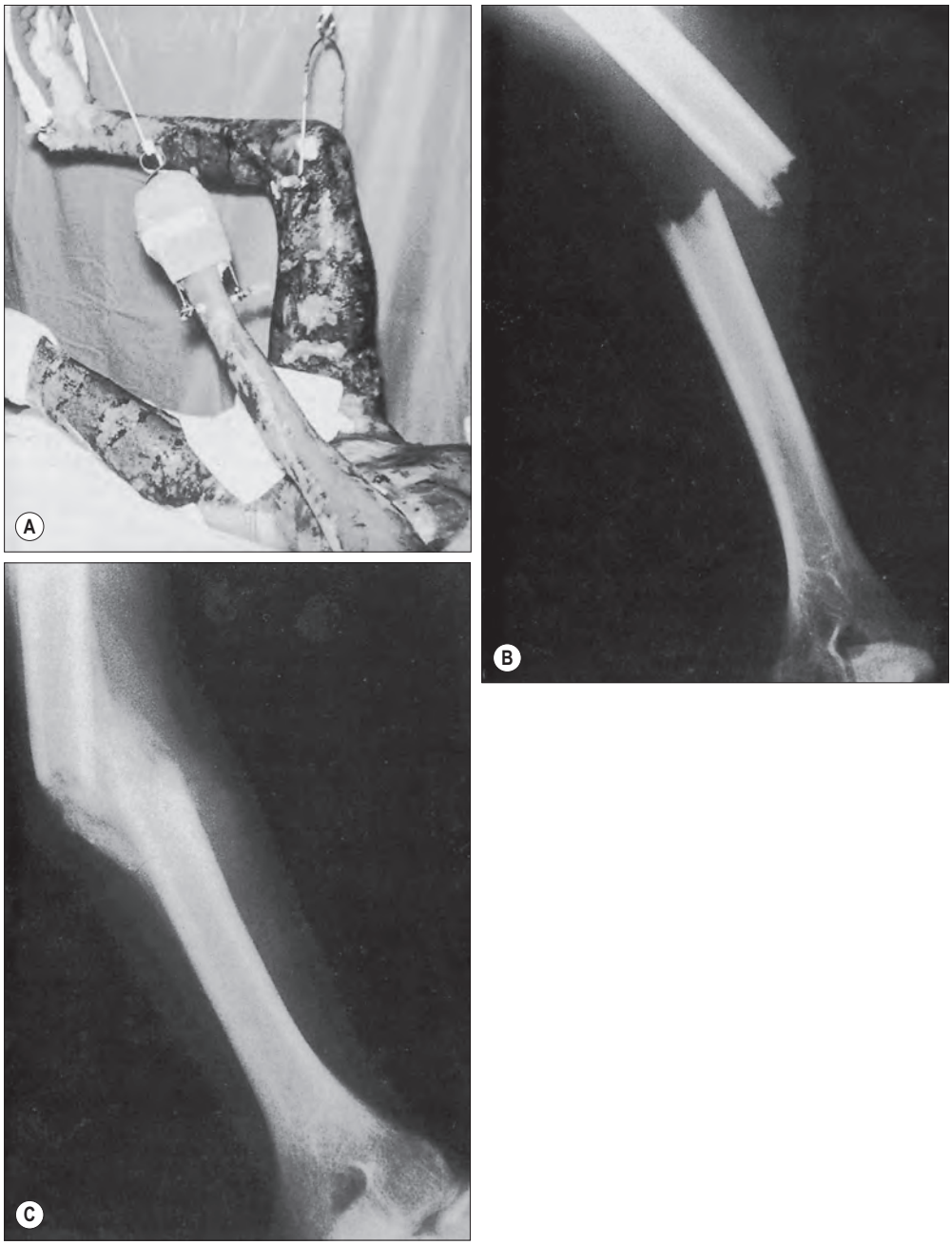

Fig. 48.4 **(A)** This 15-year-old boy sustained closed fractures of the right femur, left tibia, and left humerus at the time of a 46% total body surface area burn involving mainly the trunk and right lower extremity. The femur and humerus fractures were treated in skeletal traction. Suspension of the right lower extremity aided management of circumferential deep burns of that extremity. Lesser burns of the left leg made it possible to treat the minimally displaced fracture of the left tibia in a circular cast. All fractures consolidated in 6 weeks in satisfactory alignment. **(B)** Fracture of the left humerus as it appeared at the time of admission to the hospital. **(C)** At 5 weeks after injury, the fracture shows maturing callus. Traction was discontinued at 6 weeks.

recognized and discussed the specific and continuous difficulties encountered in the management of fractures and burns.[22]

When casts are used for stabilization of fractures in burned extremities, the wound is made inaccessible, and there is an abiding fear that the unattended wound will seriously degrade or at best not improve. Such fear may be well founded; however, Wang et al.[17] showed that a bivalved circular cast could be used effectively for an open comminuted fracture of a proximal tibia with overlying deep burns, and Choctaw et al.[16] reported successful use of a cast for immobilization of an open comminuted fracture after immediate postburn grafting of the affected extremity. Common sense should dictate which fractures can be treated with circular or bivalved casts or with splints. If casts are used over burn skin, they would need to be removable to allow burn care. If a reduced or moderately displaced but aligned fracture is so stable as to require external support only for maintenance of alignment, then cast or splint immobilization should be all that is needed. On the

other hand, if a fracture, because of instability, requires maintenance of reduction by three-point pressure or molding of the cast material, it will be better treated by other means.

English and Carmichael had 28 fractures that were treated over a 20-year span. In that study, 22 of 24 fractures available for long-term review healed in appropriate time. There were five infections noted, including two superficial pin tract infections from external fixation and three cases of osteomyelitis, all of which were open fractures. In contrast, there were no infections among Saffle's 42 fractures, nine of which were treated by ORIF.[23] With two fractures of the femur, each of which was exposed at the base of a deep chronic burn, aggressive debridement of the wounds and the fracture ends was followed by treatment with skeletal traction in one and by external fixation with the Ilizarov system in the other. Both fractures healed without further complication. Coverage of exposed bone can be done with skin grafts, local flaps, and free flaps. Burring of the exposed bone to stimulate bleeding and induce granulation tissue can be used alone or with other procedures to help cover exposed bone.[14] Newer techniques using graft substitute have shown promise in coverage of exposed bones in burn patients.[24,25]

Among severely burned patients, nondisplaced or minimally displaced fractures may not be detected until unusual local pain in an affected extremity prompts radiographic examination. A radiograph obtained for other reasons may reveal a fracture as an incidental finding. These fractures are usually of no functional significance. Modest angular deformity near a joint is more of a problem in adults than in children who still have remodeling potential. Undetected transphyseal fractures in children can be a major functional threat, however.

Changes Involving Pericapsular Structures

HETEROTOPIC OSSIFICATION

Heterotopic ossification (HO) is a rare but functionally important complication of thermal burns. The incidence in a general burn population is reported to be somewhere between 1% and 3%.[1,26–31] In select populations, the incidence may be higher, as it will be if patients with periarticular calcification are included in the statistics. For example, Tepperman et al. reported a 35.3% incidence among patients referred to a tertiary care center for rehabilitation.[32] Jackson and Mac made the observation that the incidence of HO could be expected to be less in institutions that admit patients with minor burns.[33] Munster et al.'s[34] radiographic survey of 88 adult and teenaged patients with 160 burned upper extremities yielded a 16% incidence of pericapsular calcification; the 23% incidence reported by Schiele et al.[1] included both HO and heterotopic calcification. In the early routine radiographic study reported by Evans,[20] periarticular calcification that did not progress to HO was excluded from the final calculation of an incidence of 2%. The 3.3% incidence recorded by Kolar and Vrabec[35] included patients with pericapsular calcification. Pandit[11] noted pericapsular, periarticular, and tendon calcifications at around 1.25% each in a radiographic study. Even if HO occurs infrequently in thermal burns, it remains that after it develops, it often compromises joint motion and is difficult to treat. In addition, its pathogenesis is still incompletely understood; thus, protocols for prevention may in fact miss the mark.

PATHOGENESIS OF HETEROTOPIC OSSIFICATION

The metabolic changes occurring after thermal burn are increased metabolic rate, protein catabolism, ureagenesis, fat mobilization, glycogenolysis, gluconeogenesis, elevated glucose flow, and eventual total body weight loss.[36,37] There is an accompanying suppression of the immune system that favors wound infection but at the same time favors survival of skin allografts. Infection, failure of skin graft take, or anything that delays closure of a burn wound will extend the altered metabolic state. Although it might be assumed that there occurs, along with the metabolic upheaval, an adverse change in connective tissue milieu, the exact nature of such a change is not known. It is also not known what the metabolic changes have to do with the development of HO, but it is apparent that the burn disease is necessary to its formation. Other factors to be considered in the genesis of HO are percentage of burn, location of burn, period of confinement, osteoporosis, superimposed trauma, and genetic predisposition.

Percentage of Burn Effect on Heterotopic Ossification

Most reported cases of HO have had a 20% or greater total body surface area (TBSA) burn; however, it has been found in patients with as little as 10% third-degree burn.[20] Peterson et al.,[29] Munster et al.,[34] and Elledge et al.[28] have reported affected patients with TBSA burns of 8%, 14%, and 12%, respectively. In addition, with the now extensive experience with salvage of patients with 80% or greater burns, it is clear that HO occurs no more frequently among these patients than in the general burn population. Thus, the percentage of burn is not a determining factor.

Location of Burn Effect on Heterotopic Ossification

By no means has all of the reported HO occurred in joints with overlying burn. In their initial report, Evans and Smith described HO occurring a distance from any third-degree burn involvement.[38] Johnston noted that in one of his three patients, the skin overlying one affected joint was not even superficially burned.[39] If degradation of connective tissue milieu in burns is a total-body phenomenon, it follows that heterotopic bone formation need not be burn site dependent. Thus, the location of the burn cannot alone be a determining factor.

Period of Confinement Effect on Heterotopic Ossification

Evans and Smith expressed the belief that length of bed confinement was an important factor in the development of HO.[38] At the time of that report, patients with even moderate burns might be kept in bed for several weeks. The consequences of prolonged confinement were loss of active range of joint motion and bone demineralization; it was

thought that each of these adverse changes might contribute to the formation of HO. Thus, any maloccurrence that necessitated longer confinement could be a factor in the pathogenesis. Kolar implicated wound sepsis as an independent factor along with the length of confinement.[35] Other investigators have not addressed the period of confinement as specifically as Kolar, and there have been no comparative studies of groups of confined and nonconfined patients. Thus, it may never be determined whether the current aggressive practice of early mobilization of patients will have an effect on the incidence of heterotopic bone. We believe the incidence of HO is lower at our institution after the advent of early mobilization postoperative protocols.

Osteoporosis and Heterotopic Ossification

Only Schiele et al. have found a relation between HO and osteoporosis.[1] Among their group of 70 adults with burns confined to the upper extremities, 11 of the 16 who developed HO had radiographically identifiable osteoporosis. In their series of patients, there were 24 with osteoporosis. Thus, fewer than one half of these developed HO, and there were two in the group who developed HO who did not have osteoporosis. If the findings in that study are not altogether persuasive, the matter is further confused by the knowledge that the survivors of extensive TBSA burns, who may develop profound osteoporosis, seem to have no greater liability to the formation of heterotopic bone than the general burn population.

Superimposed Trauma on Heterotopic Ossification

In one of the patients reported by Evans and Smith, the elbow of the more often used and minimally burned right upper extremity developed HO, but the elbow of the less used but more seriously burned left upper extremity did not.[38] In the same patient, the right hip spontaneously dislocated. After reduction, that hip developed extensive HO in the planes of the rectus femoris and iliopsoas. The opposite hip developed only a small, inoffensive spicule of HO anteriorly at the joint line. Experience with this one patient reinforced the authors' belief that there occurs with burns a general compromise of connective tissue that renders it particularly susceptible to superimposed trauma and that it is this liability to injury that accounts for the appearance of HO at sites of repeated stretching of soft tissue, as at the minimally burned elbow or at sites of recognized abrupt excessive stretching as with the dislocated hip. According to all reports, the elbow is the most common site of HO in adults and children.[28,29,35,40–47] Perhaps it is the regular use of this joint that accounts for that orientation. Jackson has pointed out that the elbows are subjected to pressure posteriorly and medially when they are used for leverage or are simply in contact with the bed.[33] He suggests with this observation that external pressure is a factor in the orientation of HO to the elbow. There may be other factors that favor the elbow. Commonly, the elbow is splinted in extension to prevent flexion contracture. If flexion range is lost, passive stretch and encouragement of active flexion are part of the rehabilitation effort. The posterior structures most affected by this effort are those attached to the olecranon. HO often develops medially in line with and deep to the medial fibers of the triceps. If a flexion contracture develops, the HO is commonly in the line of brachialis or biceps attachments to coronoid process and biceps tubercle. And if there is loss of pronation and supination range, stretching may cause HO to form in line with the proximal radioulnar ligaments and interosseous membrane. There is an implication here that both the quality and timing of postburn exercise may be important. Gentle passive and active motion should cause less tissue disruption than abrupt passive or active or even chronically repeated motion, and the effect of any mobilization effort must vary with the relative stiffness of the joint and the intrinsic resistance of soft tissue. The longer a joint is limited in its motion, the stiffer it will become and the greater will be the soft tissue damage with any forced manipulation.

The concept of superimposed trauma as a cause of heterotopic bone is supported by the experimental work of Evans[48] and of Michelsson and Rauschning.[49] Evans found that all burned and nonburned rabbits given a single necrotizing injection in one quadriceps muscle readily healed the lesions, but rabbits burned or nonburned that were given a second same-site injection 7 days after the first uniformly developed well-defined and histologically identifiable HO. In this experiment, it was clear that in susceptible animals, it was not the burn that made the difference but the chronicity of the wound. Michelsson and Rauschning determined that forceful or regular active remobilization of rabbit knees that had been immobilized for 1 to 5 weeks resulted in the development of heterotopic calcification and ossification in the muscles that were stretched. The response was more consistent in the quadriceps of the knees immobilized in extension than in the hamstrings of those immobilized in flexion. The longer the period of immobilization and the more vigorous the remobilization, the greater was the response. Muscle necrosis was a prominent histologic finding.[50]

Superimposed trauma is implicated in the development of HO in head-injured patients or those with posttraumatic or infectious transverse myelitis.[51–53] In these patients, it is assumed that tissue media are altered by injury to the central nervous system. The secondary injury, as in burns, is periarticular. In posttraumatic myositis ossificans, the development of HO depends on persistence of the muscle lesion and local necrosis and thus, at least by inference, on repeated insults to the affected muscle.

The development of HO in burns has been associated with the agitation of patients and their resistance to physical therapy.[38,54] Two affected adults and one affected child in a 10-year study resisted physical therapy programming.[48] One adult refused to move, and the other was extremely apprehensive. The child was likewise apprehensive and refused to cooperate with the therapist. The development in all three of posterior HO in both elbows could have been ascribed both to the difficulty encountered in mobilizing the elbows and to the continual pressure on the elbows in bed.

Genetic Predisposition to Heterotopic Bone

It is difficult to explain the low incidence of HO among great numbers of patients similarly burned except on the basis of some, as yet unidentified, inherited factor. It is known that persons with proliferative noninflammatory arthritis of the hip are more likely to develop HO after total hip replacement than persons who have hips replaced for other reasons. In this instance, the predisposing inherited abnormality is

identifiable. Although HO formation may occur more regularly among spinal cord-injured and head-injured patients than among burned ones, by no means do all persons with head and spinal cord injuries develop HO. The total burn experience at the University of Texas Medical Branch has yielded only two similarly affected siblings. Twin brothers who had 19% and 20% TBSA burns and who were mobile throughout much of their treatment and recovery period developed near-identical HO of both elbows.[55] There is, however, no scientific proof that genetic predisposition has anything to do with the formation of HO in burns. Nor is there any literature to support the idea that a person who develops HO when burned will be liable to develop it if he or she sustains head or spinal cord injury. Vrbicky,[56] in a comprehensive review of postburn HO formation, suggests that a key for the genetic predisposition may be in the human leukocyte antigen (HLA), reporting that an HLA B27 survey showed a 7% HLA distribution in the normal population compared with 70% in a population with HO.

CHARACTERISTICS AND BEHAVIOR OF HETEROTOPIC BONE

Heterotopic ossification associated with burns has been reported to occur about all major joints. The joints most commonly affected are elbow, shoulder, and hip, in that order of frequency. The early manifestations are joint swelling and tenderness not unlike any acute inflammatory process. The patient may call attention to the process by a reluctance to move the affected joint. Onset may be as early as 1 month and as late as 3 months or more after the burn, but it is more likely to be associated with the acute recovery phase of treatment than later. Crawford et al. reported that the clinical diagnosis was made in advance of radiographic changes in 9 of his 12 patients.[40] Tepperman et al.[32] and Peterson et al.[29] found that bone scans could help make a diagnosis before there were radiographic changes. The earliest radiographic alteration is local periarticular increase in soft tissue density. There follows diffuse, stippled calcification in the same distribution in or about the capsule of the joint. It is at this point that the process may reverse itself, perhaps because of the improved state of the patient. Owing to this change in course, there may be patients whose periarticular calcification is not detected. If the calcification persists, it may be assumed that bone will develop by either the intramembranous or the enchondral route or both, as it does in animal models.

The flecks of calcification appear radiographically to lie within the capsule, but HO not only may involve capsular structures but also may extend into the planes of muscles and tendons. At each major joint, there is a more or less characteristic distribution of HO, which is similar to that associated with patients with head and spinal cord injury. At the elbow, posteriorly disposed bone extends from the olecranon to the medial epicondylar ridge of the humerus in line with the medial border of the triceps muscle (Fig. 48.5A and B). At the joint, it may extend medially to bridge the ulnar groove.[57,58] The medial, rather than lateral, orientation of the heterotopic bone may be related to the medial position of the olecranon and the greater tension on soft tissue on that side, and as Jackson points out, the contact area of the elbow is consistently medial.[33] HO on the anterior surface of the elbow develops in the planes of the brachialis and biceps muscles extending from the humerus to the coronoid process or the biceps tubercle. Occasionally, a bridge of HO develops between the radius and ulna just distal to the joint. More rarely, bone has been found to fill the olecranon fossa and even to ensheathe the entire joint. At the shoulder, bone has been found to extend from the acromion to the humerus in the line of the rotator muscles or deep to the deltoid (Fig. 48.5C), to lie anteriorly in the plane of the pectoralis major, and more deeply, to parallel the subscapularis. Hoffer et al.[59] reported that HO at the shoulder lay anteriorly in the plane of the capsule. At the hip, HO may extend from pelvis to femur in the planes of rectus or iliopsoas anteriorly or in the plane of the gluteal muscles laterally. Jackson has reported HO in the plane of the quadratus femoris.[33] Similar to the shoulder, the hip may be ensheathed anteriorly with HO that appears to originate in the capsule.

When HO bridges a joint, it becomes part of the skeleton and may, if loaded, increase in dimension as a fully developed ossicle with mature cortex and medullary cavity. In children, if the bone does not bridge a joint, it will gradually disappear when the burn wound has healed and the child is healthy. In recovering adults, nonbridging bone will, in time, diminish in size, but it may not disappear. The same tendency for heterotopic bone to regress after resolution of disease was noted by Lorber, who reported on two patients with paraplegia secondary to tuberculosis in whom deposits of heterotopic bone diminished in size after return of motor function.[51] Bottu and Van Noyen[60] reported a similar experience with a patient who had transient viral meningoencephalitis, and Jacobs reported almost complete resorption of large bilateral deposits of heterotopic bone in a patient who recovered from paralytic measles encephalomyelitis.[52] Serum concentrations of calcium, phosphorus, and alkaline phosphatase (ALP) have been reported by most authors to be normal or, at best, insignificantly higher in burned patients who have developed HO.[26,34,38,61,62] In addition, there is no convincing evidence that calcium intake affects heterotopic bone formation one way or the other. Evans and Smith's limited routine studies of affected and unaffected patients led the authors to believe that the values of serum calcium, phosphorus, and ALP were so consistently normal as to make further investigation unnecessary.[38] One interesting observation was that of Koepke, whose studies suggested that those patients who were susceptible had elevation of serum ALP before development of heterotopic bone but not afterward.[27]

PREVENTION AND TREATMENT OF HETEROTOPIC BONE

The incidence of HO in burns is so low as to make it impractical to administer indometacin or other nonsteroidal antiinflammatory drugs (NSAIDs) that are currently used for patients at risk for development of heterotopic bone after major hip surgery. Rather, the thrust in prevention should be toward reducing the period of bed confinement and the duration of the postburn hypermetabolic state. The now prevailing practice of early wound excision and grafting may, in fact, address both of these problems as nearly as it is possible to do so. Even patients with extensive TBSA burns

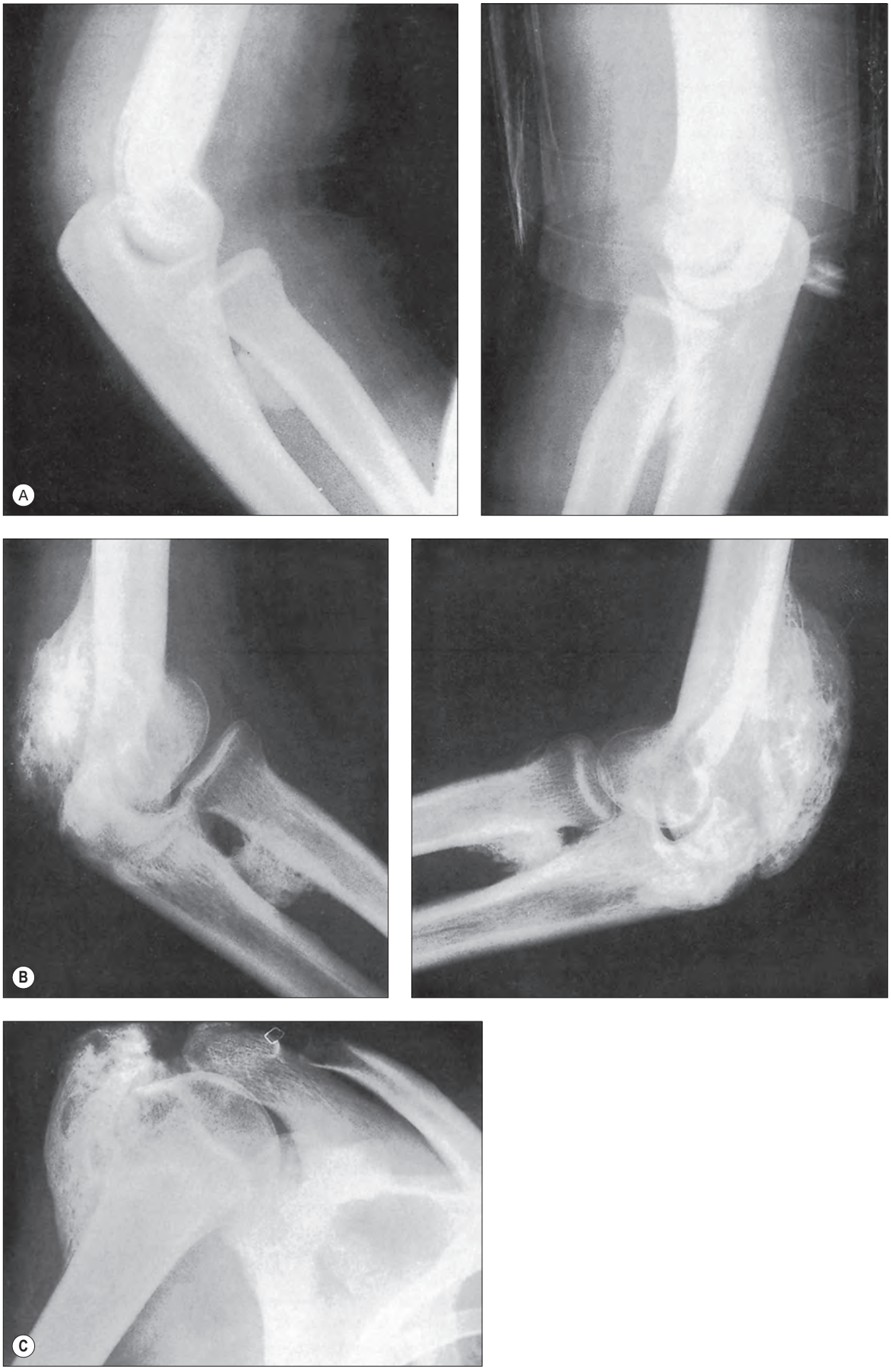

Fig. 48.5 **(A)** At 3 months after a 94% total body surface area burn of a 16-year-old man, resistance to motion, local swelling, and pain of both elbows prompted obtaining radiographs, each of which showed spotty linear soft tissue calcification and ossification along the distal humerus and between the radius and ulna at the level of the biceps tubercle. **(B)** At 6 months after burn, elbow flexion and extension were reduced to 10 degrees on the left and to less than 5 degrees on the right. Bridges of immature heterotopic bone extended from the medial epicondylar ridges to the olecranon. Forearm rotation was 0% because of interosseous bridges of heterotopic bone at the level of the bicipital tuberosities. The prognosis for restoring functional range of motion in the elbows is poor. **(C)** At 6 months postburn, glenohumeral motion on the right was limited to a few degrees by heterotopic bone underlying the deltoid. At the same time, a lesser deposit of heterotopic bone at the left hip did not limit motion.

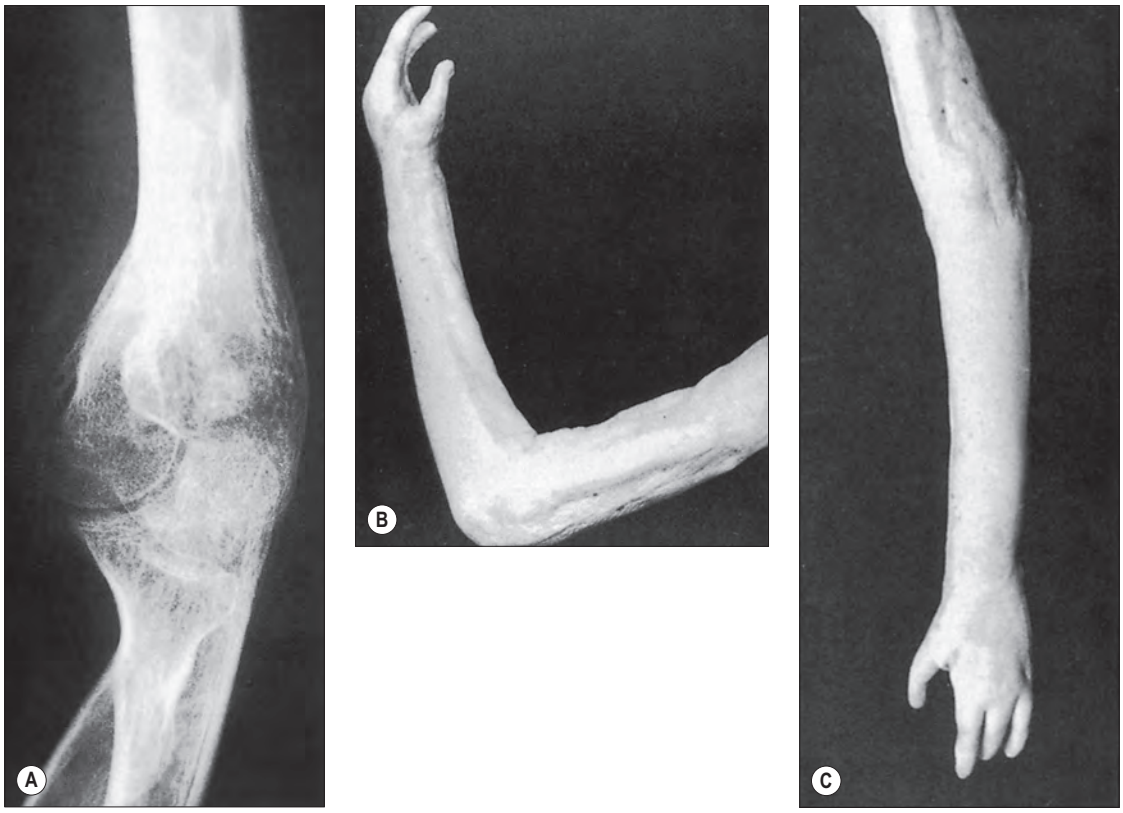

Fig. 48.6 (A) A mature sheet of heterotopic bone extends from humerus to olecranon, obliterating the olecranon fossa 11 months after a 53% total body surface area burn in a 13-year-old girl. Elbow flexion and extension range were less than 10%. Pronation and supination were near normal range. **(B** and **C)** At 3 months after excision of heterotopic bone, the patient had attained 90 degrees of elbow motion, and a continuing increase to functional (hand to mouth) range was predicted. Now the patient can extend the elbow and can flex it to 90 degrees.

may now be out of bed and walking within the first postburn week.

If certain patients are predisposed to the development of HO, the quality and timing of joint mobilization for those patients may be critical. Stretching edematous pericapsular structures in the early postburn period may very well be hazardous if additional tissue damage is the result; however, maintenance of joint motion and muscle function is part of the early excision and grafting program, and it is certain that the longer joint motion is restricted the more likely it is that pericapsular structures will be damaged by stretching. We like to think that secondary injury to soft tissue can be avoided by controlled and assisted active range of motion (ROM) and terminal resistance.

When a patient is reluctant to move a joint previously moved with relative ease, and certainly when there is evidence of unusual swelling about the joint, radiographs should be obtained to determine if there is pericapsular calcification or ossification. After heterotopic bone or calcification is recognized, joint exercise should be restricted to gentle passive and assisted active motion only. Crawford et al.[40] observed that ossification progressed to complete ankylosis in all patients who persisted in moving an affected joint beyond the pain-free range. They concluded that active ROM exercises and stretching were contraindicated if heterotopic bone or calcification was suspected, but that active ROM could be safely resumed within pain-free range after the diagnosis had been confirmed. In the series of Peterson et al.,[29] patients suspected of having HO had active ROM exercises only. Ten regained functional ROM, and eight developed ankylosis.

Surgical excision of heterotopic bone is indicated when joint motion is lost or significantly compromised by bridging bone or exostoses. Evans has suggested that surgery be postponed until the burn wound has healed, scars are soft and associated with no inflammatory response, the patient is healthy, and the offensive bone is radiographically mature (i.e., well-defined and not increasing in dimension) (Fig. 48.6).[20] This position makes sense considering the behavior of heterotopic bone (i.e., proliferation while there are open burn wounds or active scars and regression with wound healing and scar softening). For removal of heterotopic bone, surgical exposures should be planned with extensible incisions so as to facilitate total excision. When there is a bridge of bone, each end of the bridge should be slightly excavated. When there is attachment at only one end, the cartilaginous or fibrous extension should be removed along with the bone. Capsular sheets of bone should be removed completely. If bridging heterotopic bone is incompletely excised, the bridge is likely to recur. When a joint is bridged by bone in only one plane, removal of the offending bone will usually restore functional motion, and recurrence of the bridge is unlikely. When a joint is bridged in more than one plane, recurrence is more likely, and the chance for restoration of functional ROM is correspondingly diminished. When the local inflammatory process has

caused intraarticular synovial proliferation and cartilage destruction, the joint is most likely destined for ankylosis. Removal of the heterotopic bone about a joint so affected may allow more functional positioning of the joint, but it is not likely to arrest the process. On the other hand, extraarticular arthrodesis by a bridge of heterotopic bone may preserve the joint. This is particularly the case at the elbow when there is only one posterior bridge of bone from olecranon to the medial epicondylar ridge of the humerus. In this situation, the olecranon is fixed in the trochlea, but the radiocapitellar and radioulnar joints remain functional. In Evans' experience with removal of single bridges at the elbow, joint cartilage was found to be healthy as long as 5 years after ankylosis. Preservation of pronation and supination was credited with maintaining the synovial bath to provide nutrition for the humeroulnar cartilage. Indeed, when pronation and supination additionally are blocked by bridging bone, cartilage degradation is certain. Evans' further experience with long-term survival of glenohumeral cartilage after ankylosis by bridging bone from acromion to humerus is not as easily explained.

Reported experience with excision of heterotopic bone in burns has not been uniformly favorable. Dias,[62] Hoffer et al.,[59] and Peterson et al.[29] reported restoration of functional ROM in most of their patients with timely excision of heterotopic bone. Gaur et al.[41] reported good functional return in seven burned children with nine affected elbows. Ring and Jupiter[42] reported good results in a varied population, and Chung et al.[43] and Tsionos et al.[45] have reported good results with early excision a mean of 9 months after the burn. Other surgeons have reported less satisfactory results.[31] In our own experience, results have varied, as anticipated, with the severity of the condition. We have learned that if heterotopic bone recurs after excision, it is worthwhile to excise again if the joint affected remains structurally identifiable. For the most part, however, attempts to improve joint function with second operations have failed. We believe that ultimate failure can be predicted at the time of initial surgery; we are convinced that the single most important factor in successful initial excision is in timing surgery to coincide with the patient's return to good health.

Changes Involving the Joints

DISLOCATION

Luxations and subluxations of joints in burned patients may occur as a result of direct destruction by the burn of ligaments and capsules, loss of articular cartilage caused by infection, faulty positioning, and eventually scar contracture. In all phases of management, but particularly in the acute phase, positioning is of prime importance in the prevention of joint deformity. The preferred positions, listed in Table 48.1, serve as a guide for the prevention of dislocation of joints and of malposition secondary to scar contracture.

The joints most liable to structural compromise caused by exposure by the burn and loss of soft tissue support are knee, elbow, proximal interphalangeal joints of the hand, and metacarpophalangeal joints. These hinge joints have in common a subcutaneous dorsal surface, accounting for their ready exposure. The bone and joint changes are found mostly in severely burned patients and include contractures and even ankyloses of smaller joints.[11]

Table 48.1 Preferred Positions for Major Joints

Joint	Preferred Position
Neck	Midline in neutral or slight extension
Shoulders	Scapulothoracic retraction and depression, 85 degrees of glenohumeral elevation with 20–25 degrees of horizontal flexion
Elbows	Extension
Wrists	Slight extension
Metacarpophalangeal joints 2–5	80–90 degrees of flexion
Fingers	Proximal and distal interphalangeal extension
Thumbs	Carpometacarpal flexion and abduction, metacarpophalangeal flexion 5–10 degrees, interphalangeal extension
Spine	Extension with no lateral deviation
Hips	Extension and slight external rotation in 15 degrees of symmetric abduction
Knees	Extension
Ankles	Neutral
Feet	Neutral

The elbow, for its trochlear architecture, is more intrinsically stable than the other joints in this group. It requires loss of collateral support to render it easily displaceable. The knee, on the other hand, is immediately in danger of subluxation if there is loss of continuity of its central slip, the patellar tendon, even if the retinacula remain intact. In this circumstance, gravity alone will displace the tibia posteriorly in relation to the femur if the patient is recumbent. The hamstring muscles contribute to the displacement force regardless of the position of the extremity. Loss of collateral ligaments compounds the problem, but loss of collateral ligament stability in the presence of an intact patellar tendon and functioning quadriceps constitutes far less a threat than loss of patellar tendon. For the lower extremity, persistent posterior translation of the tibia beneath the femur with inefficient quadriceps function leads to severe functional problems.

For both the elbow and the knee, the protecting position is extension. These two joints are rarely at risk for articular displacement from contracture alone and, if there is no ligament or tendon loss, extension resting splints will give adequate positional support. When there is soft tissue disruption, splinting may not adequately protect either joint. An external fixator with two-pin, four-cortex fixation above and below the joint will provide stability and will permit access to the wound. For the elbow, it allows fine adjustment to the normal carrying angle as well. If the knee is accurately reducible at the time of application of the fixator, there is a good possibility that the reduction can be maintained. If the tibia cannot be brought forward completely by manual manipulation, it may be necessary to

suspend the tibia through a transverse pin at the level of the tibial tubercle. For static vertical traction, the extremity must be elevated from the bed. For dynamic traction, enough weight must be used to accomplish the same elevation. If the tibia can be brought forward by this means, an external fixator will hold the reduction. For the knee to remain stable with the tibia forward, the patellar tendon must be reattached and quadriceps integrity reestablished; otherwise, when the fixator is removed, the tibia will again begin an incremental posterior shift toward its own point of stability. No amount of external splinting or bracing is likely to prevent this shift.

The proximal interphalangeal joints of the hands are more frequently exposed by burn than any others. If the central extensor slip remains intact, there is less risk for subluxation of the joint. Even if there is loss of continuity of the central slip but preservation of the lateral bands, subluxation is easily prevented if the joint is maintained in extension while soft tissue cover is being achieved. It is with loss of the support of lateral bands and collateral ligaments that the joints become liable to dislocation. With the metacarpophalangeal joints, the tendency to displacement or subluxation may be greater because these joints are functionally multiplanar, but the interphalangeal joints are uniplanar. Fortunately, the metacarpophalangeal joints are less often exposed than the interphalangeal ones.

The protecting position for the proximal interphalangeal joints is full extension. If only the central slip is lost, the position may be held with an external splint. In states of greater instability, it may be necessary to use intramedullary transarticular Kirschner wires to hold the position. The wires, although reasonably efficient, do not control rotation, and they carry with them a risk for posttreatment joint stiffness. In small children, it is impossible to introduce the Kirschner wires through the distal phalanx; thus, it is better, with the proximal phalanx flexed to 90 degrees, to place the wire through the corresponding metacarpal head into the proximal and middle phalanges. Short-term transfixation does not harm the joint, and metacarpophalangeal flexion is the favored position for functional restoration. Pin traction through the distal phalanges in a skeletally stabilized metal splint is another method for maintaining extension of threatened digital joints.[63,64] It has the advantages of patient comfort and mobility; secure positioning of hand and upper extremity; easy maintenance of elevation; and easy access for dressings, for additional surgery, and for exercise of lesser affected joints. The system likewise makes it possible to keep digits separated, thus facilitating local care. Traction should not be used if collateral ligaments are not intact. By whatever means attained, the corrected position must be maintained until the joint is covered with graft. Protection should continue with a standard splint or brace until the joint is sound.

The two joints most likely to dislocate because of faulty positioning are the shoulder and the hip. These two ball-and-socket, multiplanar joints sacrifice stability in favor of mobility. This is particularly true of the shoulder, where the shallow glenoid contains at any one time only one third of the head of the humerus. In burns, the head of the humerus may begin to subluxate forward if, during prone positioning for management of back and buttock wounds, the arms are maintained in full abduction in the coronal plane. In this position, the arms are in at least 15 to 20 degrees of extension from the more secure neutral position in line with the scapulae, and the humeral heads are forced forward against the anterior capsule. Even when the patient is supine, full abduction and extension of the arms should be avoided. For short-term management, particularly when the patient gets out of bed each day, this position probably does not threaten the joint. But if the patient is to be bed confined and the position unrelieved for days or weeks, the head of the humerus may begin to subluxate forward. In the extreme situation, the head of the humerus will dislocate to a medial subcoracoid position. In patients with deep burns extending from the chin to the axillae to the chest, the common posture of elevation and protraction of the scapulae may be associated with upward subluxation of the humeral heads.

The head of the humerus is most secure in the glenoid fossa when the arm is adducted to neutral and internally rotated, a position that is incompatible with wound management of burns of the trunk, neck, and upper extremities. The protecting position that accommodates the need for abduction for axillary burns is elevation of the arms in line with the scapulae. The arm is then approximately 20 degrees forward of the coronal plane or in 20 degrees of horizontal flexion. When the patient is prone, the protecting position can be gained only if the chest is supported on a chest width mattress, folded blankets or towels, or a foam rubber pad, any of which will allow the arms to drop forward. When the patient is positioned this way, whether supine or prone, the forearms will be pronated, and the arms will be in sufficient internal rotation to favor seating of the head of the humerus in the glenoid.

The hip will tend to subluxate posteriorly if the thigh is persistently allowed to remain flexed, adducted, and internally rotated during the acute burn phase. For the most part, however, the protecting position of extension to neutral or 180 degrees and 15 to 20 degrees of symmetric abduction is easy to attain and maintain and is, in fact, the most desirable position for wound management.

Infection of a joint may result in its subluxation or dislocation. Hip displacement because of apparent spontaneous dissolution has been described by Evans and Smith.[38] Eszter and Istvan[65] and Cristallo and Dell'Orto[66] reported similar cases. In none of these cases, however, could it be determined that the joint destruction was attributable to infection.

SEPTIC ARTHRITIS

A joint exposed by a burn or by removal of burn eschar is presumed to be infected. The joints most frequently exposed are the knee, the elbow, the proximal interphalangeal joints of the hand, and the metacarpophalangeal joints, all on the subcutaneous dorsal surfaces. The wrist and ankle are less often affected, and other joints are affected rarely. Treatment requires stable positioning of the joint for maximum reduction of wound size so as to facilitate soft tissue closure or grafting and to allow aggressive daily lavage. The position for all of the joints listed except the ankle is extension. The ankle is positioned in neutral. External fixation, intramedullary pinning, or skeletal traction may be required to secure the position. To maintain ankle position, it is

sometimes appropriate to insert a large vertical Steinmann pin through the calcaneus and talus into the tibia. The position should be maintained until the exposed joint is covered with epithelialized granulation tissue or skin graft. Exposed adjacent bone can be shaved or drilled, as previously described, to encourage surface granulation. Drilling is particularly useful at the elbow where the olecranon is regularly exposed. Often, however, granulation tissue will quickly extend the wound margins and effectively close the wound so as to allow split-thickness skin grafting. If the burn is isolated to the joint or if the extremity is not otherwise seriously burned, a local muscle, skin, or compound flap may be used to close the joint. Free vascularized flaps are useful and should always be considered if it is anticipated that nerve graft or tendon graft or transfer at the site will be required in the future. Incremental remobilization of the joint may proceed when wound closure is sound. Culture of material from an exposed joint will likely yield a variety of organisms consistent with those of the general burn wound, thus requiring broad-spectrum antibiotic management.

The incidence of hematogenous septic arthritis is obscured by its frequent association with severe burns and because there are rarely separable clinical signs such as local heat and swelling, elevation of temperature, and elevation of sedimentation rate. Local tenderness and greater than usual pain with motion may focus attention on the affected joint. Aspiration of the joint will confirm a diagnosis. A radiograph is helpful but in the early phases of infection will show only local cellulitis as increased periarticular soft tissue density. If a patient has been receiving broad-spectrum antibiotics, material aspirated from the affected joint may not grow an organism in culture. Clearly, without organism identification and sensitivity determinations, specific antibiotic therapy cannot be initiated.

We are of the opinion that surgical debridement and exteriorization of the joint and regular vigorous lavage are as important as antibiotics in the treatment of closed infected joints. We believe now that arthroscopic debridement and closed irrigation should be considered as an alternative method of management whether or not skin over the affected joint is burned. Rarely in burns, a joint may become infected from adjacent metaphyseal osteomyelitis. In this situation, joint preservation is the treatment priority, and measures are the same as for septic arthritis of strictly hematogenous origin.[55] In children, most infected joints can be salvaged. Adult joints are less resilient. Persistent joint infection will destroy cartilage and lead to ankylosis.[67,68] All chronically infected joints are liable to dislocation because of surface destruction and capsular laxity.

AMPUTATIONS

In thermal burns, major amputations are most often performed because of nonviability of the extremity or because a surviving extremity is rendered useless by scar, deformity, or insensitivity. Occasionally, in an extensive burn, a severely burned extremity that might be salvaged in part is sacrificed to reduce the extent of the burn or as a lifesaving measure. In thermal burns, the level of extremity amputation is determined by the viability of muscles and tendons. The more distal the site, the better, and it is important to retain joints even if motion will be restricted. For example, if a forearm or leg must be sacrificed, the elbow or knee should be spared if the more proximal muscles controlling that joint are intact, if the bone bleeds, and if there is the possibility that the remaining tissue of the stump has sufficient blood supply to produce granulations for grafting. Aside from affording a better functional prospect, sparing the joint will provide the surgeon opportunity at a later time to choose an appropriate revision level if the joint does not function. The patient will at that time be healthier, and stump closure will be routine. Jackson suggests that it may be technically feasible to cover even nonviable bone with a free flap to maintain extremity length.[33] In electrical burns, the level of amputation is most often determined by muscle viability. Stump care is the same as with thermal injury.

Prostheses can be easily fitted over stumps covered with split-thickness grafts. Ridges of hypertrophic scar will break down if there is friction within the socket of the prosthesis, but scar often softens and flattens with the constant, even pressure of a well-fitted socket; prostheses fitted early over grafted stumps may prevent scar thickening. Breakdown may occur at points where the graft is adherent to bone. This problem may require surgical freeing of the adherent graft and reshaping of the bone. Minor hip and knee flexion contractures complicate the fitting and function of a prosthesis; thus, every effort should be made to maintain full extension of these joints. Late revisions of amputations in children are required when the bone overgrows in length and when offensive terminal exostoses develop. The overgrowing bone can be shortened and the exostoses removed. Klimisch et al.[69] studied 259 amputations for burns at our institution. Stump overgrowth requiring revision surgery occurred in 10% of patients and 5.8% of amputations. Lower-extremity amputations had overgrowth in about 16% of stumps and the upper extremity in 2%.

It is important in the early management of upper-extremity amputations in infants and young children to supply temporary prosthetic extensions. This provides functional orientation to a prosthesis, maintains muscle bulk and tone, and encourages continuing bimanual activity at normal extremity length until a prosthesis with an appropriate terminal device can be applied. Children quickly acquire prehension and transfer skills if they have an opposable stump, and they may reject prostheses if they are not applied early. It is equally important to restore bipedal function as soon as possible. If delay of healing or ulceration of a lower-extremity stump prevents early prosthetic fitting, an ischial weight-bearing device that suspends the stump will permit the child to walk in advance of prosthetic fitting. Inflatable plastic air bags provide both even pressure and accurate fit for weight bearing in container sockets. Early prosthetic fitting is desirable in teenagers and adults as well but is not as critical as it is in children. As in nonburned persons, an upper-extremity prosthesis may be rejected at any age if the opposite extremity is fully functional.[70]

Alterations in Growth

In 1959, Evans and Smith reported that a patient who was 24 years of age when burned had a subsequent 1.5-inch increase in height. It was suggested that one explanation

for this growth spurt might be local change in hemodynamics with stasis, passive hyperemia, and chronic inflammation. We have not since documented height changes in burned adults, but we have observed children whose growth after burn has seemed to be retarded. If growth plates remain open, it is difficult to explain overall growth retardation except on an endocrine or humoral basis. It is easy, however, to explain extremity length differences on the basis of premature closure of growth plates caused by direct involvement of the bone or the severity of an overlying burn. Frantz reported lower-limb length discrepancy in four patients with foot and ankle burns.[71] Growth plates closed prematurely in only two of the cases. Jackson described two patients with digital and lower-extremity deformity, respectively, caused by partial closure of growth plates.[33] In Ritsilä et al.'s case, contracture alone was apparently the cause of growth retardation in an upper extremity.[72] It seems reasonable, although hard to prove, that growth in a severely burned extremity would be retarded because of functional impairment.

There is yet another confusing aspect of premature closure of growth plates in that within an extremity with total full-thickness burn, only a few of the growth plates will close prematurely. The explanation for this capricious selectivity is at best obscure. Evans and Calhoun recorded an example of spotty closure of growth plates in a 14-year-old boy with a 90% total TBSA burn.[19] There was complete closure of distal tibial and fibular epiphyses 1 year after burn together with closure of all digital epiphyses in the feet and of several digital epiphyses in the hands. Other major epiphyses were spared (Fig. 48.2).

In early experience, abnormal growth plate closure was observed in a 6-year-old girl with a 50% TBSA third-degree burn that did not involve the legs or ankles.[73] Rapidly destructive septic arthritis of one ankle resulted in closure of the adjacent tibial growth plate.

Only occasionally can growth changes be anticipated because of obvious affection of the bone. More often the changes are subtle. It seems clear, thus, that among seriously burned children, regular height and extremity length measurements must be part of ongoing postburn assessment until it is determined that the extremities and trunk are developing symmetrically and on schedule. Extremity and trunk alignment must likewise be part of the assessment because subtle angular deformity can occur because of partial closure of a growth plate. Jackson's report addresses this problem.[33]

So-called growth arrest lines seen in the radiographs of nonburned children, who have serious illness or major trauma other than burns, are commonly observed in burned children. In burns, as in other conditions, these transverse markers of relatively increased mineralization represent normal recovery from an insult to enchondral bone formation due to serious stress. They are of no clinical or functional significance. They are more related to total burn than to involvement of select burned extremities as all major long bones are affected. There is no evidence that growth arrest lines per se have any effect on growth.

Complete references available online at
www.expertconsult.inkling.com

Further Reading

Chen HC, Yang JY, Chuang SS, et al. Heterotopic ossification in burns: our experience and literature reviews. *Burns*. 2009;35:857-862.
The most recent comprehensive review of the subject of heterotopic bone.

Evans EB. Heterotopic bone formation in thermal burns. *Clin Orthop Relat Res*. 1991;263:94-101.
A detailed discussion of heterotopic bone and a comprehensive cover of the subject.

Evans EB, Larson DL, Abston S, et al. Prevention and correction of deformity after severe burns. *Surg Clin North Am*. 1970;50:1361-1375.
Descriptions of burn-related deformity and management, with the important inclusion of the concepts of Barbara Willis.

Johnston JT. Atypical myositis ossificans. *J Bone Joint Surg Am*. 1957;39:189-193.
The earliest description of burns related to heterotopic bone.

Klein GL, Herndon DN, Langman CB, et al. Long-term reduction in bone mass after severe burn injury in children. *J Pediatr*. 1995;126:252-256.
A comprehensive discussion of causes and persistence of mineral loss.

Michelsson JE, Rauschning W. Pathogenesis of experimental heterotopic bone formation following temporary forcible exercising of immobilized limbs. *Clin Orthop Rel Res*. 1983;176:265-272.
This includes an introduction of the concept of superimposed trauma in burns.

Youel L, Evans E, Heare TC, et al. Skeletal suspension in the management of severe burns in children. A sixteen-year experience. *J Bone Joint Surg Am*. 1986;68:1375-1379.
Traction system in the management of wound burns.

References

1. Schiele HP, Hubbard RB, Bruck HM. Radiographic changes in burns of the upper extremity. *Diagn Radiol*. 1972;104:13-17.
2. Klein GL, Herndon DN, Langman CB, et al. Long-term reduction in bone mass after severe burn injury in children. *J Pediatr*. 1995; 126:252-256.
3. Owens N. Osteoporosis following burns. *Br J Plast Surg*. 1949; 1:245-256.
4. Colson P, Stagnara P, Houot H. [Osteoporosis in burns of the extremities.]. *Lyon Chir*. 1953;48:950-956.
5. Artz CP, Reiss E. *The treatment of burns*. 1st ed. Philadelphia: WB Saunders; 1957.
6. Klein GL, Herndon DN, Rutan TC, et al. Bone disease in burn patients. *J Bone Miner Res*. 1993;8:337-345.
7. Van der Wiel HE, Lips P, Nauta J, et al. Loss of bone in the proximal part of the femur following unstable fractures of the leg. *J Bone Joint Surg Am*. 1994;76:230-236.
8. Dowling JA, Omer E, Moncrief JA. Treatment of fractures in burn patients. *J Trauma*. 1968;8:465-474.
9. Klein GL, Herndon DN, Goodman WG, et al. Histomorphometric and biochemical characterization of bone following acute severe burns in children. *Bone*. 1995;17(5):455-460.
10. Dolecek R, Tymonova J, Admkova M, et al. Endocrine changes after burns: the bone involvement. *Acta Chir Plast*. 2003;45(3):95-103.
11. Pandit SK, Malla CN, Zarger HU, et al. A study of bone and joint changes secondary to burns. *Burns*. 1993;19(3):227-228.
12. Klein GK. Disruption of bone and skeletal muscle in severe burns. *Bone Res*. 2015;24(3):e15002.
13. Rousseau AF, Foidar-Dessale M, Ledoux D, et al. Effects of cholecalciferol supplementation and optimized calcium intakes on vitamin D status, muscle strength and bone health: a one-year pilot randomized controlled trial in adults with severe burns. *Burns*. 2015;41(2):317-325.
14. Parrett BM, Pomahec B, Demling RH, ORgill DP. Fourth-degree burns to the lower extremity with exposed tendon and bone: a ten year experience. *J Burn Care Res*. 2006;27(1):34-39.
15. English C, Carmichael KD. Management of fractures in children with thermal injuries. *J Peditr Ortho*. 2002;22(6):1-4.
16. Choctaw WT, Zawacki BE, Dorr L. Primary excision and grafting of burns located over an open fracture. *Arch Surg*. 1979;114:1141-1142.
17. Wang XW, Zhang ZN, Nie QD, et al. The successful treatment of a patient with extensive deep burns and an open comminuted fracture of a lower extremity. *Burns Incl Therm Inj*. 1984;10:339-343.
18. Barret JP, Desai MH, Herndon DN. Osteomyelitis in burn patients requiring skeletal fixation. *Burns*. 2000;26:487-489.
19. Evans EB, Calhoun JH. Musculoskeletal changes complicating burns. In: Epps CH Jr, ed. *Complications in orthopaedic surgery*. Philadelphia: JB Lippincott; 1994:1239-1278.
20. Evans EB. Orthopaedic measures in the treatment of severe burns. *J Bone Joint Surg Am*. 1966;48:643-669.
21. Brooker AF Jr. The use of external fixation in the treatment of burn patients with fractures. In: Brooker AF Jr, Edwards CC, eds. *External fixation: the current state of the art. Proceedings of the 6th International Conference on Hoffmann External Fixation*. Baltimore: Williams & Wilkins; 1979.
22. Frye KE, Luterman A. Burns and fractures. *Orthop Nurs*. 1999;18: 30-35.
23. Saffle JR, Schnelby A, Hoffmann A, et al. The management of fractures in thermally injured patients. *J Trauma*. 1983;23:902-910.
24. Verbelen J, Hoeksema H, Pirayesh A, et al. Exposed tibial bone after burns: flap reconstruction versus dermal substitute. *Burns*. 2016;42(2):e31-e37.
25. Yeong EK, Cehn SH, Tang YB. The treatment of bone exposure in burns by using artificial dermis. *Ann Plast Surg*. 2012;69(6):607-610.
26. Boyd BM Jr, Roberts WM, Miller GR. Periarticular ossification following burns. *South Med J*. 1959;52:1048-1051.
27. Koepke GD. Personal communication, 1964.
28. Elledge ES, Smith AA, McManus WF, et al. Heterotopic bone formation in burned patients. *J Trauma*. 1988;28:684-687.
29. Peterson SL, Mani MM, Crawford CM, et al. Postburn heterotopic ossification: insights for management decision making. *J Trauma*. 1989;29:365-369.
30. Chen HC, Yang JY, Chuang SS, et al. Heterotopic ossification in burns: our experience and literature reviews. *Burns*. 2009;35:857-862.
31. Hunt JL, Arnoldo BD, Kowalske K, et al. Heterotopic ossification revisited: a 21-year surgical experience. *J Burn Care Res*. 2006;27:535-540.
32. Tepperman PS, Hilbert L, Peters WJ, et al. Heterotopic ossification in burns. *J Burn Care Rehabil*. 1984;5:283.
33. Jackson D, Mac G. Destructive burns: some orthopaedic complications. *Burns*. 1979;7:105-122.
34. Munster AM, Bruck HM, Johns LA, et al. Heterotopic calcification following burns: a prospective study. *J Trauma*. 1972;12:1071-1074.
35. Kolar J, Vrabec R. Periarticular soft-tissue changes as a late consequence of burns. *J Bone Joint Surg Am*. 1959;41:103-111.
36. Heggers JP, Heggers R, Robson MC. Biochemical abnormalities in the thermally injured. *J Am Med Technol*. 1981;43:333.
37. Herndon D. Mediators of metabolism. *J Trauma*. 1981;12:701.
38. Evans EB, Smith JR. Bone and joint changes following burns: a roentgenographic study; preliminary reports. *J Bone Joint Surg Am*. 1959;41:785-799.
39. Johnston JT. Atypical myositis ossificans. *J Bone Joint Surg Am*. 1957;39:189-193.
40. Crawford CM, Varghese G, Mani MM, et al. Heterotopic ossification: are range of motion exercises contraindicated? *J Burn Care Rehabil*. 1986;7:323-327.
41. Gaur A, Sinclair M, Caruso E, et al. Heterotopic ossification around the elbow following burns in children: results after excision. *J Bone Joint Surg Am*. 2003;85:1538-1543.
42. Ring D, Jupiter JB. Operative release of complete ankylosis of the elbow due to heterotopic bone in patients without severe injury of the central nervous system. *J Bone Joint Surg Am*. 2003;85:849-857.
43. Chung D, Hatfield S, Dougherty ME, et al. Heterotopic ossification of the elbow in burn patients: results after early surgical treatment. *Proceedings of the 38th Annual Meeting of the American Burn Association*. Las Vegas, NV: American Burn Association; 2006:4–7April.
44. Djurickovic S, Meek RN, Snelling CF, et al. Range of motion and complications after postburn heterotopic bone excision about the elbow. *J Trauma*. 1996;41(5):825-830.
45. Tsionos I, Leclercq C, Rochet JM. Heterotopic ossification of the elbow in patients with burns. Results after early excision. *J Bone Joint Surg Br*. 2004;86:396-403.
46. Holguin PH, Rico AA, Garcia JP, et al. Elbow achylosis due to postburn heterotopic ossification. *J Burn Care Rehabil*. 1996;17:150-154.
47. Vorenkamp SE, Nelson RL. Ulnar nerve entrapment due to heterotopic bone formation after a severe burn. *J Hand Surg Am*. 1987;12:378-380.
48. Evans EB. Heterotopic bone formation in thermal burns. *Clin Orthop Relat Res*. 1991;263:94-101.
49. Michelsson JE, Rauschning W. Pathogenesis of experimental heterotopic bone formation following temporary forcible exercising of immobilized limbs. *Clin Orthop Rel Res*. 1983;176:265-272.
50. Klein MB, Logsetty S, Costa B, et al. Extended time to wound closure is associated with increased risk of heterotopic ossification of the elbow. *J Burn Care Res*. 2007;28:447-450.
51. Lorber J. Ectopic ossification in tuberculous meningitis. *Arch Dis Child*. 1953;28:98-103.
52. Jacobs P. Reversible ectopic soft tissue ossification following measles encephalomyelitis. *Arch Dis Child*. 1962;37:90-92.
53. Garland DE, Blum CE, Waters RL. Periarticular heterotopic ossification in head-injured adults. Incidence and location. *J Bone Joint Surg Am*. 1980;62:1143-1146.
54. VanLaeken N, Snelling CT, Meek RN, et al. Heterotopic bone formation in the patient with burn injuries. A retrospective assessment of contributing factors and methods of investigation. *J Burn Care Rehabil*. 1989;10:331-335.
55. Evans EB. Musculoskeletal changes complicating burns. In: Epps CH Jr, ed. *Complications in orthopaedic surgery*. Philadelphia: JB Lippincott; 1978:1133-1158.
56. Vrbicky B. Postburn heterotopic joint ossifications. *Ann Burns Fire Disasters*. 1991;4:161-164.
57. Cope R. Heterotopic ossification. *South Med J*. 1990;83:1058-1064.
58. Peters WJ. Heterotopic ossification: can early surgery be performed, with a positive bone scan? *J Burn Care Rehabil*. 1990;11:318-321.
59. Hoffer M, Brody G, Ferlic F. Excision of heterotopic ossification about elbows in patients with thermal injury. *J Trauma*. 1978;18:667-670.
60. Bottu Y, Van Noyen G. Un cas d'ossification reversible des tissus mous chez une petite patiente paraplégique. *Acta Paediatr Belg*. 1963;17:223.

61. Proulx R, Dupuis M. [Para-articular ossifications and calcifications following burns: review of the literature and presentation of 3 cases.]. *Union Med Can*. 1972;101:282-293.
62. Dias DA. Heterotopic para-articular ossification of the elbow with soft tissue contracture in burns. *Burns*. 1982;9:128-134.
63. Harnar T, Engrav L, Heimbach D, et al. Experience with skeletal immobilization after excision and grafting of severely burned hands. *J Trauma*. 1985;25:299-302.
64. Youel L, Evans E, Heare TC, et al. Skeletal suspension in the management of severe burns in children. A sixteen-year experience. *J Bone Joint Surg Am*. 1986;68:1375-1379.
65. Eszter V, Istvan S. Atipusos septicus arthritisek spontan luxatiok egesi serulteken. *Orv Hetil*. 1972;113:48.
66. Cristallo V, Dell'Orto R. [Pathological dislocation of the hip due to burns]. *Arch Ortop*. 1966;79:57-61.
67. Evans EB, Larson DL, Abston S, et al. Prevention and correction of deformity after severe burns. *Surg Clin North Am*. 1970;50:1361-1375.
68. Jackson D, Mac G. Burns into joints. *Burns*. 1976;2:90-106.
69. Klimisch J, Carmichael KD, Murdov P, Evans EB. Prevelence of stump overgrowth in pediatric burn patients with amputations. *J Pedi Ortho*. 2011;31(2):216-219.
70. Malone JM, Fleming LL, Roberson J, et al. Immediate, early, and late postsurgical management of upper-limb amputation. *J Rehabil Res Dev*. 1984;21:33-41.
71. Frantz CH, Delgado S. Limb-length discrepancy after third-degree burns about the foot and ankle. Report of four cases. *J Bone Joint Surg Am*. 1966;48:443-450.
72. Ritsilä V, Sundell B, Alhopuro S. Severe growth retardation of the upper extremity resulting from burn contracture and its full recovery after release of the contracture. *Br J Plast Surg*. 1976;29:53-55.
73. Evans EB, Larson DL, Yates S. Preservation and restoration of joint function in patients with severe burns. *JAMA*. 1968;204:843-848.

49 Reconstruction of Bodily Deformities in Burn Patients: An Overview

LARS-PETER KAMOLZ, PAUL WURZER, and TED HUANG

The severity of burn injuries can usually be ascertained if not by patient survival then by the consequences of the injury: scar hyperplasia/hypertrophy, scar contracture, and structural deformities due to loss of bodily components. Since bodily deformity is closely related to the magnitude of injury, restorative procedures are seldom indicated if the depth of injury is superficial and the burned area limited (Fig. 49.1). However, these procedures are required for deep burns (Fig. 49.2).

Formation of scar tissues at a wound site and contraction of those scar tissues are the normal consequences of an injury. At a microscopic level, thickened and contracted scar tissues (i.e., changes that are "normal" and "expected" consequences of the wound-healing processes) appear as collagens arranged in whorls and nodules. These changes can be observed as early as 3–4 weeks following the injury, and they are cosmetically unsightly and disturb function (Fig. 49.3).

Reconstruction of Burn Deformities

GENERAL PRINCIPLES

Burn injury is a traumatic condition resulting in aberrant physiological processes caused by thermal destruction of the skin. These physiologic alterations affect not only healing of the original burn wounds, but also healing as part of secondary surgical procedures. The treatment should aim to repair the burn wounds first, and attempts to restore deformities should be delayed until recovery from the initial phase of injury is complete.[1] As initially described by Knobloch and Vogt,[2] each surgical approach and reconstructive procedure interacts with another. Hence burn reconstructive surgery can best be viewed as reconstructive clockwork (Fig. 49.4).

EARLY TREATMENT OF DEFORMITY AND TIMING OF SURGICAL INTERVENTION

Making a decision of *how* to operate on a patient with burn deformities is quite simple. In contrast, deciding *when* to operate on a patient with burn deformities can be difficult. Creating a realistic plan to restore physical function and to alleviate pain and discomfort in the area of injury requires an in-depth analysis of the physical deformities and psychological disturbance sustained by the patient. Psychiatric, psychosocial, and physiotherapeutic care, in this sense, must be continued while the surgical treatment plan is instituted.

Although the true efficacy of a nonsurgical regimen, such as pressure garments (Fig. 49.5), to control deformities has not been established, the frequency of secondary joint release among individuals who endured the morbidities associated with proper joint splinting for a period of at least 6 months has been noted.[3,4] The use of pressure dressings, especially in areas such as the upper and lower limbs, with proper splinting of the hand and fingers, is strongly recommended soon following the injury. The nonsurgical management of burn deformities must include daily physiotherapy and exercise to maintain joint mobility and to prevent muscle wasting.

The basic principle of restoring bodily deformities that impose functional difficulties before directing surgical efforts to restore appearance should be followed. The surgeon's efforts should be concentrated on restoring the deformed bodily parts essential for physical functions. For example, an exposed skull or a calvarial defect, contracted eyelids, constricted nares, contracted major joints, and a urethral and/or anal stricture in individuals with severe perineal burns are prime indications for early surgical intervention. In contrast, restoration of contour deformity can be delayed until the scars reach their final structure. In fact, in children reconstruction of the nose and the ear, for instance, should not be initiated until their growth patterns have reached the growth peak; ear reconstruction may be initiated once the child has reached 6–8 years of age, while nasal reconstruction should be delayed until 16–18 years.

Although the exact scientific basis remains unclear, it has been advocated that attempts at reconstructing burn deformities should be delayed for at least 2 years after burn—the time needed for scar maturation. During the interim, the use of pressure garments and splinting is recommended to facilitate scar maturation and minimize joint contracture. The true efficacy of pressure garments in facilitating scar maturation remains undefined. Lack of a reliable method to determine various stages of scar maturation and subjective differences in assessing scar appearance could account for the controversy. On the other hand, splinting a joint embedded in burn scars with an external device to maintain a proper joint angulation has been found to be effective in reducing the need for reoperation to achieve joint function. However, this is possible only if the patient wears the splint faithfully for a minimum period of 6 months. A physical exercise regimen providing vigorous movements of burned joints has been found to be effective in reducing the need for surgical intervention.

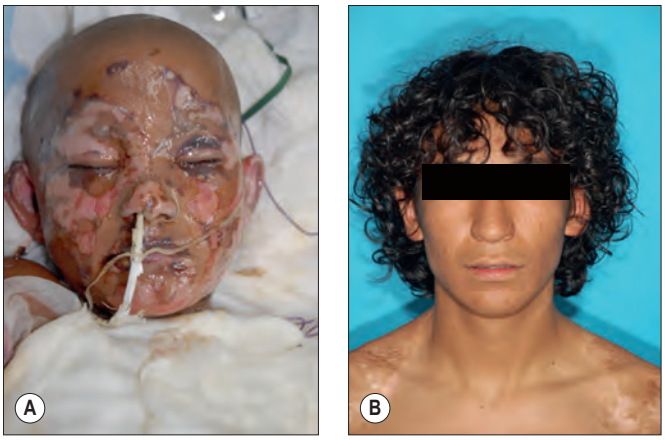

Fig. 49.1 **(A)** An 8-year-old boy sustained flash flame burns of the face. The depth of injury was judged to be superficial. **(B)** The wounds healed spontaneously. The scar formed was judged to be minimal 5 years later.

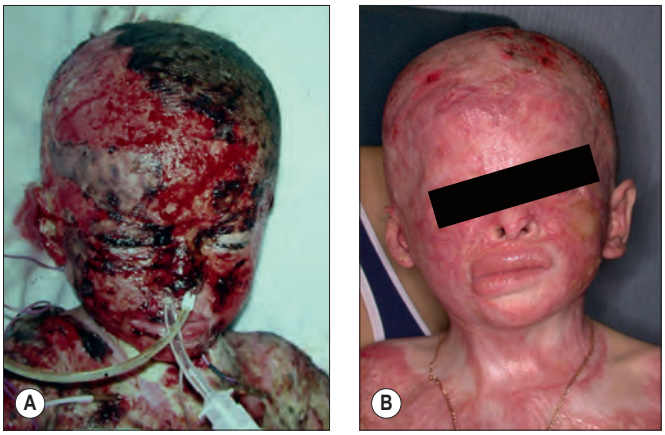

Fig. 49.2 **(A)** A 4-year-old boy sustained flame burns involving 75% of his total body surface. **(B)** The injury was extensive; the wound required staged debridement and skin grafting, resulting in extensive scarring.

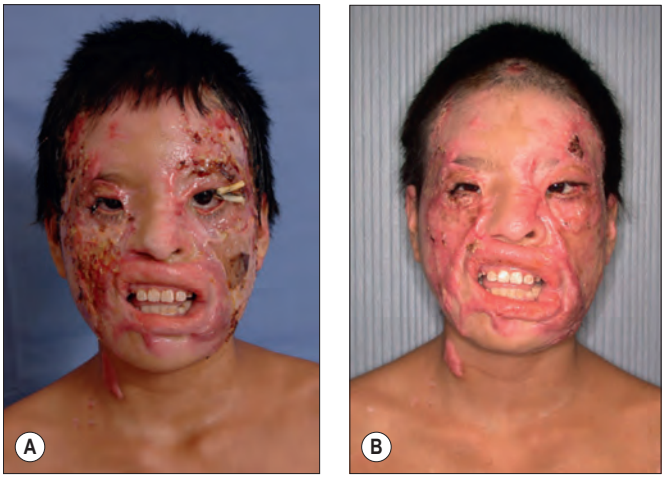

Fig. 49.3 **(A)** Scarring around the injured sites became apparent within 3 weeks. **(B)** Thickening of the scar continued during the subsequent 5–6 months. Contraction of scars caused difficulty in closing and opening the eyelids and mouth.

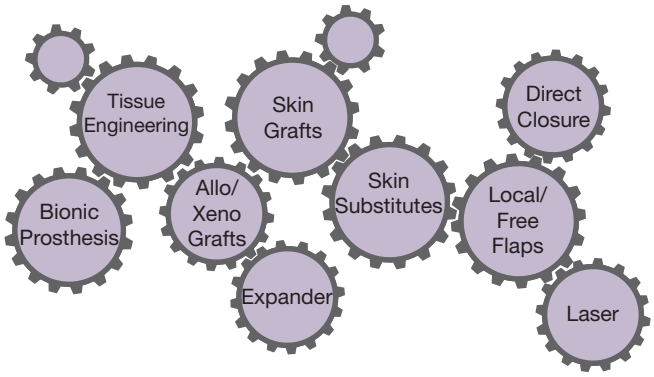

Fig. 49.4 Reconstructive clockwork shows the interaction between the different reconstructive methods.

Fig. 49.5 The use of splints over the mobile joints and pressure garments is an essential component of patient management.

The 2-year moratorium on early burn reconstruction is, in some ways, justifiable. Operating on an immature scar characterized by redness and induration is technically more cumbersome; hemostatic control of the wound is difficult, and inelasticity and lack of tensile strength of scar tissues render tissue manipulation more difficult. A high rate of contracture has been noted in instances where a partial-thickness skin graft is used to release a wound showing active inflammatory processes, further supporting the 2-year delay in initiating burn reconstruction.[5]

We have recently changed our approach to handling individuals in need of reconstruction based on the finding that contracted bodily parts can be effectively reconstructed in the first 2 years postburn if skin flap, fasciocutaneous (FC) flap, or musculocutaneous (MC) flap techniques are used. Reconstruction is initiated in individuals as early as 3–6 months following the initial injury. The approach is well-suited for those encountering functional difficulties because of scarring and scar contracture.[6]

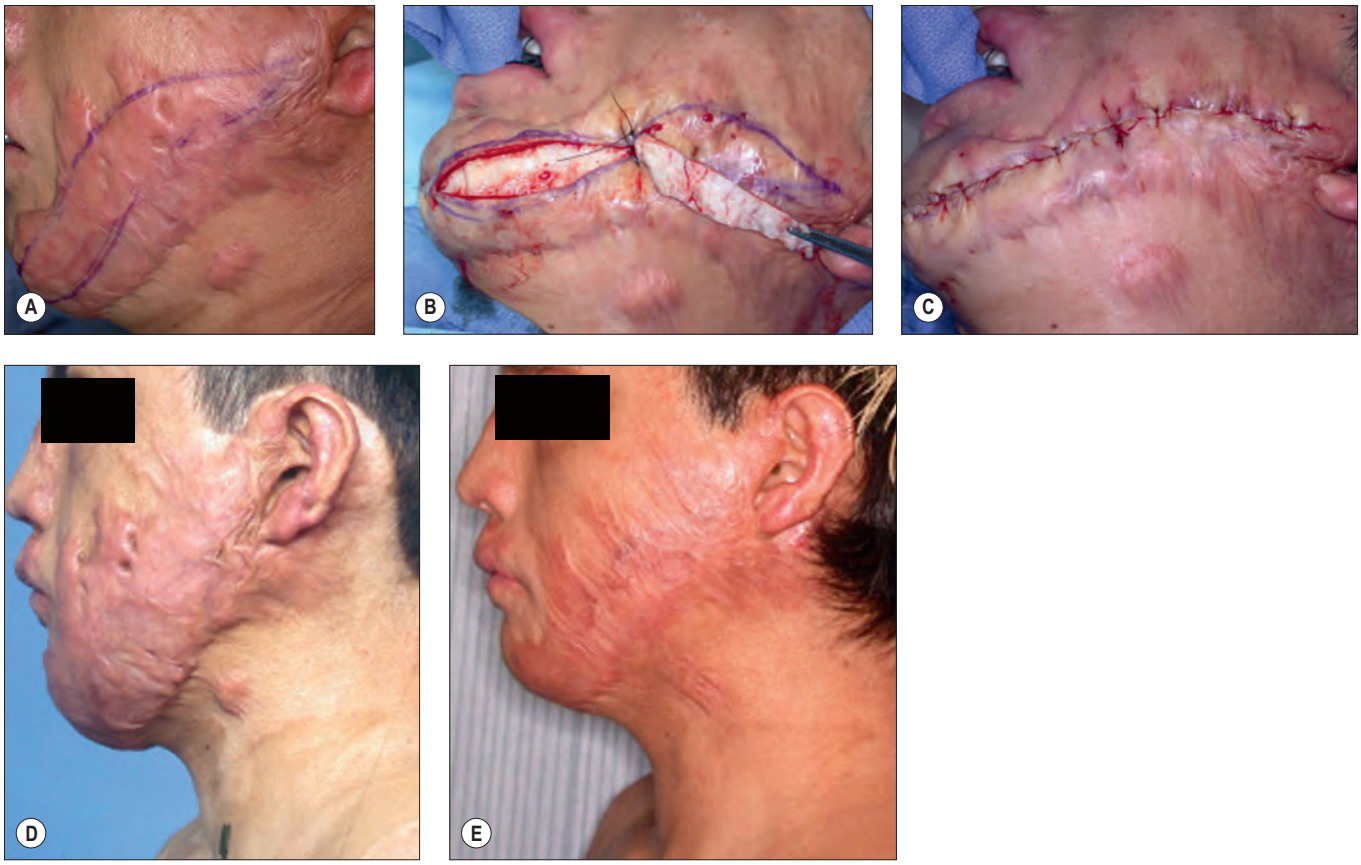

Fig. 49.6 **(A)** The scar formed in the left submental area was pruritic and unsightly. The extent of the excision was marked, and the area was infiltrated with 0.25% lidocaine containing 1 : 400,000 epinephrine to achieve hemostasis. **(B)** The epidermal layer was sharply excised, leaving the dermal layer intact. **(C)** The wound edges were closed primarily in layers using nylon sutures. **(D)** The extent and appearance of scarring noted before excision, 10 months following the initial burns. **(E)** The appearance of the operative site 5 years following partial scar removal.

THE TECHNIQUES OF RECONSTRUCTION

There are several techniques routinely used to reconstruct bodily deformities common to burn injuries (i.e., unsightly scars, scar contractures, and joint contractures). Principally they are as follows: (1) excision of scars with a primary closure technique; (2) wound closure following scar excision with grafting of a piece of free skin, with or without the use of a dermal template; (3) an adjacent skin flap technique; (4) an adjacent FC flap technique; (5) an adjacent MC flap technique, and (6) a distant skin, FC flap, or MC flap via microsurgical technique.

Primary Wound Closure Technique

Excision of an unsightly scar with layered closure of the resultant wound is the simplest and most direct approach in burn reconstruction. The margins of the scar requiring excision are first marked. It is important to determine the amount of scar tissue that can be removed, yet will allow the resultant defect to be closed directly. "Pinching" the edge of scar at three or four different sites along its length to determine the mobility of the wound edges is the simplest yet most reliable method to determine the amount of scar tissue that can be safely removed. Leaving a rim of scar tissue is generally necessary unless the scar is so small that removal and direct closure of the resultant wound would not lead to contour deformity. A circumferential incision is made along the marked line and is carried through the full thickness of the scar down to the subcutaneous fatty layer. While the outer layer of the scar tissue is excised, 4–5 mm of collagen layer is left attached to the base. The conventional approach of wedged scar excision will result in a depression along the scar excision site, an iatrogenic consequence that could be difficult to amend secondarily. To minimize interference to the vascular supply along the wound edges, the undermining of scar edge should be kept minimal. Synthetic sutures are preferred for wound closure (Fig. 49.6).

Skin Grafting Technique

Free Skin Graft Without Incorporating a Dermal Template. Covering an open wound with a piece of skin graft harvested at an uneven thickness is the conventional approach to wound closure. While the whole structure of the skin removed as an intact unit (i.e., epidermis and dermis) is defined as a full-thickness skin graft, a piece of skin cut at a thickness varying between 8/1000ths of an inch (0.196 mm) and 18/1000ths of an inch (0.441 mm) is considered to be a partial- or a split-thickness skin graft. The thickness of a full-thickness skin graft is quite variable depending on the body site. A full-thickness skin graft harvested from the back, for instance, will be 16/1000ths of an inch (4 mm) in thickness, whereas one harvested from the upper eyelid will be around 35/1000ths of an inch

(0.8 mm). The difference is attributable to the difference in the thickness of the dermis.

Although a power-driven dermatome is usually used to harvest a partial- (split-) thickness skin graft, a free hand knife can be used to cut a piece of full-thickness skin graft. A paper template may be made to determine the size of skin graft needed to close a wound. The skin graft is laid onto the wound, colloquially known as the "wound bed," and is anchored into place by suturing the graft to the wound edge-to-edge at various sites. An apposition of the skin graft with the wound bed is essential to ensure growth of the vascular network into the graft within 3–5 days and to ensure graft survival. Any mechanical barriers, such as blood clots or pools of serous or purulent fluid, will prevent the vascularizing process and lead to graft loss. A gauze or cotton bolster tied over a graft has been the traditional technique to anchor the graft and to prevent fluid from accumulating underneath it even though no objective evidence supports the efficacy of this maneuver. A quilting technique has been found to be more effective than the bolstering technique in immobilizing skin grafts and is associated with fewer morbidities (Fig. 49.7).

Free Skin Graft With Prior Incorporation of a Dermal Regenerative Template. For the past several years, artificial dermal substitutes have been manufactured from alloplastic or xenographic materials (e.g., Alloderm and Integra; the manufacturing process was initially described by Yannis and Burke in 1980). These biosynthetic, two-layered membranes are composed of a three-dimensional porous matrix of fibers and cross-linked bovine tendon and glycosaminoglycan (chondroitin-6-sulfate). When implanted over an open wound, this material forms a layer of parenchymal structures resembling a dermis, enabling wounds to be covered with an autologous skin graft when immediate closure is not possible. The need for a staged approach to wound grafting, however, is considered cumbersome (Fig. 49.8).

Skin Flap Technique

The approach of using a segment of skin with all attached structural components to restore a destroyed and/or absent bodily part follows the fundamental principle of reconstructive surgery. However, this approach will cause not only skin scarring at the flap donor site, but also a donor site contour alteration that may be considered cosmetically unsightly. Loss of a skin flap, more commonly encountered in burn patients when the vascular supplies to the skin are altered by injuries and surgical treatment, could render this technique unsuitable, if not undesirable. Despite the drawbacks, the approach to restoring a damaged bodily part with a piece of analogous tissue is technically sound, and the procedure will restore bodily function and contour. The technical innovation of incorporating a muscle and/or

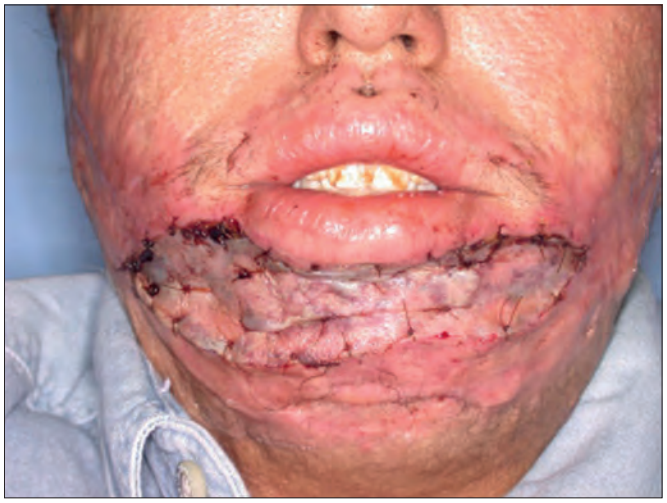

Fig. 49.7 A partial-thickness skin graft was used to cover an open wound resulting from releasing of a contracted lower lip.

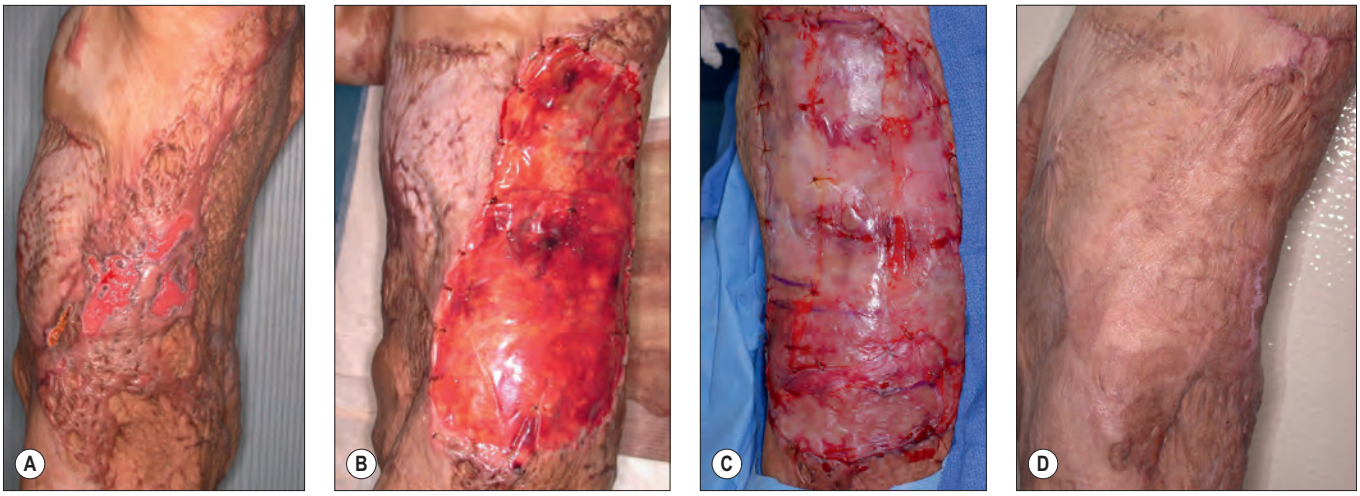

Fig. 49.8 **(A)** A 6-year-old girl bothered by recurrent infection caused by scar-embedded inclusion cysts in the left flank area that extended from the lower axilla to the upper trochanteric region. **(B)** A piece of Integra was used to cover a wound that was 25–30 cm × 10–15 cm. **(C)** The vascularized Integra-covered wound was covered with a partial-thickness skin graft of 8/1000ths of an inch in thickness 3 weeks later. **(D)** The appearance of the grafted area a year following the operation. The scar was noted to be soft and pliable.

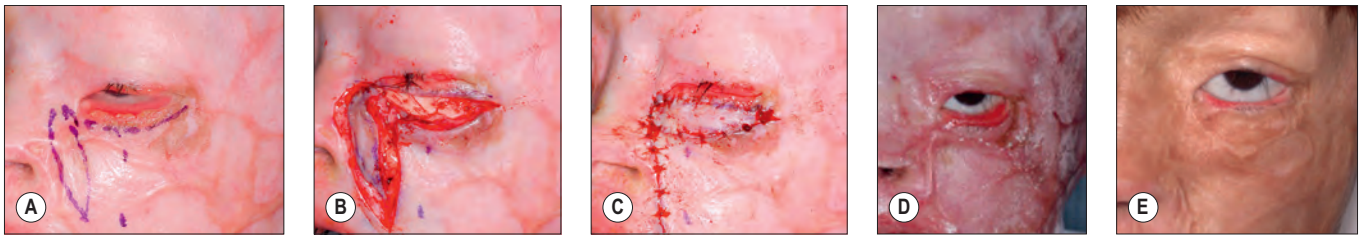

Fig. 49.9 **(A)** A triangular skin mark made over the right nasolabial area to mark an axial skin flap fabricated for left lower eyelid ectropion reconstruction. **(B)** The size of skin flap was equal to the size of the lower eyelid defect to cover an open wound that had a cartilage graft for tarsal replacement. **(C)** The triangular flap was rotated cephalad and laterally to fill the left lower eyelid tissue defect. **(D)** The left lower eyelid ectropion consequential to the loss of eyelid skin and the tarsus. **(E)** Appearance of the left lower eyelid 3 years following the reconstructive procedures.

fascial layer in skin flap design, especially in burned areas, has further expanded the scope of burn reconstruction because more burned tissues can now be used for flap fabrication.

The Axial Skin Flap. The skin in many areas is nourished directly by known cutaneous arteries. A skin flap, regardless of its length-to-width ratio requisite, may be fabricated if the vascular trees are included in the flap pattern (Fig. 49.9).

The Z-Plasty Technique. Briefly described, this technique is based on the principle of mobilizing a full segment of skin, with its vascular supplies undisturbed, from an area adjacent to the site needing tissue replacement. This is conventionally achieved by interposing two skin flaps of an equilateral triangle (i.e., 60 degrees) that has a common limb drawn along the scarred area. A scarred and contracted area is released as the flaps are interposed in an opposite direction. Any space defect due to skin and underlying tissue movement is made up by mobilizing tissues from an adjacent area (Fig. 49.10).

The Modified Z-Plasty Technique; Alias Three-Quarters Z-Plasty Technique. As in the conventional z-plasty technique, two flaps of a right-angled triangle are used. That is, one has an internal 90-degree angle, and the other has a "modified" 45-degree angle; the angle for the triangular flap has decreased from a conventional 60 degrees to 45 degrees; hence the "three-quarters" *z-plasty technique*. The limb of the 90-degree triangle is made in the scarred area resulting from the tissue loss. The second limb of the triangle is made perpendicular to the first one. The angle formed by the second limb of the right-angled triangle and the hypotenuse of the second right-angled triangle is 45 degrees. A triangular skin flap fabricated in this manner is rotated to fill a tissue defect formed from surgical release of a contracted scarred area. The procedure, in this sense, is a variant of the conventional rotational/interpositional skin flap technique in which the 45-degree triangular skin flap is singularly rotated to make up the defect (Fig. 49.11).

Musculocutaneous or Fasciocutaneous Flap Technique

Inclusion of not only the skin, but also the subcutaneous tissues, fascia, and muscle is necessary to fabricate a skin flap to reconstruct tissue defects in individuals with deep burn injuries. That is, fabricating a flap in a burned area is possible if the underlying muscle or the fascia is included in the design.

Musculocutaneous Z-Plasty Technique. While the skin pattern in this technique is identical to that in the conventional z-plasty technique, the muscle underneath must be included in the flap fabrication. Although physical characteristics of normal skin (i.e., the skin pliability and expandability) are absent if scarred skin is included in the flap design, a scarred-skin MC or FC flap can be safely elevated and transferred to close an open wound. In practice, the MC z-plasty technique is useful in neck release and in the eyelid because of the character of the underlying muscle; the platysma and orbicularis oculi muscles are thin, pliable, and easily movable (Fig. 49.12).

Fasciocutaneous Z-Plasty Technique. This is a technical modification of the MC z-plasty technique in which only the muscular fascia is included. Separation of skin and its subcutaneous tissues from the underlying fascia must be avoided to ensure that the blood supply to the flap is not impaired. In practice, the technique is useful in reconstructing contractural deformities around the knee and ankle areas.

Three-Quarter Fasciocutaneous Z-Plasty Technique. A 45-degree triangular FC flap that includes the fascial layer may be fabricated anywhere in the body. The flap is elevated and then turned 90 degrees to cover a tissue defect resulting from a released contracted wound. Although unburned skin is more versatile when used to fabricate a triangular flap, scarred skin with or without subcutaneous tissues may also be used for flap fabrication. Suturing the fascia to the skin edge is a useful maneuver to avoid accidental separation of the fascia from the overlying skin and interrupting vascular supply to dermal structures (Fig. 49.13).

Paratenon Cutaneous Z-Plasty and Three-Quarter Paratenon Cutaneous Z-Plasty Techniques. In instances where fabrication of a composite skin flap is indicated in the distal section of the upper and lower extremities (i.e., wrist and ankle), the paratenon, a fascial extension of the voluntary musculatures, should be included in the flap design and fabrication (Fig. 49.14).

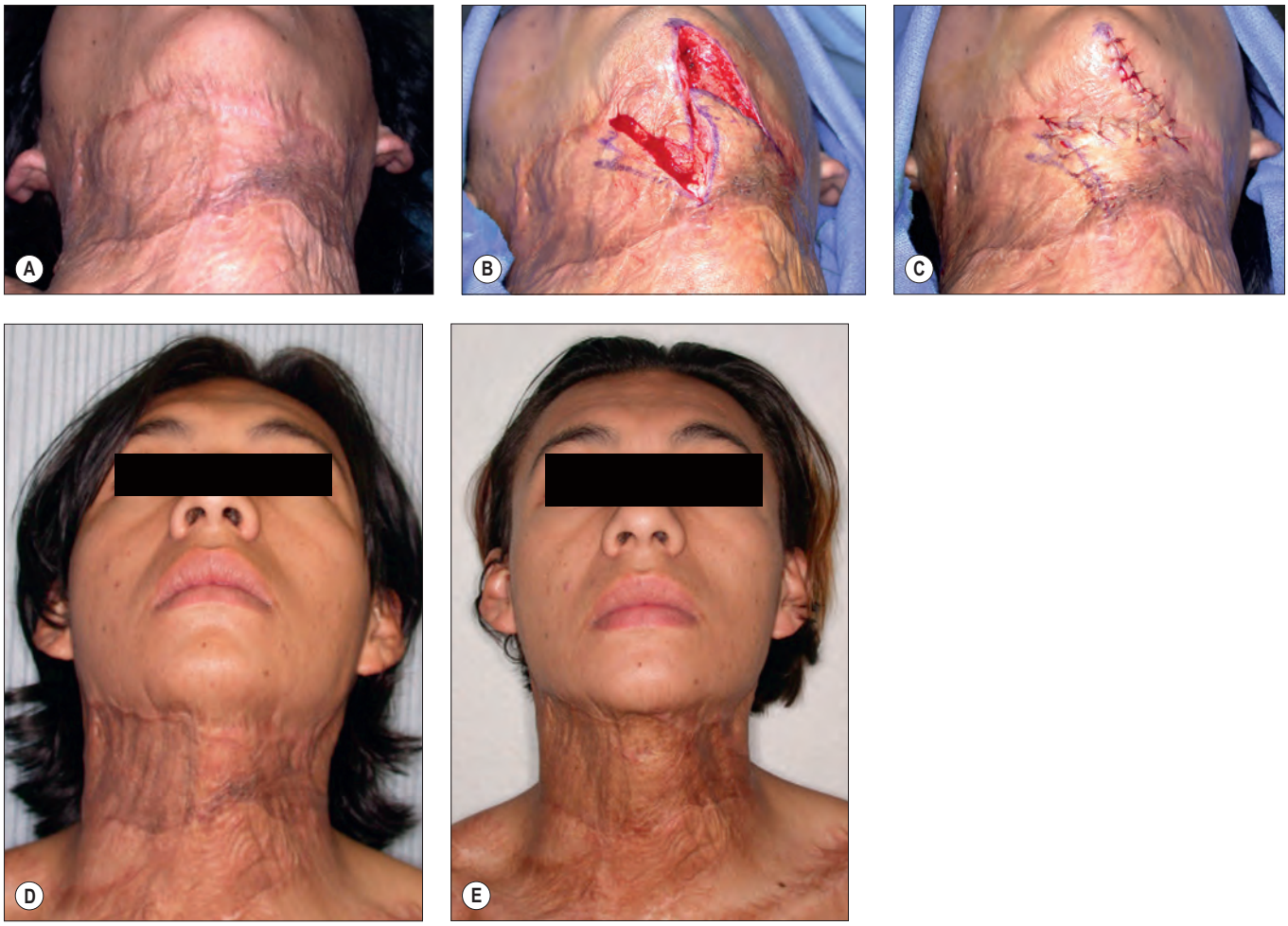

Fig. 49.10 **(A)** Neck scar. **(B)** Two equilateral triangles were marked into a "z" and incisions were made to free up two triangular skin flaps. **(C)** Two flaps were interposed to achieve the release. **(D)** Before release, the patient, a 13-year-old boy, complained of tightness over the neck area caused by a tight scar band. **(E)** The appearance of the neck 4 years following releasing procedures. The z-plasty procedure alleviated the neck tightness.

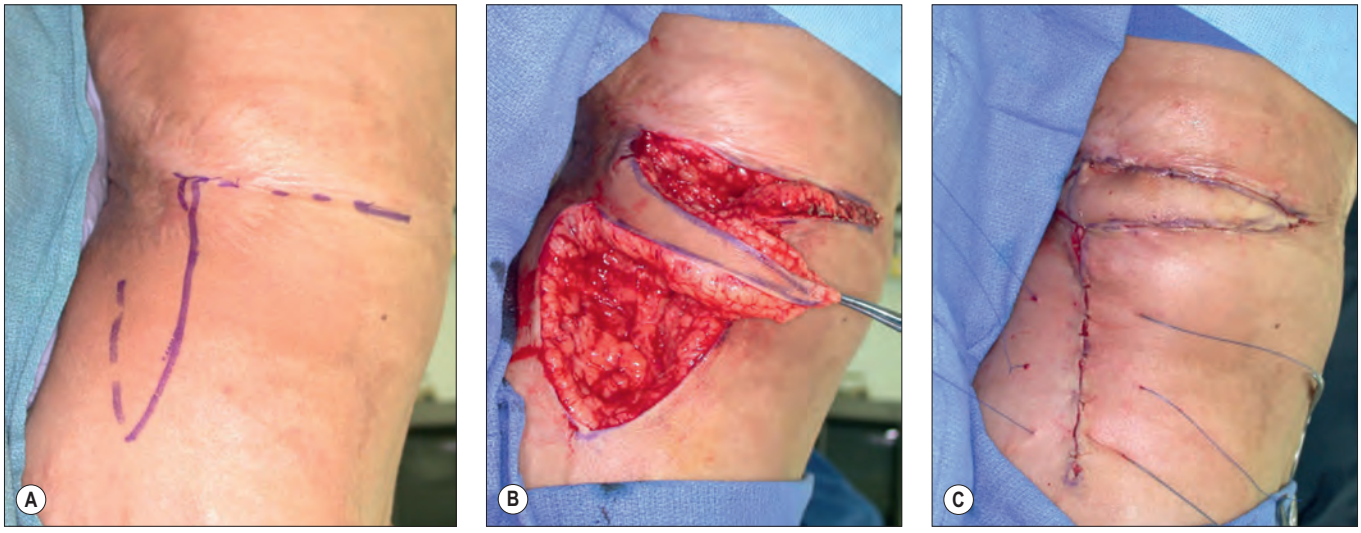

Fig. 49.11 **(A)** A horizontal line was drawn along the site of tightness. A triangular skin marking was also drawn with its cathetus perpendicular to the line of release. **(B)** The triangular flap was rotated cephalad and medialward to make up the wound defect that resulted from release. **(C)** The flap donor site closure as well as the inset of flap was achieved primarily.

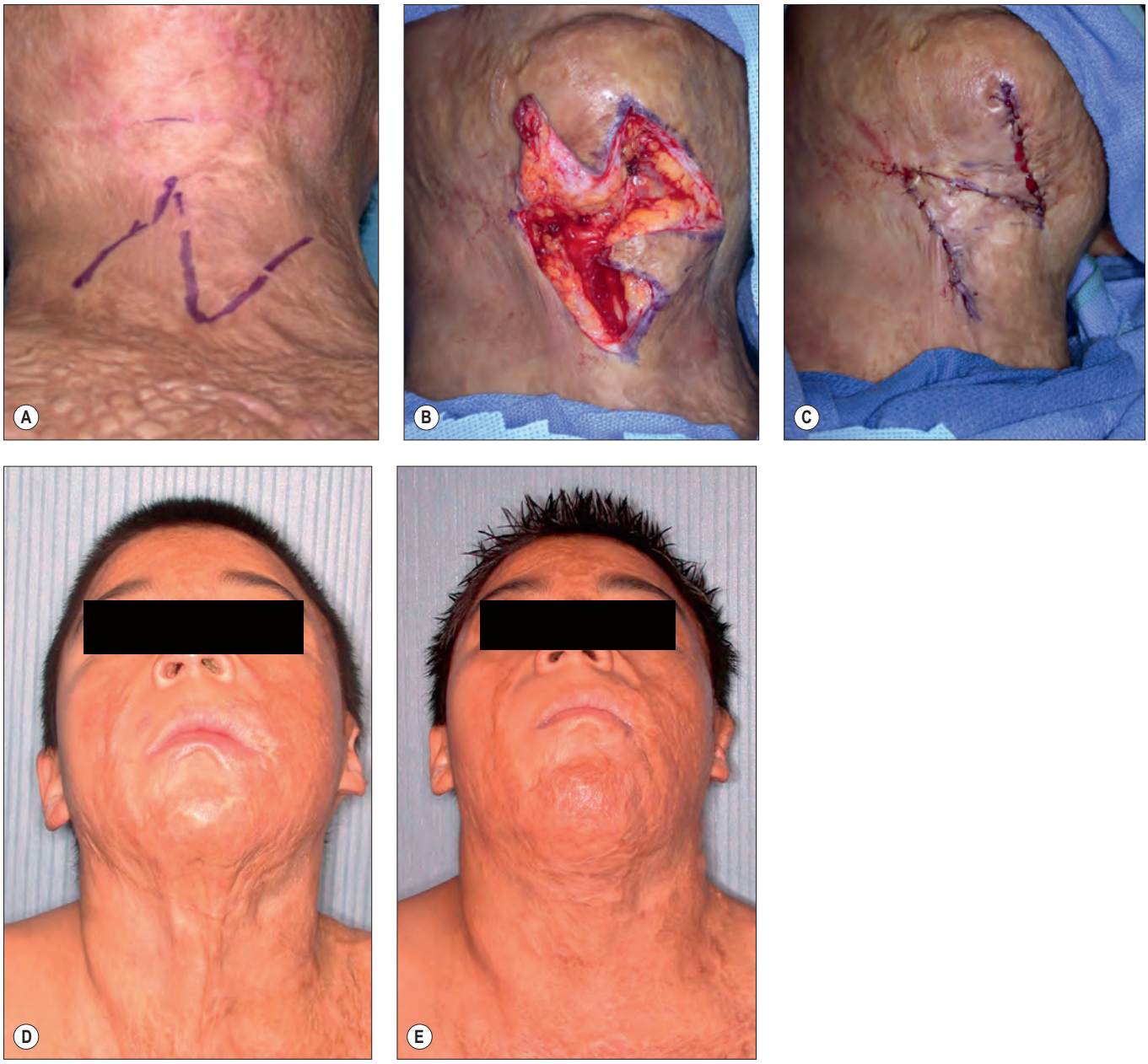

Fig. 49.12 **(A)** Two equilateral triangles were marked into a "z." **(B)** Incisions were made to free up two triangular skin flaps that included the platysmal musculatures underneath. **(C)** Two flaps were interposed to achieve the release. **(D)** Before release, the patient, a 9-year-old boy, complained of tightness over the neck area caused by a tight scar band. **(E)** The appearance of neck 4 years following releasing procedures. The z-plasty procedure alleviated the neck tightness.

Tissue Expansion Technique

An extreme stretching of the integument is quite commonly observed in human bodies. The tissue expansion technique follows the same principle, except it is carried out intentionally with an inflatable device, known as a *tissue expander*. Because excessively active scarring processes are frequently seen after burns, especially during the period immediately following the accident, choosing a time to initiate the procedure is difficult. Use may be limited because of pain and discomfort associated with expansion (Fig. 49.15).

Free Composite Tissue Transfer via Microsurgical Technique

With the advent of microsurgical techniques, transplantation of a composite tissue can now be carried out with minimal morbidities. However, opportunities for using this approach may be limited in burn care because of a paucity of donor materials. It is ironic that burn patients with suitable donor sites seldom require such elaborate treatment. Those who are in need of microsurgical tissue transplantation are inevitably those with no appropriate donor sites because of extensive tissue destruction.

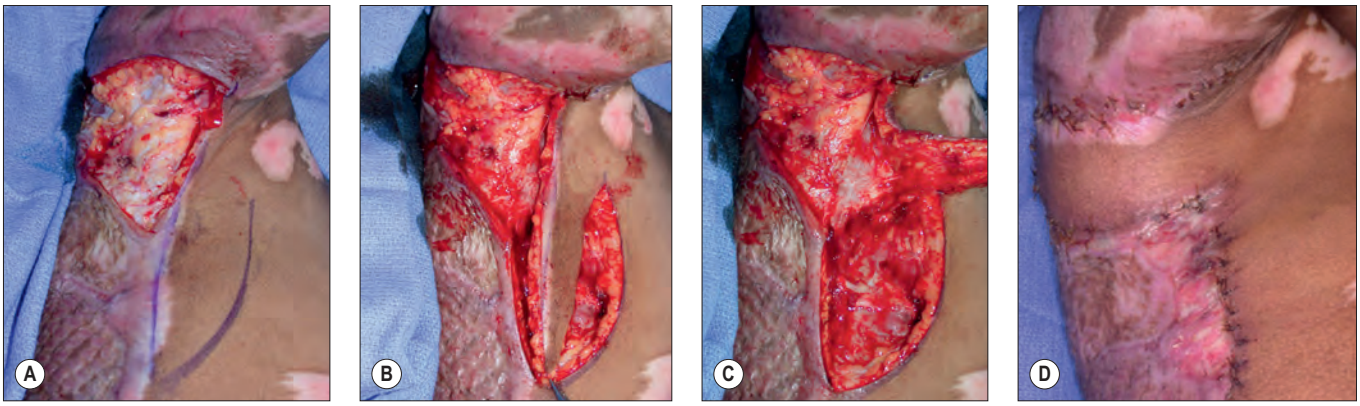

Fig. 49.13 **(A)** A triangular skin marking was made with its cathetus drawn along the line of contracture and perpendicular to the inferior wound edge resulting from the release. **(B)** Incisions were made along the skin marking for flap fabrication. **(C)** The triangular skin flap was elevated to include the fascial layer to form a random fasciocutaneous flap. **(D)** The appearance of flap and the wound 10 days following the release and flap reconstruction.

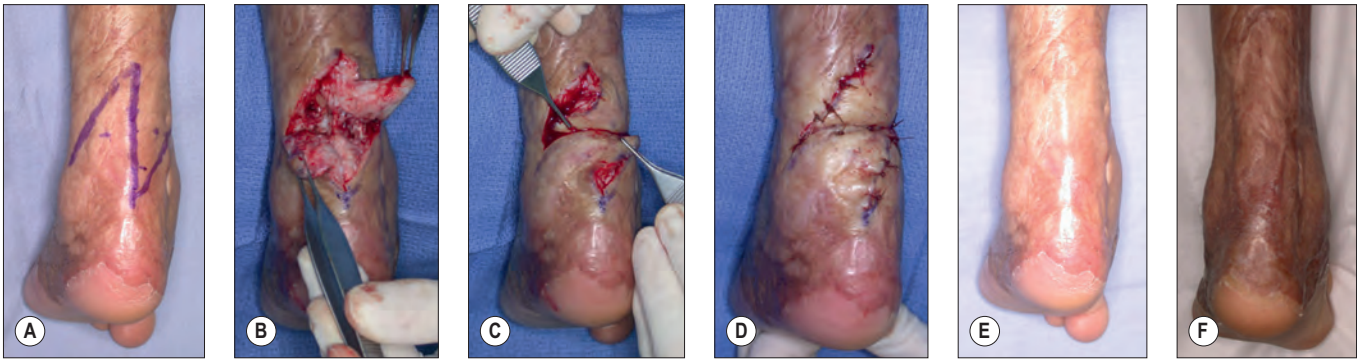

Fig. 49.14 **(A)** Two equilateral triangles were marked over the left heel cord, the area felt to be tight. **(B)** The skin flap was fabricated to include the fascial layer underneath. **(C)** Two fasciocutaneous flaps were interposed to achieve the release. **(D)** The inset of two flaps completed. **(E)** The appearance of left heel cord before release. **(F)** The appearance of left heel cord 4 years following release.

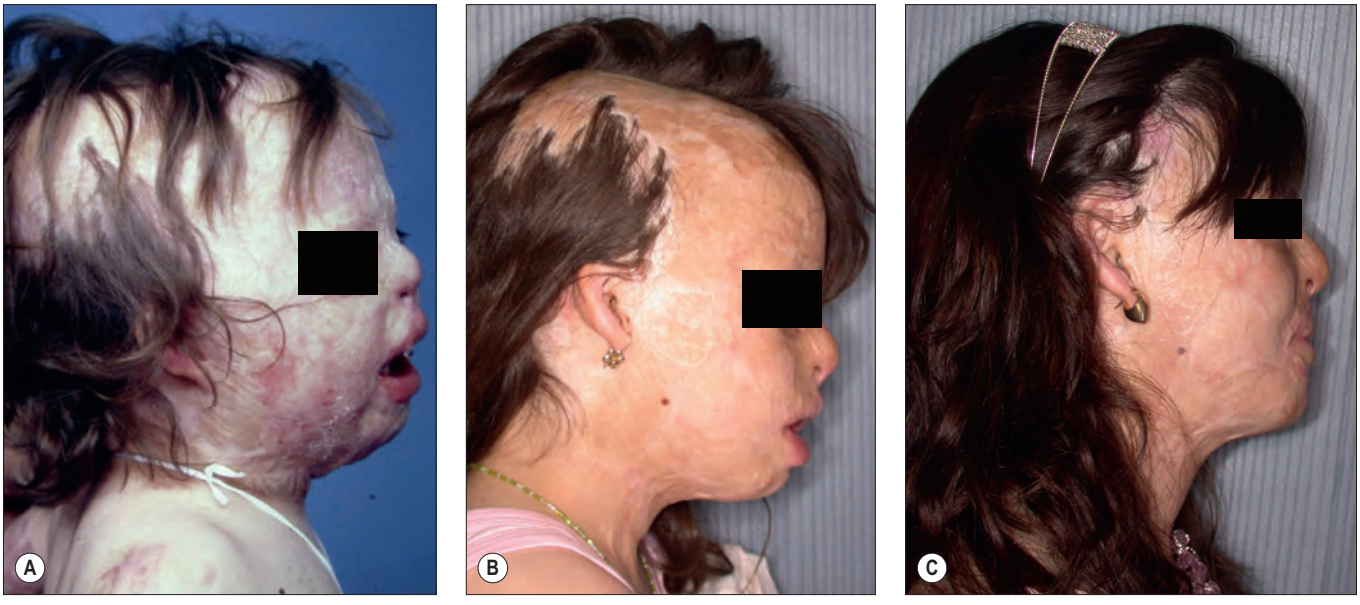

Fig. 49.15 **(A)** A 4-year-old patient with scalp alopecia resulting from extensive burns involving the scalp and the face area. **(B)** No attempt was made to reconstruct the scalp alopecia until she was 8 years of age. The tissue expander technique was used to expand the left side of the scalp for wound coverage. **(C)** The appearance of right temporal scalp following two scalp expansion-advancement procedures.

Fat Grafting Technique

Recently the use of subcutaneous fat has been gaining popularity as a tool to increase postburn wound healing and reduce scarring.[7] The fat is usually harvested by lipoaspiration. Current research is focused on several approaches that can be taken to use fat as a source of stem cells or as an additional layer between the wound and skin graft. Fat can be sprayed directly onto the wound site, transferred with dermal replacements onto the wound, or directly injected into scars to make them smother. Further prospective clinical trials are warranted to prove the safety and efficacy of fat grafting in burn patients.

Allotransplantation: Facial Transplantation

The face may be the most challenging area to reconstruct after burns. Every face is unique and matches each personality. Moreover, facial expressions are important parts of daily conversations and interactions between people. Hence composite tissue transplantation and face transplantation are more topical than ever. In 2009, Lantieri[8] performed the first face transplant in a burn patient. Unfortunately, the patient died during the recovery phase from severe infection and heart failure. The same group recently published long-term results on patients who received facial transplantations; not all were burn patients, but they showed that careful preoperative patient selection and strict local as well as institutional regulations are needed to improve outcomes following composite tissue transplantation and face transplantation.[8]

Comments

Burn treatment regimens have changed drastically over the past 60 years, and a more aggressive approach in managing burned wounds was adopted in the 1980s. Early debridement and wound coverage initially with biological dressing and later with autologous skin grafts has enhanced the survival rate. Ironically this improved survival has caused an upsurge in patients needing reconstruction: everyone now surviving burns is in need of reconstruction, functional or otherwise.

Unsightly hypertrophic scars, scar contractures (particularly those affecting the joint structures), and destroyed body parts are still the most common sequelae of burn injuries. Although the use of skin grafting and skin flaps has remained a mainstay of burn reconstruction, the outcomes can still be suboptimal because the techniques cannot correct the three above-mentioned problems.

The exact time at which to initiate reconstruction of burn deformities remains unsettled. Difficulty in obtaining suitable tissues for replacement, morbidities associated with surgical procedures that involve tissues with active scarring processes, and outcomes that cannot be assured may account for the controversy. Novel approaches using adipose-derived stem cells and other cultured cells may open new avenues, but the safety of these techniques must be proved in daily clinical practice. On the other hand, flap techniques, particularly the three-quarter FC z-plasty and three-quarter paratenon cutaneous z-plasty, are established approaches that enable reconstruction of contractural deformities involving the major joints as well as eyelid deformities as early as 4–6 months following the injury.

Although many questions remain concerning the ideal approach in managing burn deformities, the science of regenerative medicine and tissue engineering, which includes bionic prostheses, could lead to the formation of body parts that could be used to replace absent or destroyed body components.

Complete references available online at www.expertconsult.com

Further Reading

Brou J, Robson MC, McCauley RL. Inventory of potential reconstructive needs in patients with burns. *J Burn Care Rehabil*. 1989;10:556-560.

Condé-Green A, Marano AA, Lee ES, et al. Fat grafting and adipose-derived regenerative cells in burn wound healing and scarring: a systematic review of the literature. *Plast Reconstr Surg*. 2016;137(1):302-312.

Huang T, Larson DL, Lewis SR. Burned hands. *Plast Reconstr Surg*. 1975;56:21.

Lantieri L, Grimbert P, Ortonne N, et al. Face transplant: long-term follow-up and results of a prospective open study. *Lancet*. 2016.

Larson DL, Abston S, Willis B, et al. Contracture and scar formation in burn patients. *Clin Plast Surg*. 1974;1:653.

References

1. Brou JA, Robson MC, McCauley RL, et al. Inventory of potential reconstructive needs in the patient with burns. *J Burn Care Rehabil*. 1989;10(6):555-560.
2. Knobloch K, Vogt PM. The reconstructive sequence in the 21st century. A reconstructive clockwork. *Chirurg*. 2010;81(5):441-446.
3. Huang T, Larson DL, Lewis SR. Burned hands. *Plast Reconstr Surg*. 1975;56:21.
4. Celis MM, Suman OE, Huang T, et al. Effect of a supervised exercise and physiotherapy program on surgical intervention in children with thermal injury. *J Burn Care Rehabil*. 2003;24:57.
5. Robson MC, Barnett RA, Leitch IOW, et al. Prevention and treatment of postburn scars and contracture. *World J Surg*. 1992;16:87-96.
6. Huang T, Herndon D. *The early burn reconstruction in burned patients*. Presented at the annual meeting, Texas Surgical Society, San Antonio, Texas, April 1, 2005.
7. Condé-Green A, Marano AA, Lee ES, et al. Fat grafting and adipose-derived regenerative cells in burn wound healing and scarring: a systematic review of the literature. *Plast Reconstr Surg*. 2016;137(1):302-312.
8. Lantieri L, Grimbert P, Ortonne N, et al. Face transplant: long-term follow-up and results of a prospective open study. *Lancet*. 2016.

50 Reconstruction of the Head and Neck after Burns

MATTHIAS B. DONELAN and BRANKO BOJOVIC

Introduction

Reconstruction of the head and neck[1] following burn injuries presents great challenges and great opportunities. Successful treatment requires sound surgical judgment and technical expertise, as well as a thorough understanding of the pathophysiology of the burn wound and contractures. Many disciplines are required to successfully care for patients with burns of the head and neck. These include skilled nursing, experienced occupational and physical therapy, and psychological and social support systems. The surgeon must also have familiarity and expertise with nonsurgical treatment modalities such as pressure therapy, steroids, and laser therapy. Realistic expectations on the part of both patients and surgeons are essential to achieve successful treatment outcomes. Burns to the head and neck of a serious nature result in tissue injury with scarring, and complete removal of scars is not possible. A scar can only be modified or exchanged for another scar or tissue of a different variety. Despite this fundamental limitation, reconstruction of the burned face and neck creates great opportunities for plastic surgery to significantly improve functional and aesthetic deformities resulting in profound improvement for this large group of challenging patients.

Recent advances in technology and improved understanding of wound-healing physiology are transforming the ways we should look at, and think about, burn scars and contractures. This change in perspective is particularly important in the head and neck because normal appearance and normal function in this area are of paramount importance. The presence of visible scarring and even minimally grotesque deformity is particularly debilitating in the face and neck. Since the early 20th century and the brilliant work of Sir Harold Gillies reconstructing facial deformities with tubed pedicle flaps, scar excision in the head and neck and replacement with flap tissue, either from regional or distant donor sites, has dominated facial burn reconstruction thinking. This was further popularized by the concept of aesthetic unit scar excision coupled with ever-improving surgical ability to transplant tissue. It is time to rethink this paradigm. It is now possible to dramatically rehabilitate hypertrophic and contracted scars on the face and neck to the point where the scars are often the patient's best reconstructive anatomy. That is because the scars are autologous, in the right location, and the closest match to normal because they are the "original equipment." Excision and replacement of facial scars creates iatrogenic donor sites and requires extensive surgery to replace the scars with uninjured tissue from other areas of the patient's body. This surgery is typically complex and morbid with potentially severe complications. Scar rehabilitation is minimally morbid and has few complications. The secrets to success with scar rehabilitation in the head and neck are accurate early diagnosis, conservative management, and the effective use of new technologies and treatments to enable patients to reap the maximum benefit from their own amazing wound-healing and scar remodeling capabilities (Fig. 50.1). This new approach will be discussed in this chapter along with more traditional methods of reconstruction in the head and neck.

Burn injuries constrict and deform the face; distorting its features, proportions, and expression.[1] Burns also alter the surface of the facial mask by causing scars and altering texture and pigmentation. The changes to the surface of the skin are deforming but are much less important to facial appearance than are the changes in proportion, features, and expression. The removal of scars *should not* be the primary goal of facial burn reconstruction. A normal-looking face with scars is always better looking than an even slightly grotesque looking face with fewer scars. Mature scars that result from burn injury will often be less conspicuous than surgically created scars after excision or surgically transferred flaps or grafts. The subtle and gradual transition between unburned skin and burn scar is an excellent example of nature's camouflage and can render scarring remarkably inconspicuous. New techniques of scar rehabilitation using lasers and carefully crafted, minimally morbid surgery helps scars blend even better. The principal goal of facial burn reconstruction should be the restoration of a pleasing and tension-free facial appearance with appropriate animation and expression.[2] If this goal is kept in mind and is pursued with persistence and determination, the amount of improvement that can result after severe facial burn injury can be remarkable. Ignoring this basic principle can result in iatrogenic catastrophes during reconstructive surgery of the head and neck following burns.

Successful reconstruction of burn deformities of the head and neck requires a well-functioning and extensive team.[3] Major burn deformities in this area can easily be intimidating and overwhelming. Experience and a specialized infrastructure are required to take care of these patients comfortably and successfully. Familiarity with their unique problems and a firm commitment to correcting their challenging deformities is required from all members of the reconstructive team. The care of a patient from the onset of a major burn involving the head and neck to a successful reconstructive outcome requires skill, patience, determination, and enthusiasm from all who are involved.

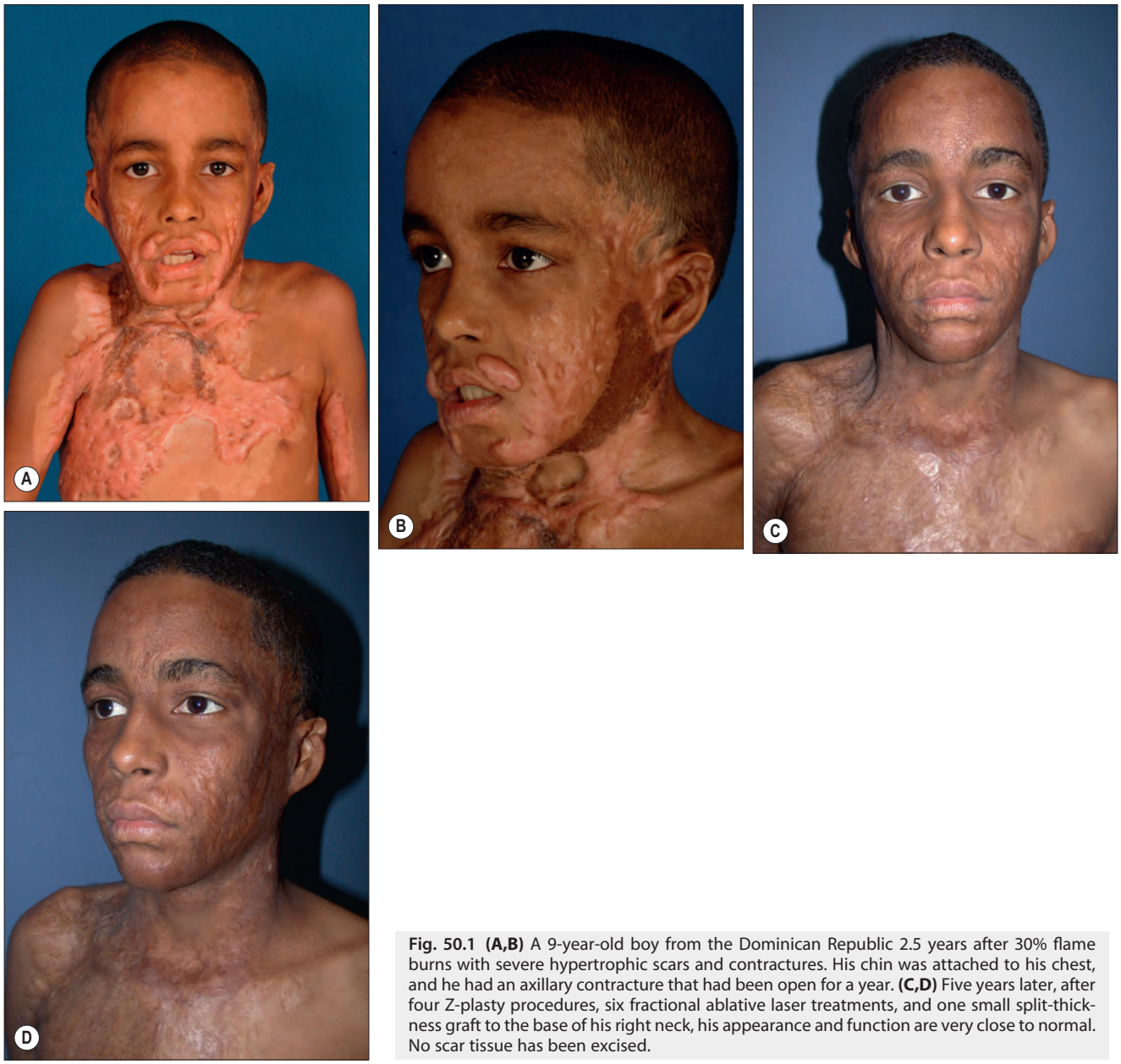

Fig. 50.1 (A,B) A 9-year-old boy from the Dominican Republic 2.5 years after 30% flame burns with severe hypertrophic scars and contractures. His chin was attached to his chest, and he had an axillary contracture that had been open for a year. **(C,D)** Five years later, after four Z-plasty procedures, six fractional ablative laser treatments, and one small split-thickness graft to the base of his right neck, his appearance and function are very close to normal. No scar tissue has been excised.

Acute Management

Although the main focus of this chapter is the reconstruction of established facial burn deformities, an understanding of the acute care of facial burn injuries is necessary in order for the surgeon to have an accurate perspective. Excision and grafting of deep second-degree and full-thickness burns has become the standard of care since it was first proposed in 1947.[4–6] It remains controversial whether this is the optimal treatment for facial burn injuries. Early excision and grafting of the face is problematic because of difficulty in diagnosing the depth of the facial burn and accurately predicting an individual patient's long-term prognosis both functionally and aesthetically. Laser Doppler imaging is a validated way to improve diagnosis in these difficult cases and can decrease the risk of overly aggressive excision. Preventing unnecessary early excision is particularly important with current improved techniques to rehabilitate hypertrophic scars. The overwhelming majority of facial burns treated conservatively with a moist regimen of topical antibiotics will heal within 3 weeks. Burns that are clearly full-thickness are best treated by early excision and grafting within 7–10 days to promote early wound closure and minimize contractile forces (Fig. 50.2). The problem cases are those where healing has not occurred by 3–4 weeks or longer. Early tangential excision and grafting has been proposed for these patients in order to achieve more favorable healing with less eventual contracture deformities.[7] Proponents of conservative therapy argue that early excision and grafting may result in a patient with a grafted face who would otherwise have healed favorably by successfully epithelializing their partial-thickness burn from skin appendages.[8] Conservative management has been facilitated by the

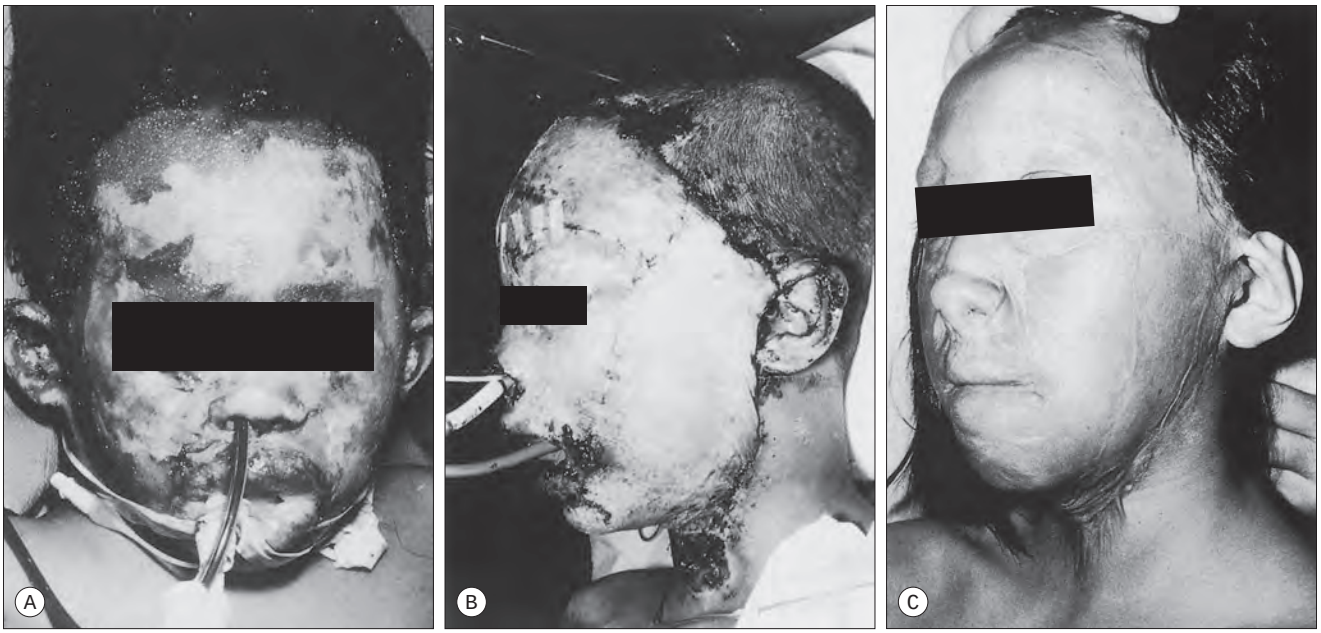

Fig. 50.2 **(A)** A 5-year-old Native American girl, 3 days after deep second- and third-degree burns to her face. **(B)** Tangential excision and split-thickness autografting were performed on the 10th postburn day. **(C)** Five years after facial excision and grafting. She has had a subsequent nasal reconstruction.

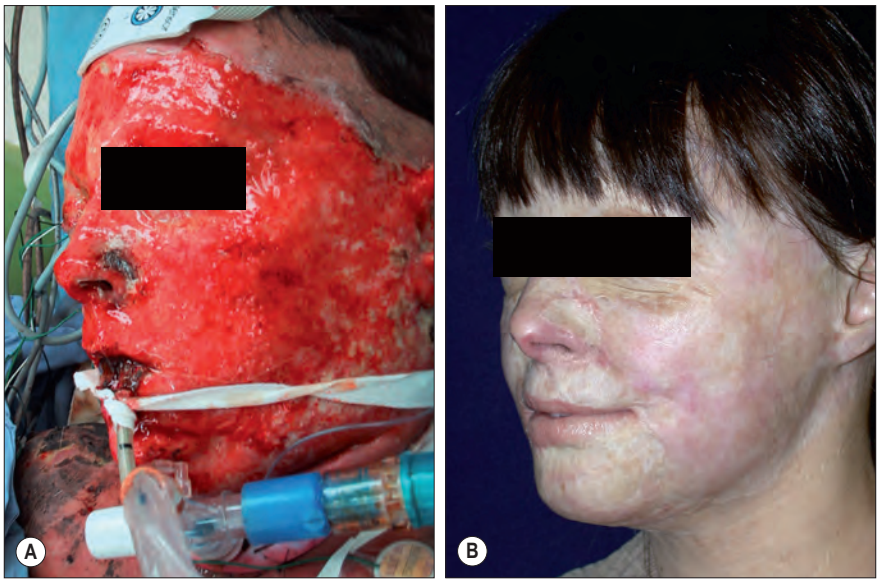

Fig. 50.3 **(A)** Ungrafted facial burn injury 30 days following 85% burn in a 34-year-old electrician. Wound closure was obtained with split-thickness grafts at 5 weeks. **(B)** Four years following burn injury. Lower lids and alar lobules have been released and grafted.

myriad ancillary techniques currently available to favorably influence the healing of facial burns such as pressure, silicone, silicone-lined computer-generated facemasks, topical and intralesional steroids, vitamin E, massage, and treatment with pulsed dye lasers (PDLs) and ablative fractional CO_2 lasers. Impressive results have been obtained by advocates for early excision and grafting.[9] Very good outcomes, however, can also be achieved by being more conservative with this difficult group of patients (Fig. 50.3). The benefits in appearance and function of rehabilitated scars over early excision and grafting are dramatically demonstrated by the patients and accompanying videos in Figs. 50.4 and 50.5. Committing a patient to a grafted face should only be done when it is clearly the best alternative. The majority of acute facial burns are treated conservatively in most burn centers, with early excision and grafting limited to those cases where it is clear that a full-thickness burn injury has occurred.

Pathogenesis

Superficial-thickness, second-degree burns usually heal without scarring or pigmentary changes. Medium-thickness, second-degree burns that epithelialize in 10–14 days usually heal without scarring, although there can be

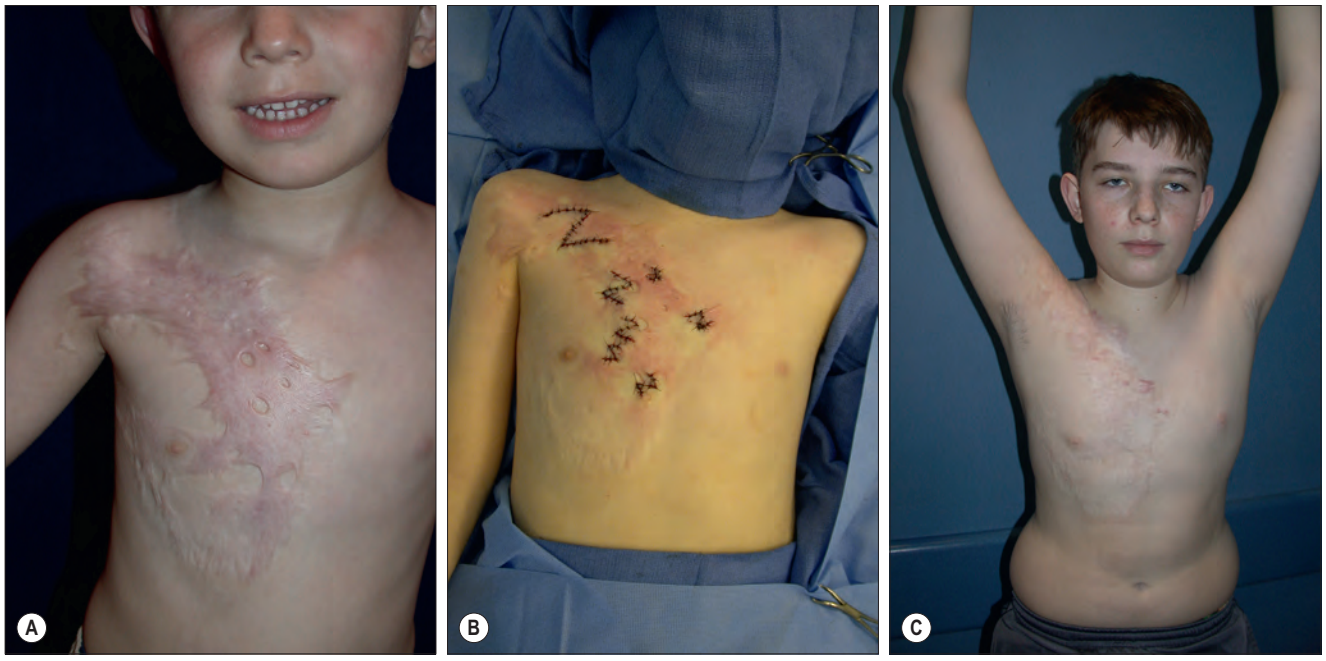

Fig. 50.4 (A) Four-year-old male 2 years after a mixed second- and third-degree scald burn from hot coffee. Parents refused excision and grafting. Scars are hypertrophic and inelastic with a significant contracture across the deltopectoral groove. **(B)** Multiple Z-plasties separated the scars into smaller, discreet areas with focal reductions in tension. Pulsed dye laser therapy was initiated at his first Z-plasty procedure. **(C)** Seven years later, after two small Z-plasty procedures and 21 laser treatments using both pulsed dye laser and fractional ablative CO_2, his chest scars are flat, soft, thin, inconspicuous, and elastic. **(D)** Video demonstrating the function of the scars after treatment.

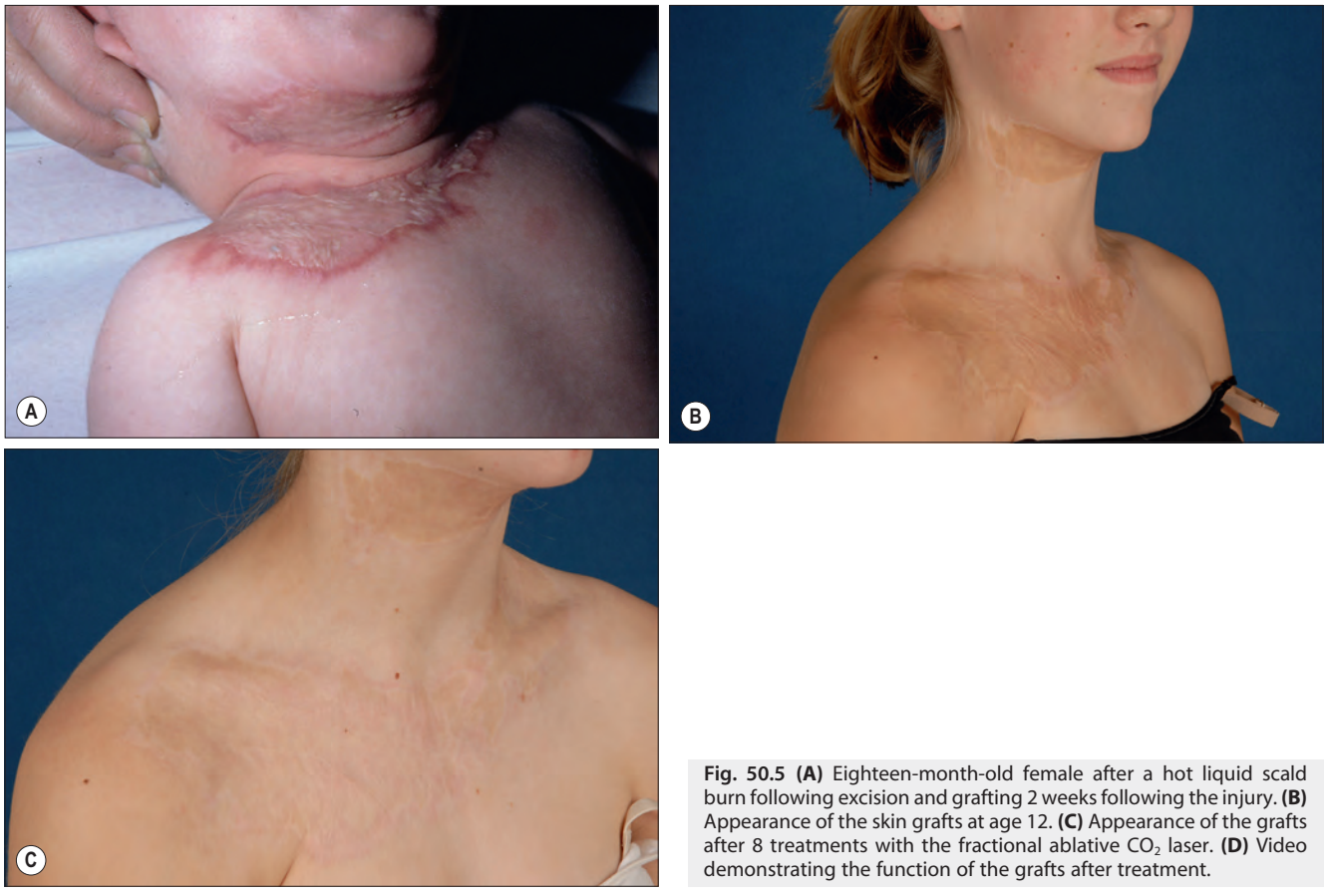

Fig. 50.5 (A) Eighteen-month-old female after a hot liquid scald burn following excision and grafting 2 weeks following the injury. **(B)** Appearance of the skin grafts at age 12. **(C)** Appearance of the grafts after 8 treatments with the fractional ablative CO_2 laser. **(D)** Video demonstrating the function of the grafts after treatment.

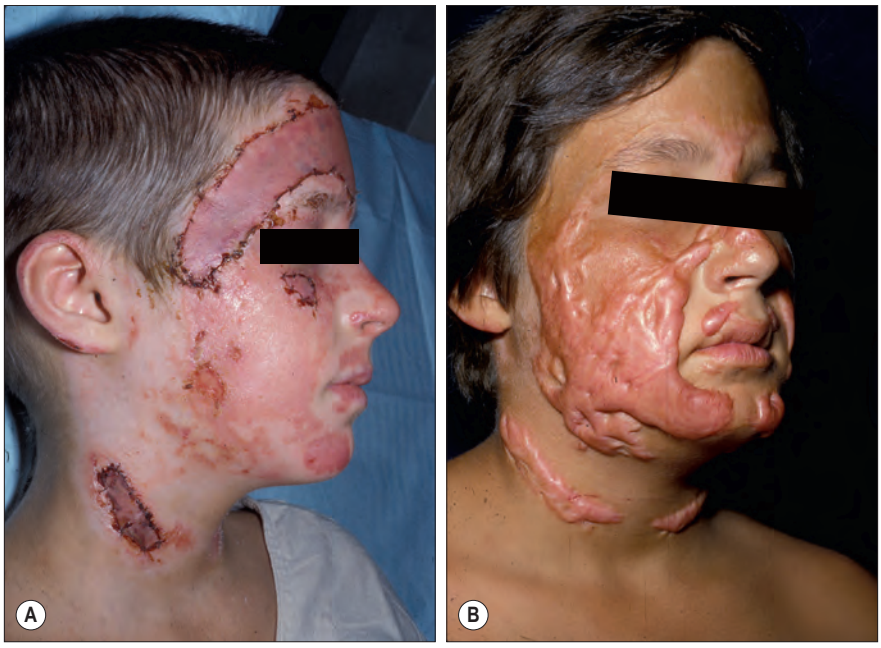

Fig. 50.6 **(A)** One month following a flash burn, the right cheek is epithelialized. **(B)** Ten months later, there is massive hypertrophy despite conservative therapy with pressure.

long-term changes in skin texture and pigmentation. Deep-thickness, second-degree burns that epithelialize after 21 days or longer are unpredictable and must be carefully managed because they have a propensity to develop severe late hypertrophic scarring (Fig. 50.6). These patients should be closely monitored after initial healing and, at the first sign of hypertrophy, must be managed with all available ancillary treatment modalities. Pressure garments have been shown over several decades to be effective in suppressing and reversing hypertrophic scarring. Adding silicone to pressure therapy seems to increase its efficacy. Computer-generated clear face masks lined with silicone have improved the ability to deliver pressure to facial hypertrophic scars and are better tolerated by patients (Fig. 50.7). The vascular-specific PDL decreases hyperemia and seems to diminish hypertrophy. When tension plays a role in the development of early hypertrophic scarring, relief of the tension with either focal Z-plasty or judicious release and grafting can be very helpful. Ablative fractional CO_2 laser therapy can be used to decrease tension and also deliver corticosteroids into the hypertrophic scars with encouraging results. Definite full-thickness facial burns should usually be excised and grafted unless focal and small.

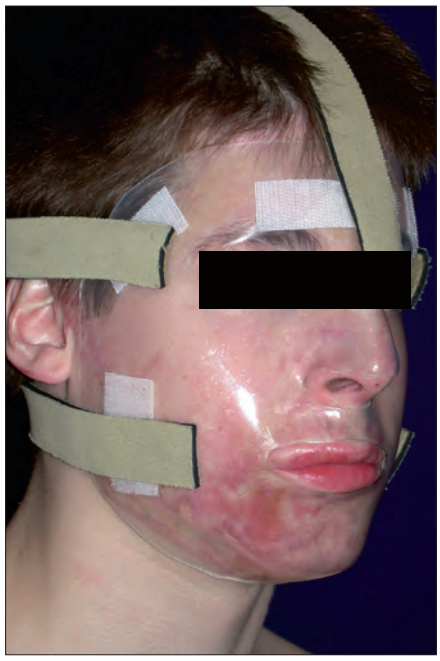

Fig. 50.7 Computer-generated clear silicone-lined masks are well tolerated and more efficacious than previous devices.

Evaluation of Facial Burn Deformities

Facial burn reconstruction should be based on an overall strategy and a clear understanding of the fundamental problems. Many reconstructive techniques have been described in the literature and can result in improvement if the strategic goals are appropriate.[10–12] The new era of scar rehabilitation has changed older strategies, and where this will eventuate is unclear at this time. It seems likely that scar excision and replacement with other parts of the patient's body will be less common in the future. The best reconstructive plan for the facial scar tissue will be scar rehabilitation using all available modalities to preserve its unique advantages as much as possible. Improved outcomes will be achieved with a judicious combination of contracture releases by Z-plasty, grafts, and flaps, followed by appropriate scar revision and laser therapy. Laser therapy *preceding* scar revision improves scar quality and facilitates surgery. Extensive scar excisions in aesthetic units and replacement

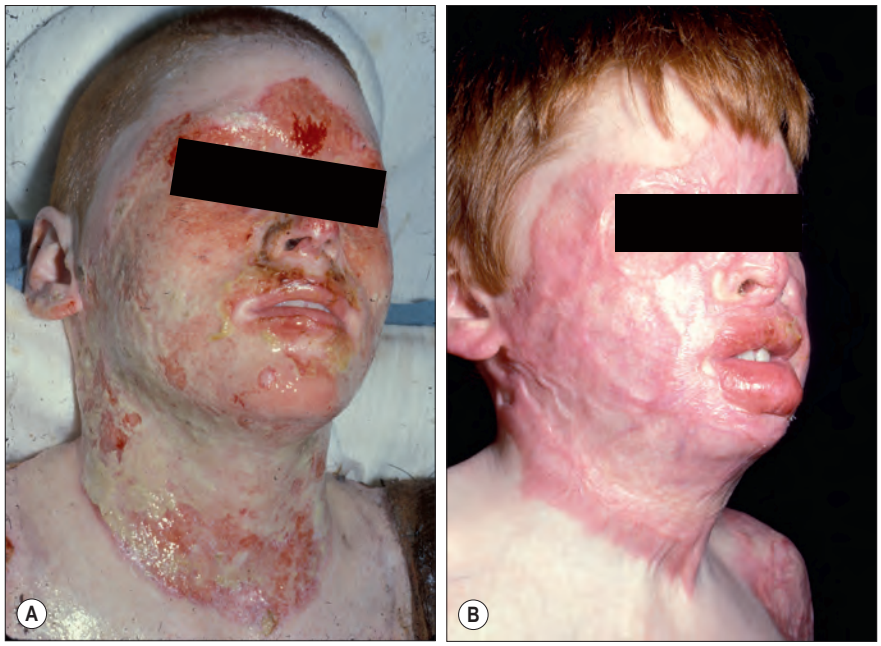

Fig. 50.8 **(A)** Three weeks following a deep second-degree burn with essentially normal facial features and proportions. **(B)** Six months later, contraction and hypertrophy have created facial burn stigmata.

Box 50.1 Stigmata of Facial Burns

- Lower eyelid ectropion
- Short nose with ala flaring
- Short retruded upper lip
- Lower lip eversion
- Lower lip inferior displacement
- Flat facial features
- Loss of jawline definition

Box 50.2 Facial Burn Categories

Type I
Essentially normal facies with focal or diffuse burn scarring with or without contractures

Type II
Pan-facial burn deformities with some or all of the stigmata of facial burns

with microvascular free tissue transfer from distant sites will likely become less frequent. The role of face transplantation in burn reconstruction of the head and neck is unclear at this time.

Deep second- and third-degree burns heal by contraction and epithelialization. The more severe the burn injury, the more contraction takes place during the healing process. The changes in facial appearance following a deep second-degree burn injury are dramatically demonstrated in Fig. 50.8. Three weeks following a deep second-degree burn, the patient's facial features and proportions remain essentially normal. Six months later, contractile forces have deformed the facies in a pattern that is repeated to a variable degree in virtually all severe facial burns. These changes make up the stigmata of facial burn injury and are listed in Box 50.1. The eyelids are distorted with ectropion, the nose is foreshortened with ala flaring, the upper lip is shortened and retruded with loss of philtral contour, the lower lip is everted and inferiorly displaced, the lower lip is wider than the upper lip in anterior view. The tissues of the face and neck are drawn into the same plane with loss of jawline definition. The severity of these changes is proportional to the severity of the injury.

Fortunately the majority of facial burn injuries are not severe and do not involve the entire face. A relatively small number of patients sustain injuries that deeply involve the entire face, such as shown in Fig. 50.8. It can be helpful to separate patients with facial burn deformities into two fundamentally different categories, as described in Box 50.2. Type I deformities consist of essentially normal faces that have focal or diffuse scarring from their burns and may have associated contractures. Type II deformities make up a much smaller number of patients who have "pan-facial" burn deformities with some or even all of the facial burn stigmata. Although these categories are not rigidly defined, and there are some patients who do not fit neatly into one or the other, understanding the fundamental difference between these two groups of patients can help define treatment goals. It can also aid in selecting the most appropriate methods for reconstructive surgery.

Patients with type I deformities have an essentially normal facial appearance despite scars from their burns. In these patients, one must be certain that surgical intervention does not adversely alter normal facial features or create distortion from iatrogenically induced tension. Overall facial appearance should not be sacrificed in an effort to "excise scars" (Fig. 50.9). The best reconstructive options today for patients with type I facial burn deformities are

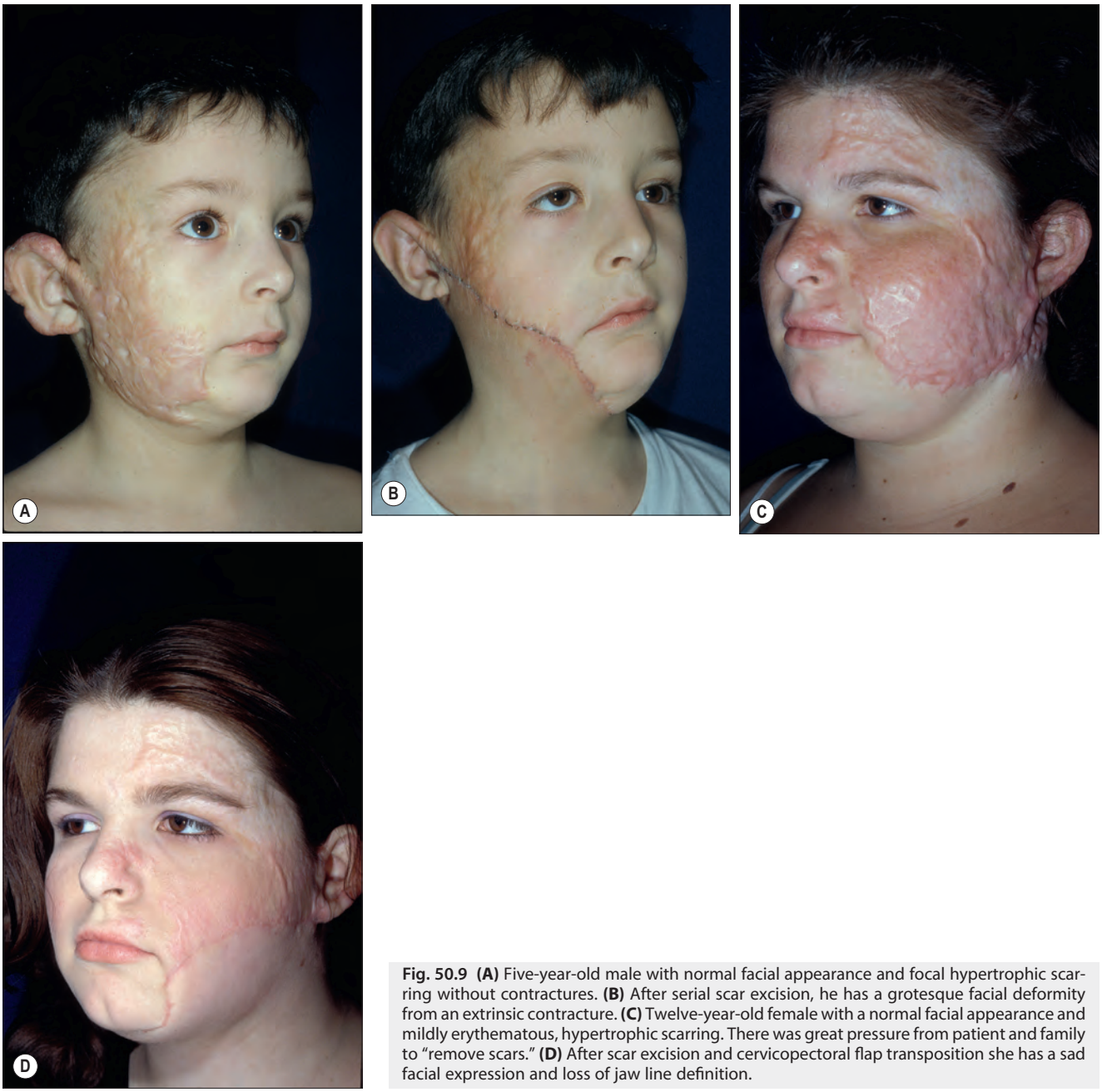

Fig. 50.9 **(A)** Five-year-old male with normal facial appearance and focal hypertrophic scarring without contractures. **(B)** After serial scar excision, he has a grotesque facial deformity from an extrinsic contracture. **(C)** Twelve-year-old female with a normal facial appearance and mildly erythematous, hypertrophic scarring. There was great pressure from patient and family to "remove scars." **(D)** After scar excision and cervicopectoral flap transposition she has a sad facial expression and loss of jaw line definition.

laser therapy combined with scar release and revision with Z-plasties when indicated or tissue rearrangement with local flaps. The PDL was the first laser to have demonstrated efficacy in the treatment of hypertrophic and contracted facial burn scars[13] and can be helpful for decreasing post-burn erythema and treating persistently erythematous burn scars. Z-plasties in combination with the PDL can be a powerful scar-improving combination[14] (Fig. 50.10). Full-thickness skin grafts are excellent for focal contractures. Excision of scars and resurfacing operations in aesthetic units and major flap transpositions, with or without tissue expansion, are rarely indicated.

The much less frequently encountered group of patients with type II facial burn deformities presents a completely different clinical situation. Examples of patients falling into the type II category are shown in Fig. 50.11. The surgical goals for this group of patients should be the restoration of normal facial proportion and, as much as possible, the restoration of the position and shape of normal facial features. The intrinsic and extrinsic contractures that exist in these patients require large amounts of skin. The correction of these contractures should be carried out in a carefully planned and staged fashion. The best sequence of operations is usually the following: eyelids, lower lip and chin, upper lip, cheeks, nose, and then other residual deformities. As each area is reconstructed, the addition of skin results in the relief of tension, which benefits other areas of the face. Excision of normal skin or elastic healed second-degree burned skin is almost *never* indicated. After facial proportion has been achieved and facial features have been

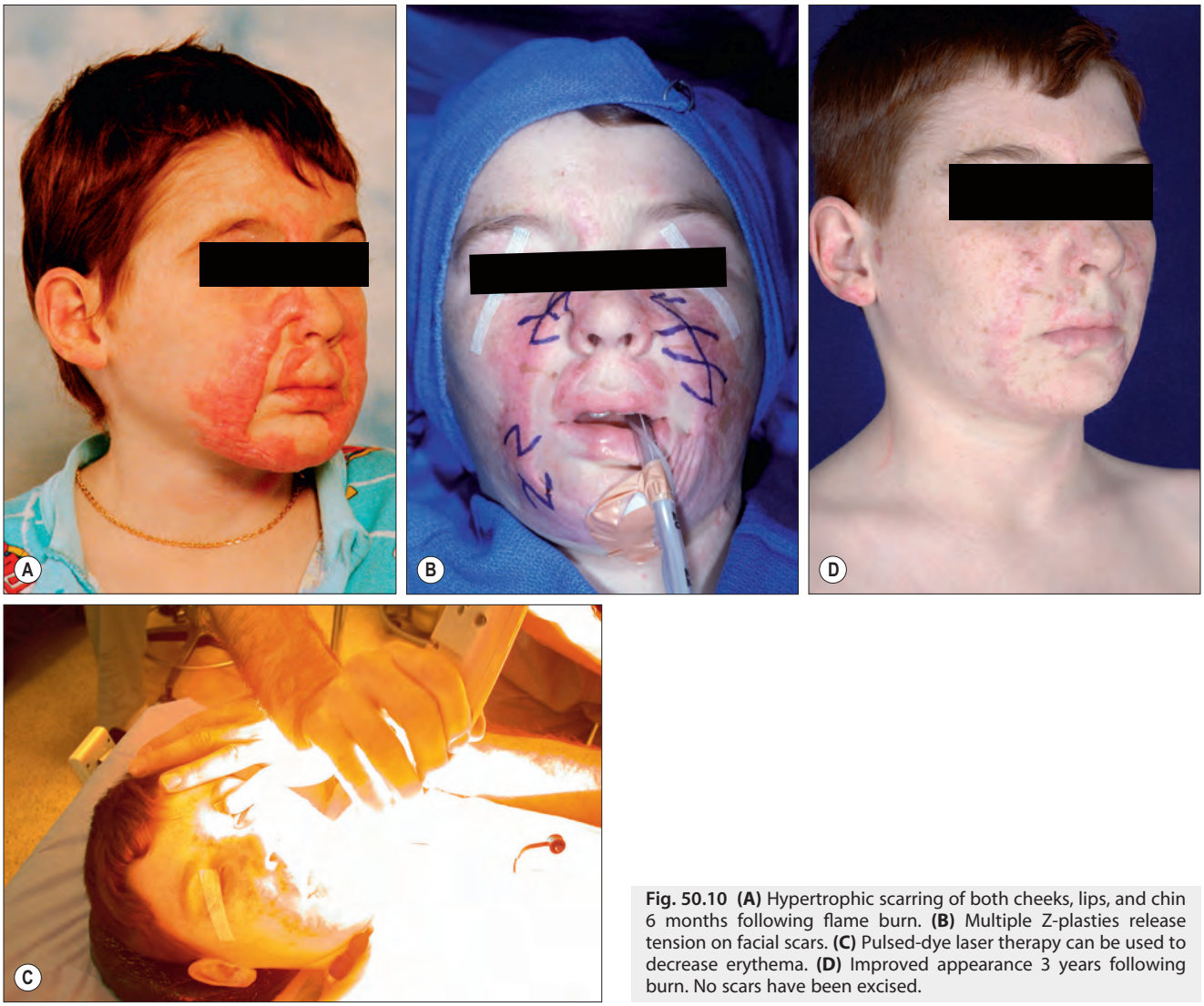

Fig. 50.10 **(A)** Hypertrophic scarring of both cheeks, lips, and chin 6 months following flame burn. **(B)** Multiple Z-plasties release tension on facial scars. **(C)** Pulsed-dye laser therapy can be used to decrease erythema. **(D)** Improved appearance 3 years following burn. No scars have been excised.

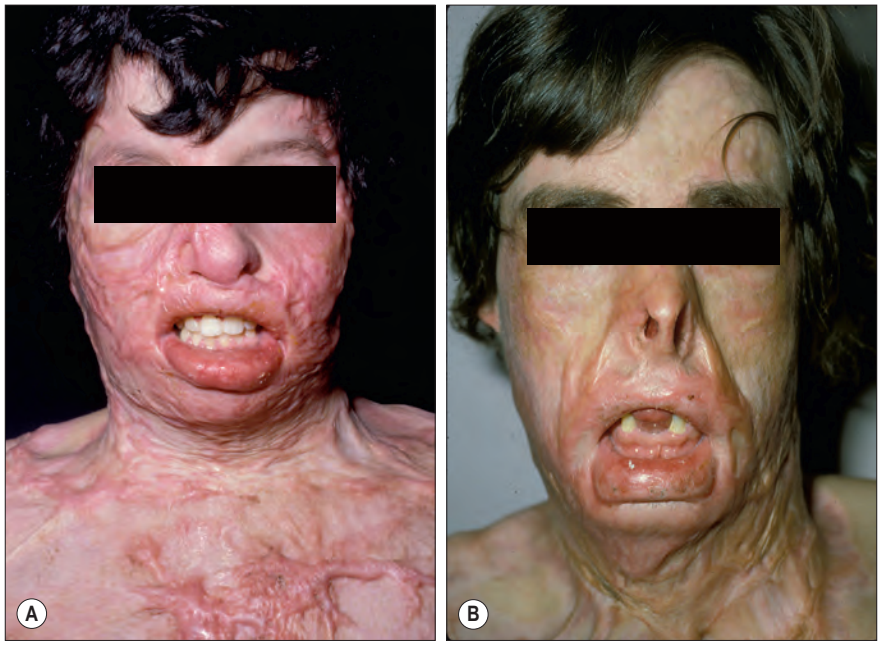

Fig. 50.11 **(A,B)** Typical examples of patients with "pan-facial" burns resulting in type II facial deformities.

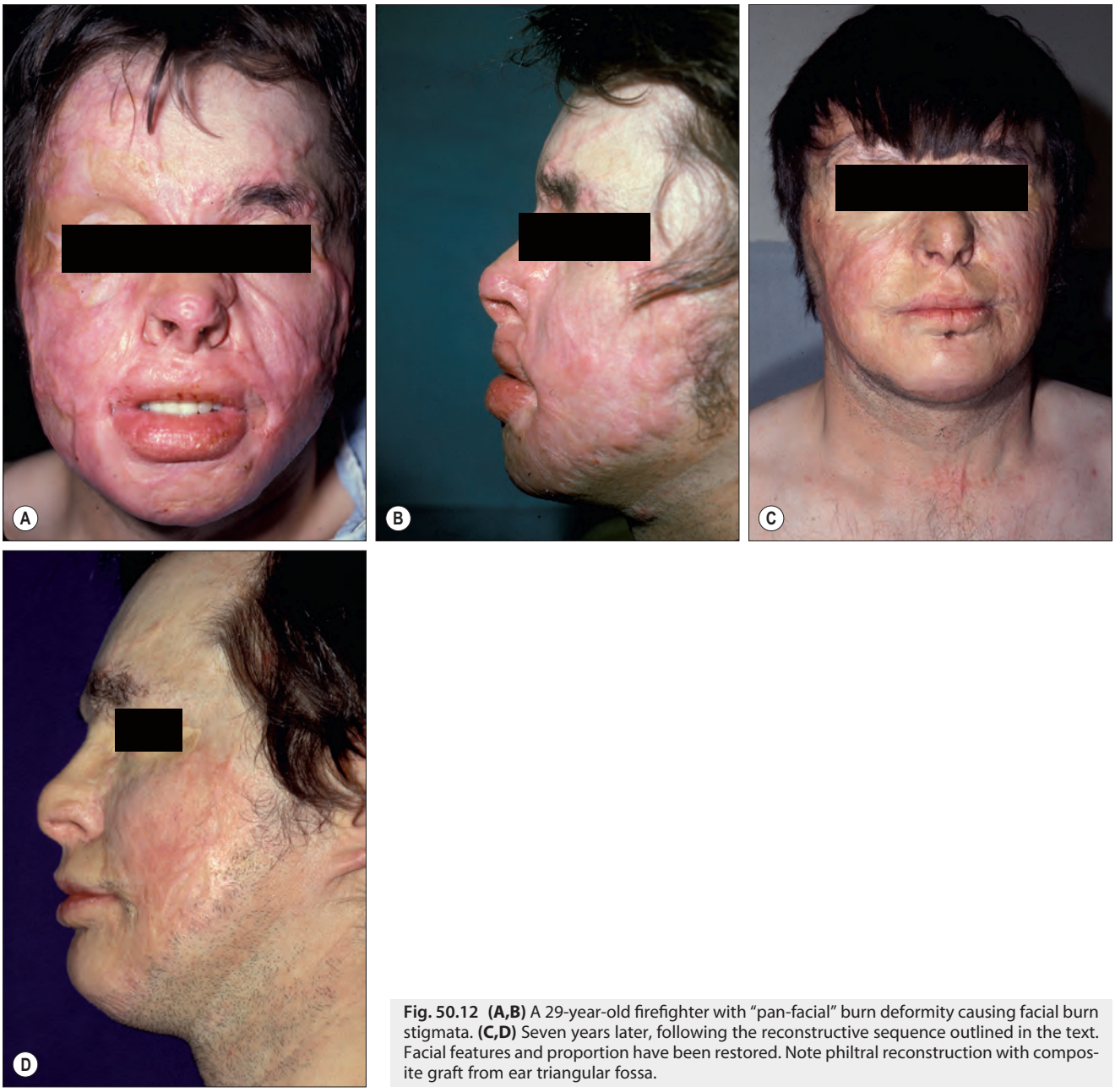

Fig. 50.12 (A,B) A 29-year-old firefighter with "pan-facial" burn deformity causing facial burn stigmata. **(C,D)** Seven years later, following the reconstructive sequence outlined in the text. Facial features and proportion have been restored. Note philtral reconstruction with composite graft from ear triangular fossa.

restored to their normal location and shape without tension, scar revision can be carried out to smooth and blend the remaining junctional scars (Fig. 50.12).

Normal faces are a mosaic of colors, textures, wrinkles, and irregularities. In a face that has undergone major burn injury, a mosaic appearance of scars, grafts, pigmentary abnormalities, and other flaws can be attractive as long as the facial features are restored to a normal location and are sufficiently loose and mobile for normal and appropriate facial expression. Laser therapy with vascular and fractional ablative CO_2 devices further blends, obscures, thins, and softens scars, enhancing facial expression and a more natural appearance (Fig. 50.13). Cosmetics can be useful for blending and camouflaging areas of pigmentary and textural abnormality, particularly in females.

Fundamental Principles and Techniques

CONTRACTURES

Burn injuries result in open wounds that either heal by contraction and epithelialization or are closed by skin grafting. Contractures result from both of these forms of wound healing. Contractures are either intrinsic or extrinsic. Intrinsic contractures result from loss of tissue in the injured area with subsequent distortion of the involved anatomic part. Extrinsic contractures are those in which the loss of tissue is at a distance from the affected area but the distorted structures, such as eyelids or lips, are not injured themselves.

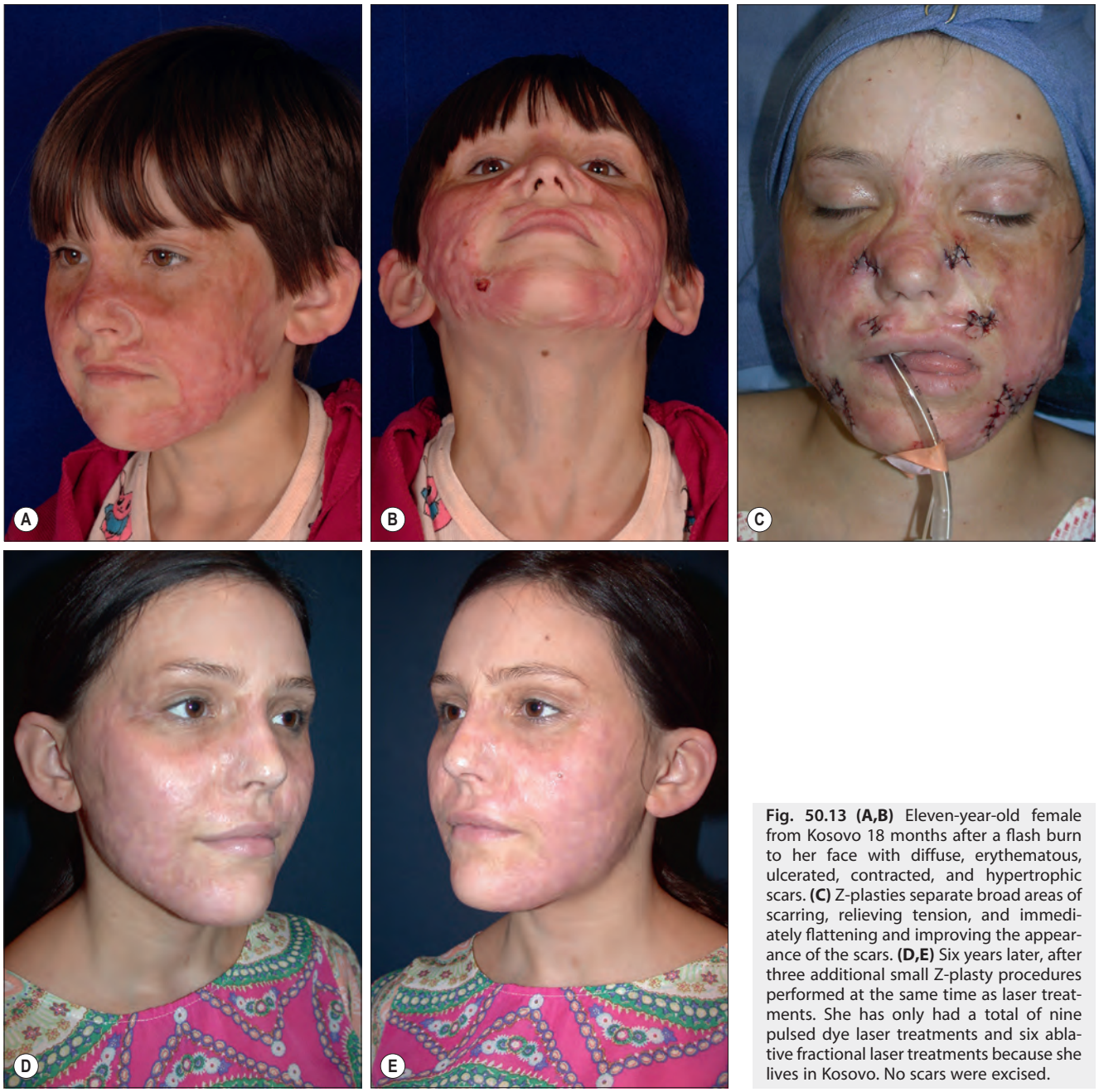

Fig. 50.13 (A,B) Eleven-year-old female from Kosovo 18 months after a flash burn to her face with diffuse, erythematous, ulcerated, contracted, and hypertrophic scars. **(C)** Z-plasties separate broad areas of scarring, relieving tension, and immediately flattening and improving the appearance of the scars. **(D,E)** Six years later, after three additional small Z-plasty procedures performed at the same time as laser treatments. She has only had a total of nine pulsed dye laser treatments and six ablative fractional laser treatments because she lives in Kosovo. No scars were excised.

Corrective measures should be directed at the cause of the contracture in order to provide optimal benefit and prevent iatrogenic deformities. It is helpful to minimize the amount of skin and scar excised when correcting facial contractures. When tension is released, many scars will mature favorably and become inconspicuous. Even long-standing scars will respond to a change in their environment. Healed second-degree burns under tension may be unattractive but when restored to a tension-free state can be superior in function and appearance to any replacement tissue. Minimizing excision also decreases the amount of new skin that must be provided in the reconstruction. Every effort should be made to relieve tension from the face when performing burn reconstruction. Tight faces are never attractive. Tight scars are always hypertrophic and erythematous. Relaxed scars are happy scars. The fractional ablative laser has created a new paradigm for the management of tight, hypertrophic, erythematous, and even ulcerated pan-facial scarring with contractures. It is a clearly more powerful and efficacious treatment modality than the PDL. The patient shown in Fig. 50.13 is a perfect example of this beneficial change in the management of facial burn scars. Her scars were more diffuse and severe than those of the patients shown in Fig. 50.9 who were severely deformed by scar excision surgery. Her face is essentially normal after the rehabilitation of her "original equipment."

AESTHETIC UNITS

The concept of facial aesthetic units has profoundly affected plastic surgical thinking since its introduction by Gonzalez-Ulloa.[15] Initially conceived as the ideal approach for resurfacing the face following burn injury, this important concept has been emphasized in virtually all subsequent writings about facial burns. It is important to keep facial aesthetic units in mind during burn reconstruction, but the desire to adhere to this concept should not supersede common sense. When small, unburned, and unimportant islands of skin are in an aesthetic unit that is being resurfaced, they can be sacrificed. Otherwise the excision of normal facial skin is rarely indicated in burn reconstruction. All burned faces to some degree are mosaic. Scar revision with Z-plasties is an excellent technique to camouflage scars in a burned face. Mosaic faces that are proportional, tension free, and normally expressive appear much better in real life than they do in images. Lasers, as noted previously, also aid in obscuring marginal scars and add to the camouflage effect.

Z-PLASTY

The Z-plasty operation is a powerful tool in the surgeon's armamentarium for facial burn reconstruction. The Z-plasty has been used for more than 150 years to lengthen linear scars by recruiting lax adjacent lateral tissue.[16] Z-plasty can also cause a profound beneficial influence on the physiology of scar tissue when it is carried out within the scarred tissues rather than after excising them.[17] The physiology of this phenomenon is related to the immediate and continuing breakdown of collagen that occurs in hypertrophic scars following the relief of tension.[18–20] Z-plasty also narrows scars at the same time that it lengthens them. In addition, the Z-plasty adds to scar camouflage by making the borders of the scar more irregular. In order for Z-plasties to lengthen a burn scar and restore elasticity, the lateral limbs of the Z-plasty must extend beyond the margins of the scar. The improvement in the appearance of facial scars following Z-plasty and without any scar excision can be dramatic, particularly when combined with PDLs and fractional ablative laser treatments (Figs. 50.1, 50.10, 50.13, 50.19).

LASER THERAPY

Hypertrophic scarring is a frequent complication after partial-thickness facial burn injuries that take longer than 3 weeks to completely epithelialize.[21] Despite conservative management and close monitoring, hypertrophic scarring can become severe during the first 2 years after the burn (Fig. 50.6).[22–24] The PDL has emerged as a successful treatment modality during this period of scar proliferation and is an effective alternative to scar excision in patients with hypertrophic facial burn scars.[14,25] Multiple studies have demonstrated its beneficial effect on scar erythema and hypertrophy.[26–30] The PDL also rapidly decreases pruritus and pain[26,27] and provides an additional, low-morbidity therapeutic intervention for patients and their families during the often prolonged period of scar maturation. Restoration of hypertrophic facial scars to their previous state of a flat, epithelialized surface is a superior outcome to surgical excision with its concomitant increase in facial tension.[14] The development of fractional ablative and nonablative laser therapy using various types of lasers, including CO_2 and erbium-YAG, offers promising new options for the management of facial burn scars in the future.[31]

GRAFTS

Skin grafts are an essential part of facial burn reconstruction. Surgical decisions regarding donor site selection, the use of split-thickness versus full-thickness grafts, the timing of intervention, and the postoperative management of grafts often determine the success or failure of facial burn reconstruction. Split-thickness skin grafts contract more than full-thickness grafts, wrinkle more, and always remain shiny, with a "glossy finish" look. Split-thickness skin grafts should be used primarily in the periphery of the face unless the limited availability of donor sites requires their use in more prominent areas. Split-thickness skin grafts can be excellent for upper eyelid releasing and resurfacing. Hyperpigmentation of split-thickness grafts on the face is a frequently occurring problem in dark-skinned patients, particularly those of African descent.

The full-thickness skin graft is a reliable workhorse in facial burn reconstruction. The broad, central, conspicuous areas of the face such as the cheeks, upper and lower lips, and dorsum of the nose are excellent sites for the use of full-thickness grafts. The missing or damaged parts in the vast majority of even severe facial thermal burns are the epidermis and the dermis, and that is what full-thickness skin grafts provide. After facial burns, the subcutaneous fat may be compressed or distorted by contractures but it is rare that it is injured or completely lost. Adequate skin must be provided when doing definitive resurfacing operations with full-thickness grafts. Contractures must be overcorrected, and postoperative management with conformers and pressure is essential. Full-thickness skin grafts are very reliable when used electively in the face for reconstruction after burns.[32]

FLAPS

Flaps can be useful for facial burn reconstruction, but they must be used judiciously and skillfully, recognizing their problems and limitations. The thickness of skin flaps from all distant donor sites is greater than that of the normal facial skin. The face is tight following burn injury, and flaps tend to contract when transferred. They can therefore compress or obscure underlying tissue contours. Transposing or advancing flaps from the neck and chest up to the face can easily create extrinsic contractures that adversely affect facial appearance. When flaps have been enlarged by tissue expansion, they are even more dangerous in this regard. Contractures with a downward vector create a "sad" facial appearance that is distressing to patients (Fig. 50.9). Cervicopectoral flaps provide the best color match in color and texture to facial skin. Distant flaps, whether transferred by traditional technique or microsurgery, share the common flaw of poor match in terms of color and texture.

TISSUE EXPANSION

Tissue expanders must be used with caution in the reconstruction of the head and neck. The underlying theme of almost all burn deformities is tension secondary to tissue deficiency. Stretching adjacent tissue in order to carry out scar excision can easily result in an increase in tension and therefore create iatrogenic contour abnormalities. The complication rate of tissue expansion following burn injury is high, especially in the neck area and the extremities.[33–35] The scalp is a privileged site, however, that tolerates tissue expansion quite well, even in the burn patient population.[36] As noted earlier, care must be taken when advancing or transposing expanded flaps from the cervicopectoral area to the face because this can create extrinsic contractures with a downward vector.

Timing of Reconstructive Surgery

The timing of reconstructive plastic surgery following facial burn injury falls into three separate phases: acute, intermediate, and late. Specialized burn centers create an ideal patient care environment where acute care and reconstructive surgery can be planned and carried out in optimal circumstances with collaboration among acute and reconstructive physicians and surgeons. The reconstruction of facial burn injuries to the head and neck should optimally begin with the acute care.

Acute reconstructive surgery occurs during the first months following the burn injury and includes urgent procedures that are required to facilitate patient care or to prevent acute contractures from causing permanent secondary damage. Acute reconstructive intervention is most frequently indicated in the eyelid, perioral, and cervical areas. Intermediate reconstructive surgery takes place during the months to years after wounds are closed and the scar maturation process is proceeding. During this phase of recovery, some patients will present to the reconstructive surgeon after having received their acute burn care at another facility. Timely intervention when indicated is important in this group of patients because it can positively influence further maturation of scars and grafts. Scar rehabilitation with lasers has emerged as probably the most effective treatment modality in this intermediate phase of facial burn deformity reconstruction. Late-phase reconstructive patients present to the reconstructive surgeon with established facial burn deformities many years following their acute injury. Careful scar analysis and judicious use of the right techniques is essential during this period. It is the responsibility of the treating surgeon to weigh all the options and select the best combination of treatments to maximize the patient's own healing capabilities.

ACUTE-PHASE RECONSTRUCTION

Eyelids

Upper and lower eyelid ectropion can occur from burn injuries to the periorbital region (intrinsic contracture) or may arise secondarily as a result of the contracture of open wounds and skin grafts at more distant sites (extrinsic contracture). With severe ectropion, such as shown in Fig. 50.14A, early intervention is mandatory in order to prevent irreversible injury to the cornea. Conservative measures to protect the cornea, such as temporary sutures or contact lenses, are often ineffective. Tarsorrhaphy can cause irreversible iatrogenic injury and should not be used unless absolutely necessary. The best treatment is early intervention with release of contracture and resurfacing with split-thickness skin grafts (Fig. 50.14B). Release of even extreme contractures with grafting can be done in the presence of open wounds and effectively restores protective eyelid function.

Perioral Deformities

Microstomia occurs from circumferential scarring at the junction between lips and cheek. Perioral scarring from either open wounds or contraction of skin graft suture lines can act as a pursestring, resulting in diminished oral opening (Fig. 50.15). This can compromise alimentation and airway access. Microstomia is best addressed by the

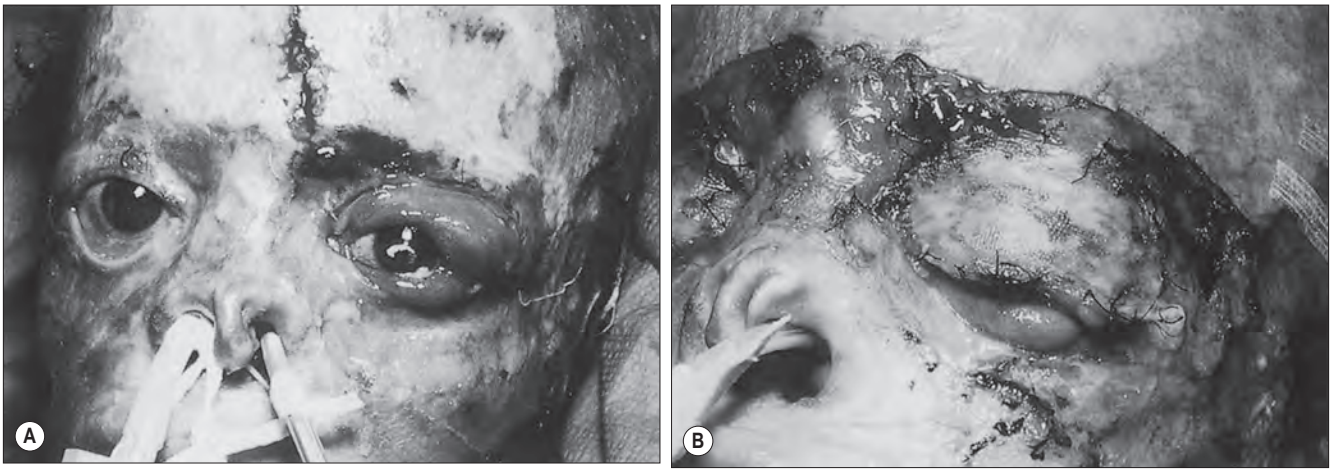

Fig. 50.14 (A) Extreme eyelid ectropion during early acute phase. **(B)** Successful correction of ectropion with release and graft despite operative wounds.

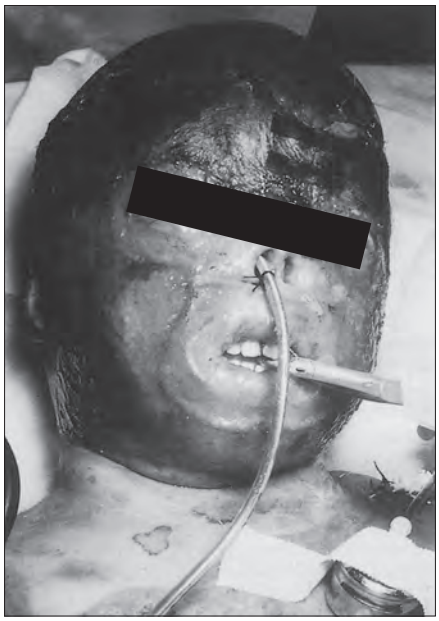

Fig. 50.15 Microstomia during acute phase as a result of circumoral contracture.

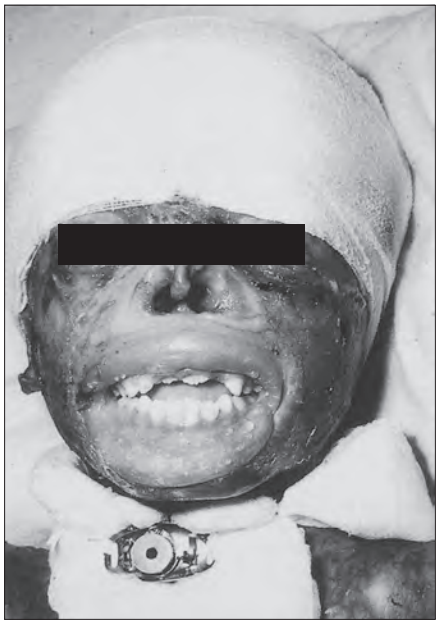

Fig. 50.16 Macrostomia secondary to contracture of open wounds and grafts with lip eversion and loss of oral competence.

acute release of the oral commissures, taking care to avoid extensive transverse releasing incisions in the aesthetic units of the cheek. Overcorrection can easily result in macrostomia. As soon as adequate oral opening is achieved for feeding and airway access, definitive reconstruction is best left for the postacute period.

Macrostomia is caused by rapid contraction of open wounds or grafts in the cheek and perioral region, resulting in eversion of the upper and lower lips and lateral movement of the oral commissures (Fig. 50.16). The loss of an effective oral sphincter causes drooling and desiccation of the oral mucosa and can result in irreversible damage to the dentition. Early intervention with release and grafting of the lower and/or upper lips should be carried out as soon as possible. Definitive reconstruction is best carried out at a later period.

Cervical Deformities

Anterior neck contractures in the acute period are best prevented by aggressive splinting and incisional releases and grafting when indicated.[37] When severe anterior neck flexion contractures occur, early release and grafting are necessary to allow for adequate airway access and to minimize hypertrophic scarring as a result of excessive and persistent tension (Fig. 50.17). Although secondary releases and grafts are often necessary, permanent correction of neck contractures with split-thickness skin grafts is frequently possible when postoperative management includes proper splinting and pressure (Fig. 50.17).[37]

INTERMEDIATE-PHASE RECONSTRUCTION

The intermediate phase of plastic surgical intervention consists of scar modification designed to favorably influence the healing process in the early months to years following acute wound closure. The treatment options during this period are multifaceted and are continuing to evolve. Significant progress is being made with these types of interventions.

It is often recommended that definitive reconstructive surgery be carried out after facial scars and skin grafts are mature, soft, and supple. This process takes at least a year and frequently takes many years to fully occur. The maturation of facial burn scars takes much longer than is generally appreciated by patients and reconstructive surgeons alike. If scars are continuing to improve, it is usually best to allow them to continue to mature. If scars are not maturing favorably or are improving very slowly, well-timed and well-conceived surgical intervention to favorably influence the clinical progress can be beneficial. The scar maturation process after facial burns is influenced by multiple factors. The most important factor, other than the initial severity of the injury, is the amount of tension present in the face and acting on the scars. Surgical procedures to decrease tension and to favorably alter the direction and contour of scars can achieve significant improvement in scar maturation for many years following a burn. Whenever healing burns cross concave surfaces, there is a tendency for hypertrophic scarring to develop. Examples in the face are the glabella, the nasojugal groove, the crus helicis of the ear, and the infracommissural folds. Relieving tension with Z-plasties without scar excision is very effective in correcting hypertrophy (Figs. 50.10 and 50.13). Steroids, both topically, intralesionally, and through ablative laser delivery, can be helpful during this period but must be used sparingly to avoid atrophy, telangiectasia, and erythema. In more severe cases, tension can also be relieved by judiciously placed releases and skin grafts (Fig. 50.18). The skin grafts can be of either split-thickness or full-thickness variety. Split-thickness skin grafts are best used where the location of the graft will be inconspicuous or where large amounts of skin are required to relieve the contractures. This is frequently indicated when there are associated neck contractures. Tension from the neck must be eliminated as much as

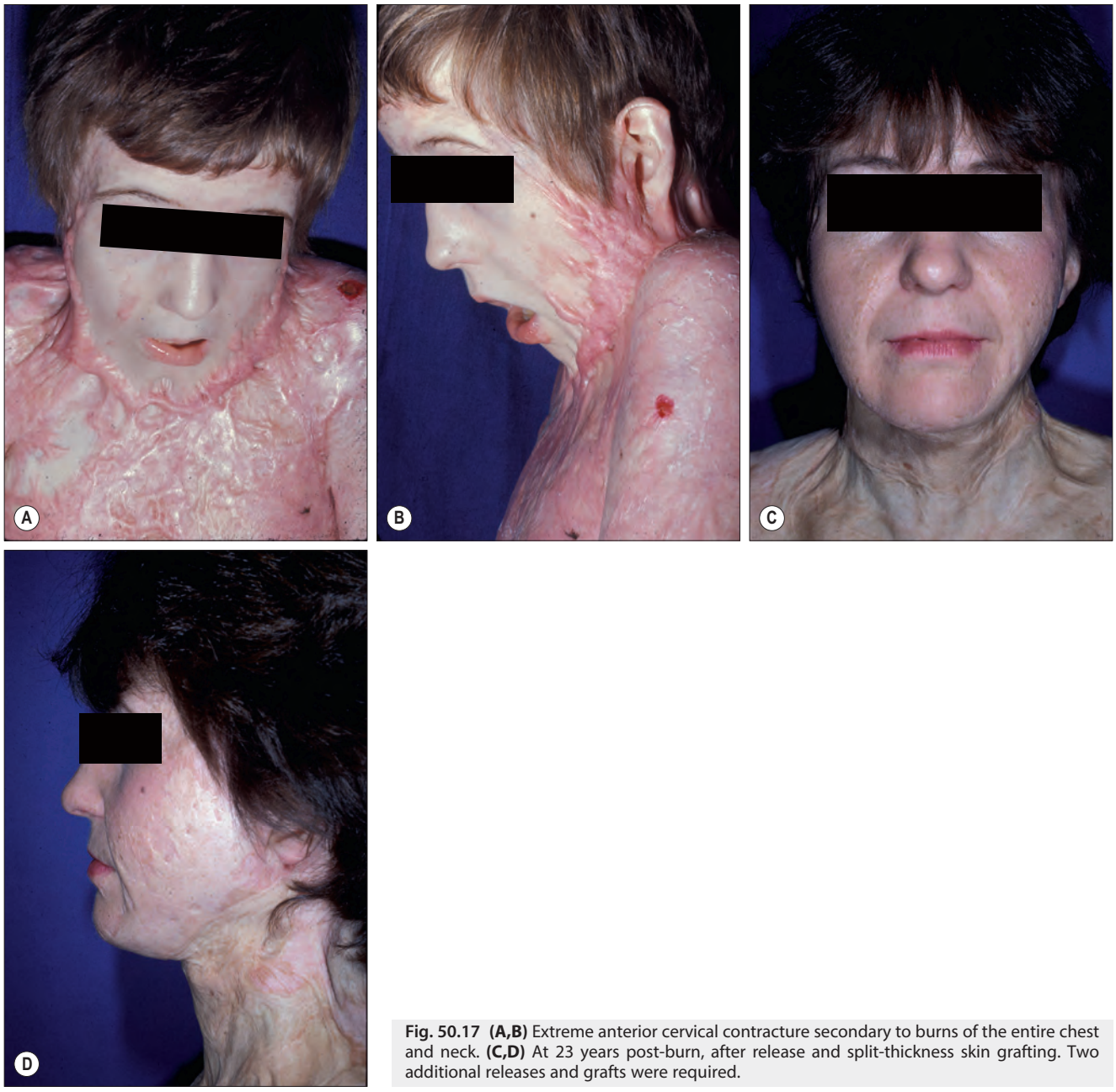

Fig. 50.17 (A,B) Extreme anterior cervical contracture secondary to burns of the entire chest and neck. **(C,D)** At 23 years post-burn, after release and split-thickness skin grafting. Two additional releases and grafts were required.

possible to allow for favorable maturation of facial burn scars. The use of full-thickness skin grafts during the intermediate phase of reconstruction should be rare and limited to circumstances where definitive repair is being carried out and there is little chance that further skin will be required in that region. The PDL is a proven adjunctive therapy that can decrease erythema and speed the rate of scar maturation (Fig. 50.10). Fractional ablative laser treatment is a paradigm-changing new intervention during this intermediate phase of recovery and reconstruction. It is an effective way to enhance the remarkable ability of scars to regenerate and remodel themselves. Every scar has the right to live, if it can be rehabilitated. The patient shown in Fig. 50.19 would certainly have achieved an even better result if vascular and ablative fractional lasers were available at the time of his reconstruction (Fig. 50.13). The result would also have been achieved more expeditiously, with fewer operations and less morbidity.

LATE-PHASE RECONSTRUCTION

Late-phase reconstructive surgery takes place when scars are mature and the patient's deformities are essentially stable. In some patients, scars will be soft and supple, but, in others, even long-standing scars may be hypertrophic and hyperemic many years following the burn injury because of persisting tension or unfavorable orientation. Scars can remain indurated and hyperemic for decades following a facial burn. Reorientation in this late phase with Z-plasties and treatment with the PDL can result in

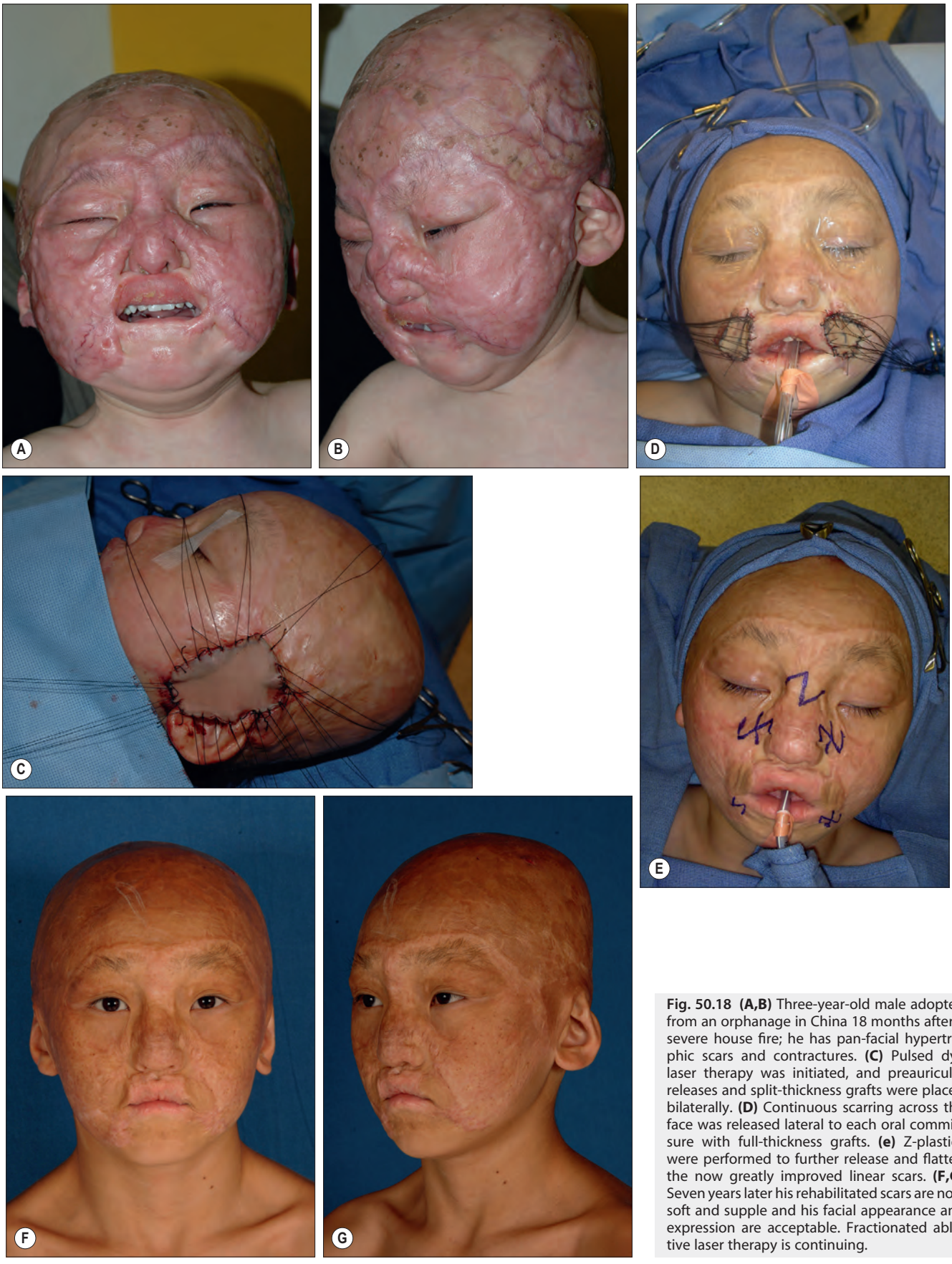

Fig. 50.18 (A,B) Three-year-old male adopted from an orphanage in China 18 months after a severe house fire; he has pan-facial hypertrophic scars and contractures. **(C)** Pulsed dye laser therapy was initiated, and preauricular releases and split-thickness grafts were placed bilaterally. **(D)** Continuous scarring across the face was released lateral to each oral commissure with full-thickness grafts. **(e)** Z-plasties were performed to further release and flatten the now greatly improved linear scars. **(F,G)** Seven years later his rehabilitated scars are now soft and supple and his facial appearance and expression are acceptable. Fractionated ablative laser therapy is continuing.

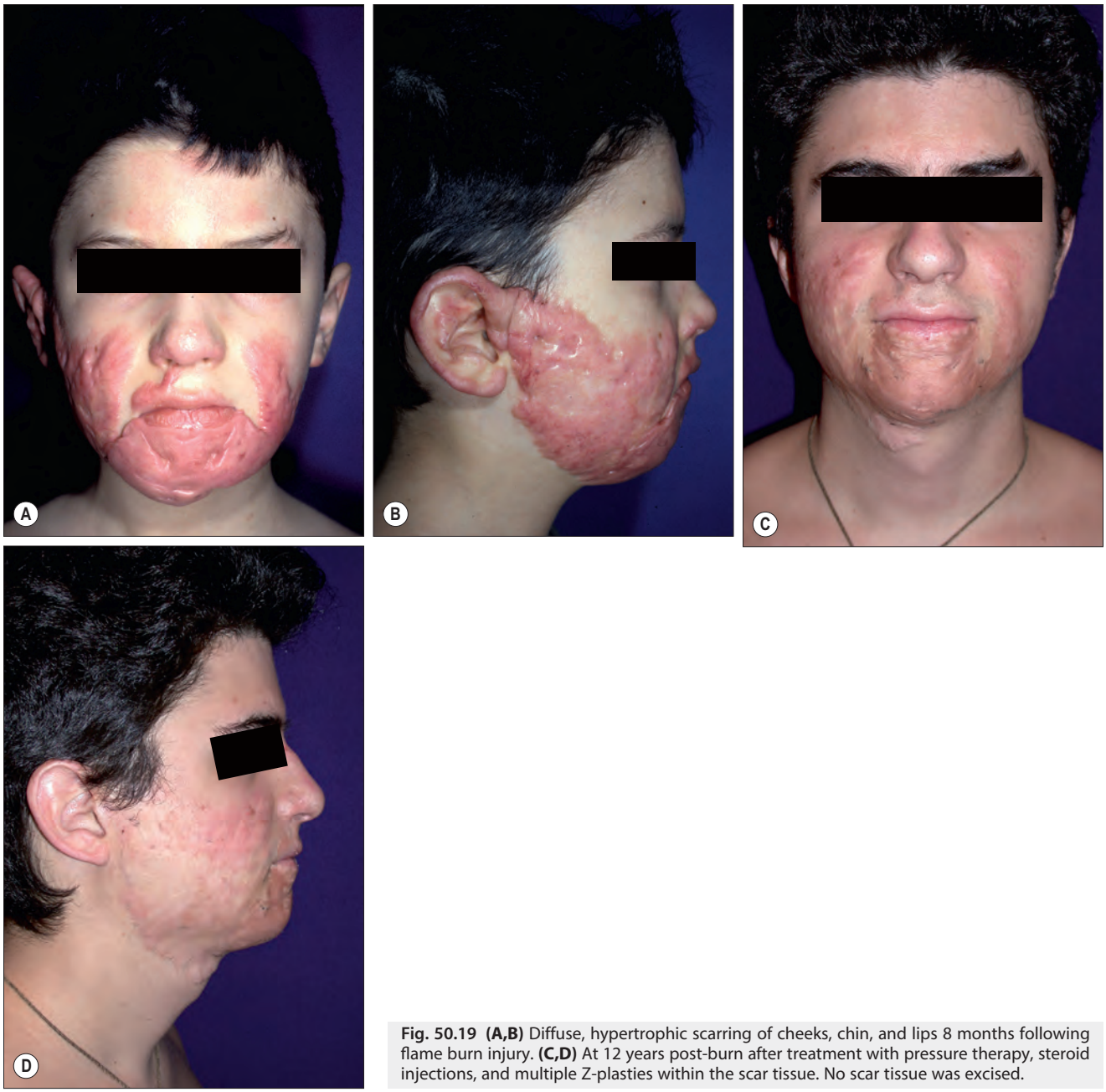

Fig. 50.19 (A,B) Diffuse, hypertrophic scarring of cheeks, chin, and lips 8 months following flame burn injury. **(C,D)** At 12 years post-burn after treatment with pressure therapy, steroid injections, and multiple Z-plasties within the scar tissue. No scar tissue was excised.

remarkable improvement (Fig. 50.20). Fractional ablative lasers have also been shown to benefit facial burn scars many years after the injury. Scar excision can often be avoided, with its concomitant increase in facial skin tension and distortion of facial features.

Reconstruction of Specific Areas of the Head and Neck

SCALP

Scalp alopecia is seen in as many as 25% of children who suffer burn injuries of the head and neck.[38] McCauley et al. devised a system of classification for burn alopecia based on the pattern and extent of deformity.[39] They describe the pattern of alopecia as uniform, segmental, patchy, or total (types I–IV, respectively) and the extent of alopecia as 25% of the scalp, 25–50%, 50–75%, or more than 75% (subtypes A–D, respectively). Their system serves as both the means of description and an initial step in planning operative care. Previously described reconstruction techniques include serial excision, rotational scalp flaps, free hair follicle transplantation, and staged scalp tissue expansion.[40] Of patients with scalp injuries, associated adjacent burn deformities were commonly found involving the ear, nose, and eyebrow.[41] These injuries included ear deformity (46%), nasal deformity (27%), and eyebrow

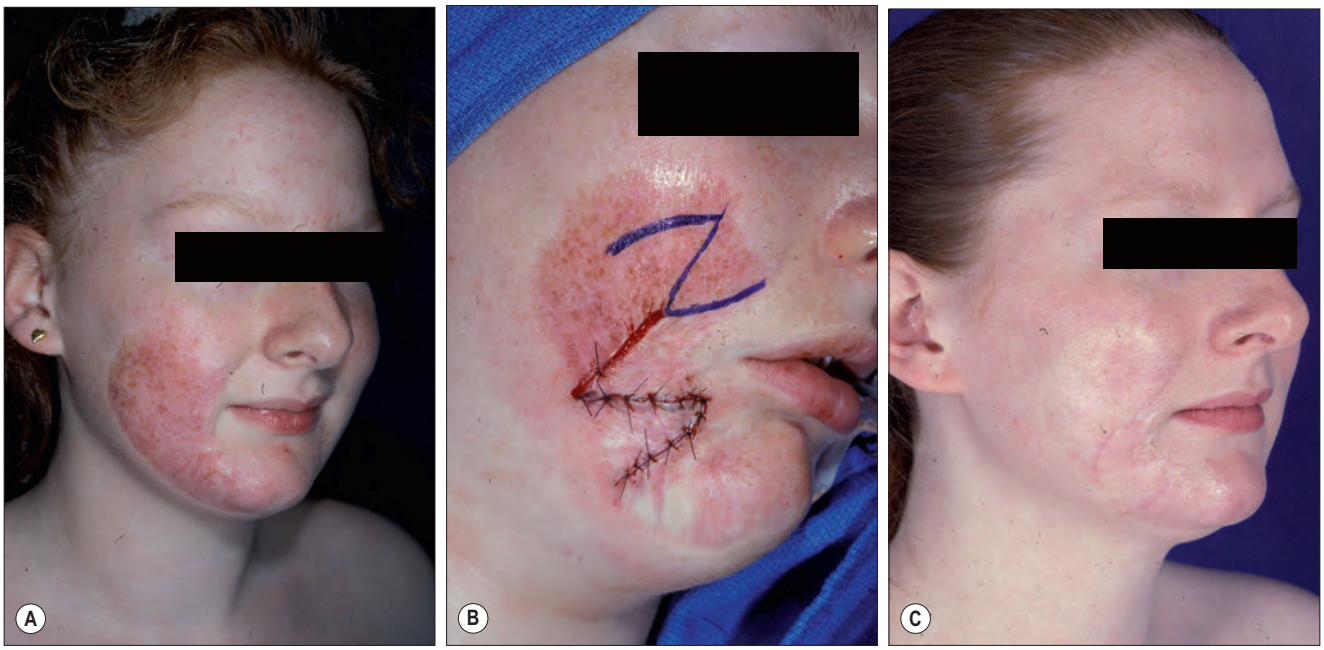

Fig. 50.20 **(A)** A 16-year-old female 11 years following contact burn. Right cheek scar remains erythematous, indurated, and conspicuous. **(B)** Relaxation and reorientation of scar tissue with Z-plasty. **(C)** Five years later, after six treatments with the pulsed-dye laser.

deformity (46%). Therefore, in planning the surgical reconstruction for pediatric scalp alopecia, it is helpful to evaluate each patient for adjacent structure burn injuries requiring reconstruction. Therefore, as one plans the stages of tissue expansion procedures, one can plan concurrent reconstruction of associated burn injuries, sometimes taking advantage of the region of expected alopecia excision.

EYEBROWS

Eyebrow reconstruction following complete loss is an unsolved surgical problem. Composite grafts of hair-bearing scalp from carefully selected sites in the retroauricular area can satisfactorily transfer hair.[42–44] Unfortunately the hair is scalp hair that grows rapidly and is more projecting than the tangential delicate hair of the normal eyebrow. For complete eyebrow replacement, the technique of composite grafting as described by Brent[42] is most useful. For partial eyebrow loss, micro- and mini-grafting of scalp hair can be efficacious. Occasionally, borrowing composite grafts from a contralateral unburned eyebrow is appropriate. Temporal artery island flaps for eyelid or eyebrow reconstruction have been used for many years.[44–46] When used for eyebrow reconstruction, they can be bushy and conspicuous and should be used with caution, particularly when carrying out unilateral eyebrow reconstruction.

Burn injuries of the scalp and upper face often result in scars that distort the relative positions of the anterior hairline, eyebrows, and upper eyelid. Contour of the brow is distorted with exaggerated elevation of the central peak. Furthermore, scar contracture involving the upper eyelid can result in cicatricial ectropion associated with effacement of the supratarsal fold and corneal exposure. This stereotypic set of upper facial deformity can be treated with tissue expansion and antegrade forehead plasty.[47] In this technique, the scalp and forehead areas are tissue expanded. The tissue expander is removed and the scalp aponeurosis is advanced antegrade and loaded in redundant fashion over the brows at the level of the arcus marginalis. Accounting for the fourth dimension of time and tissue recoil, the brows are returned to a natural contour and improved position (Figs. 50.21 and 50.22).

EYELIDS

Correction of upper and lower eyelid contractures in the late reconstructive period can be a daunting and humbling challenge. The periorbital region is made up of complex three-dimensional anatomy and requires abundant skin to appropriately drape the contours of both the upper and lower eyelids. The slightest amount of excessive tension from either the eyelid skin itself or contractures in adjacent regions such as the forehead or cheek can profoundly and adversely affect eyelid function and appearance. Reconstructive goals should be restoration of a normally shaped palpebral fissure with appropriate orientation of upper and lower eyelashes at rest and in the open position whenever possible. This often requires extensive releasing incisions extending medial to the medial canthus and lateral to the lateral canthus in order to adequately release all the contracted tissues. When ectropion is the result of a distant contracture, the normal eyelid skin should always be returned to its normal location. Incisions should not be made at the eyelid margin, thereby separating the normal eyelid skin from the ciliary line and replacing it with a graft. When overlying scar is released, care must be taken to prevent injury to the underlying orbicularis oculi muscle. This is often rolled up and contracted and is rarely completely lost. It must be unfolded to its normal flat broad shape and the

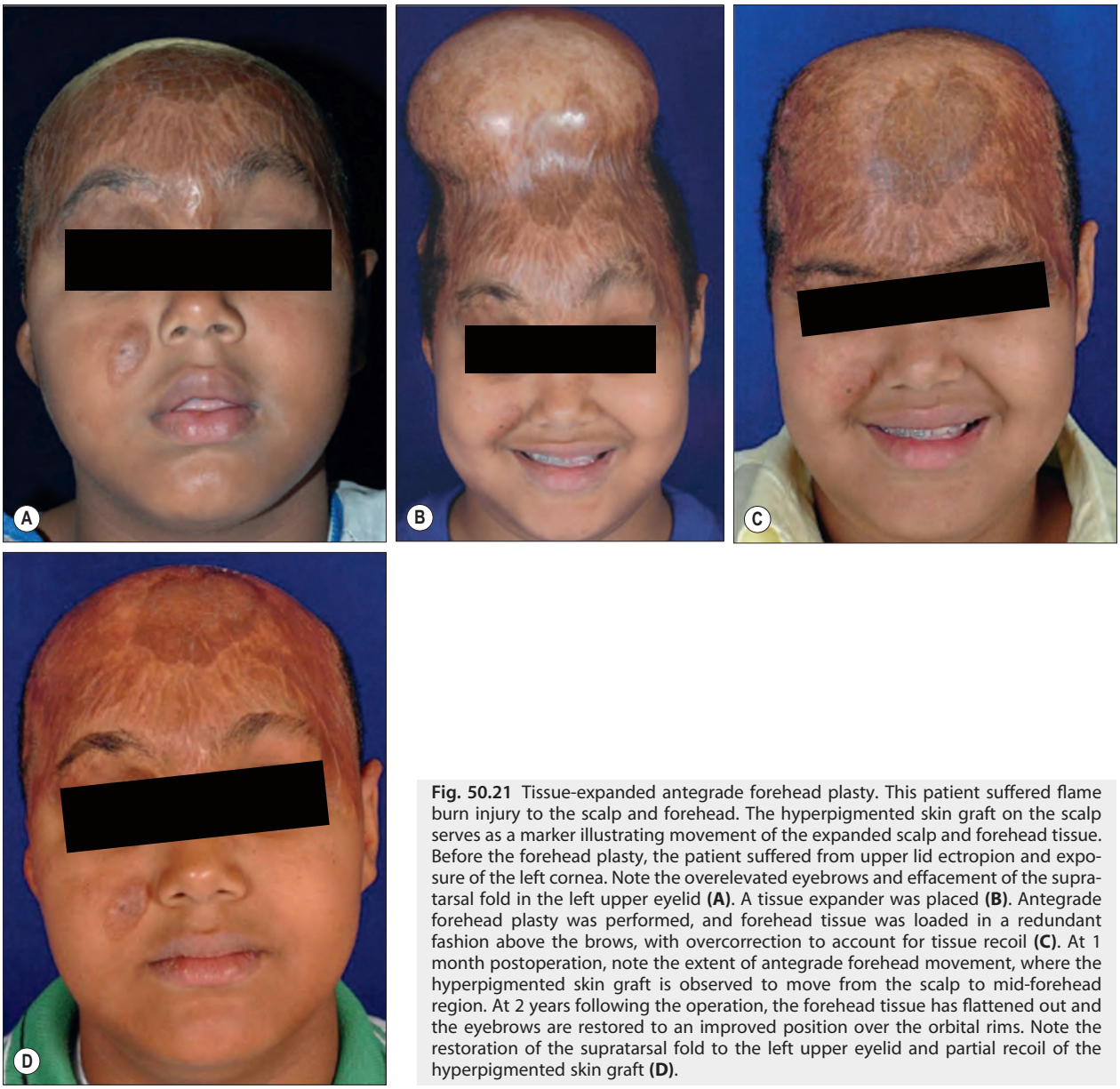

Fig. 50.21 Tissue-expanded antegrade forehead plasty. This patient suffered flame burn injury to the scalp and forehead. The hyperpigmented skin graft on the scalp serves as a marker illustrating movement of the expanded scalp and forehead tissue. Before the forehead plasty, the patient suffered from upper lid ectropion and exposure of the left cornea. Note the overelevated eyebrows and effacement of the supratarsal fold in the left upper eyelid **(A)**. A tissue expander was placed **(B)**. Antegrade forehead plasty was performed, and forehead tissue was loaded in a redundant fashion above the brows, with overcorrection to account for tissue recoil **(C)**. At 1 month postoperation, note the extent of antegrade forehead movement, where the hyperpigmented skin graft is observed to move from the scalp to mid-forehead region. At 2 years following the operation, the forehead tissue has flattened out and the eyebrows are restored to an improved position over the orbital rims. Note the restoration of the supratarsal fold to the left upper eyelid and partial recoil of the hyperpigmented skin graft **(D)**.

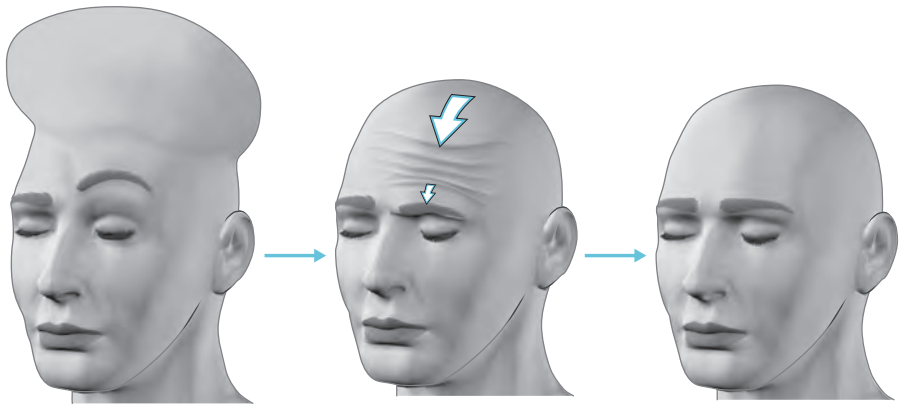

Fig. 50.22 Diagram illustrating tissue movements of antegrade forehead plasty. Scalp tissue is maximally expanded, with consequent further exaggeration of eyebrow elevation (left). Tissue expander is removed and the expanded scalp and forehead skin are advanced anteriorly, loaded in redundant fashion over the eyebrows (middle). Over time, the redundant skin recoils, restoring the eyebrows to a more natural position (right).

resulting defect resurfaced with abundant skin graft. Upper eyelid resurfacing is best carried out with split-thickness skin grafts from the best available donor site.[44] Full-thickness skin grafts in the upper eyelid usually transfer a thick dermal component that compromises the delicate contour of the supratarsal fold. Lower eyelid resurfacing may be done with either split-thickness skin grafts or appropriate full-thickness grafts when indicated. For minor contractures of either upper or lower eyelids, the perfect reconstructive material can be obtained from an unburned contralateral upper eyelid. Medial canthal folds are best corrected with Z-plasties when there is not a significant tissue deficiency.[48]

LOWER LIP AND CHIN

Deformities of the lower lip and chin usually occur in combination. Contracting forces result in inferior dislocation and eversion of the lower lip. In addition, there is compression of the soft-tissue contours of the chin prominence. Release should be carried out at the vermillion scar junction and the lower lip carefully unfurled, taking care to prevent iatrogenic injury to the underlying orbicularis oris muscle.[11] The resulting defect is then resurfaced with split-thickness skin grafts or full-thickness grafts when indicated. Restoration of chin contour can be improved with chin implants.

UPPER LIP DEFORMITIES

The upper lip is usually shortened and retruded by severe facial burn injuries. Releasing and grafting should be carried out, taking care not to overcorrect the deformity and create a long upper lip.[11] Full-thickness grafts from the best available donor sites are usually the best option for resurfacing. Reconstruction of the philtrum when indicated is best performed by the technique of Schmid,[49] using a composite graft from the triangular fossa of the ear (Figs. 50.12 and 50.23).

ELECTRICAL BURNS OF THE ORAL COMMISSURE

Electrical burns of the oral commissure constitute a unique and challenging burn injury to the head and neck. The injury occurs in small children and usually results from placing a live extension cord outlet in the mouth. Most of these injuries are minor and all should be treated conservatively in the acute period. If there has been minimal tissue loss, reconstructive surgery using local flaps can improve aesthetics.[50–52] When there has been extensive full-thickness loss of skin, vermillion, mucosa, and muscle, as shown in Fig. 50.24, reconstruction requires complete release of the contracture and replacement with adequate tissue of suitable quality.[53] A ventral tongue flap provides abundant mucosa and muscle and allows the lips and cheek to return to their proper location and shape. Normal facial appearance, mobility, and expression can be restored (Fig. 50.25).

NASAL DEFORMITIES

Burn injuries to the nose result in a broad range of deformities which can be focal and minor or can result in complete nasal amputation. Minor deformities are best dealt with by local scar revision, particularly with Z-plasties to relieve contractures, or releases in combination with full-thickness skin grafting. Shortening of the nose with flaring or partial loss of the alar rims is common in more severe facial burns. Local release of the alar lobules with full-thickness skin grafts is a useful technique for minor to moderate contractures. Complete excision of dorsal scar and graft in an aesthetic unit with a full-thickness skin graft is useful for more severe shortening. When the lower third of the nose has been amputated by the burn injury, inferiorly based, turn-down flaps of the dorsal nasal tissues can provide satisfactory lengthening and improved contour to the tip and alar lobules. More severe cases of nasal deformity can be treated by either dorsal turn-down flaps or other forms of total nasal reconstruction. The dorsal turn-down flap usually requires at least two stages but can be effective in even near total nasal amputation (Fig. 50.23). Forehead flaps are usually unavailable in patients who have sustained facial burns severe enough to result in total nasal amputation. Distant flaps can be used with either microsurgical transfer using a radial forearm flap or using the frequently unburned skin of the upper inner arm for a Tagliacozzi flap. If the face is otherwise composed of burn scar and graft, these distant flap nasal reconstructions have the disadvantage of appearing to be "stuck on" and stand out in the midst of the otherwise mosaic appearance of the face. When the face has required resurfacing with flaps, a nasal reconstruction with flap tissue is the best option (Fig. 50.26).

EAR DEFORMITIES

Improved care in the acute phase of burn injury has greatly decreased the incidence of helical chondritis and the resulting associated deformities of crumpled or lost cartilage. Minor ear deformities are often seen in patients with little or no hair loss and can easily be camouflaged. Larger defects can be treated by myriad local reconstructive techniques.[12,54–56] Subtotal ear amputation (Fig. 50.27) often lends itself to reconstruction with a conchal transposition flap and skin graft.[57] Complete ear loss can be masked by the use of a prosthesis. Fixation has been improved by the use of osteo-integrated implants, but cost and color changes remain problematic. Selected patients can be appropriate candidates for total ear reconstruction using autologous cartilage and soft-tissue coverage from either temporalis fascia flaps or expanded local tissue.[58] Alloplastic materials should not be used in the reconstruction of post-burn ear deformities due to an unacceptably high extrusion rate.[59]

Burn Neck Contractures

PREVENTION

Cervical contractures are a major problem in burns involving the chest, neck, and face. The anterior neck skin is thin, and the neck is a highly mobile flexion area easily prone to contracture. As noted previously, severe neck flexion neck contractures in the acute phase often require early reconstruction to aid in airway management. Neck contractures should usually be dealt with prior to carrying out facial burn reconstruction because the extrinsic contractile forces from the neck cause facial deformities and can adversely

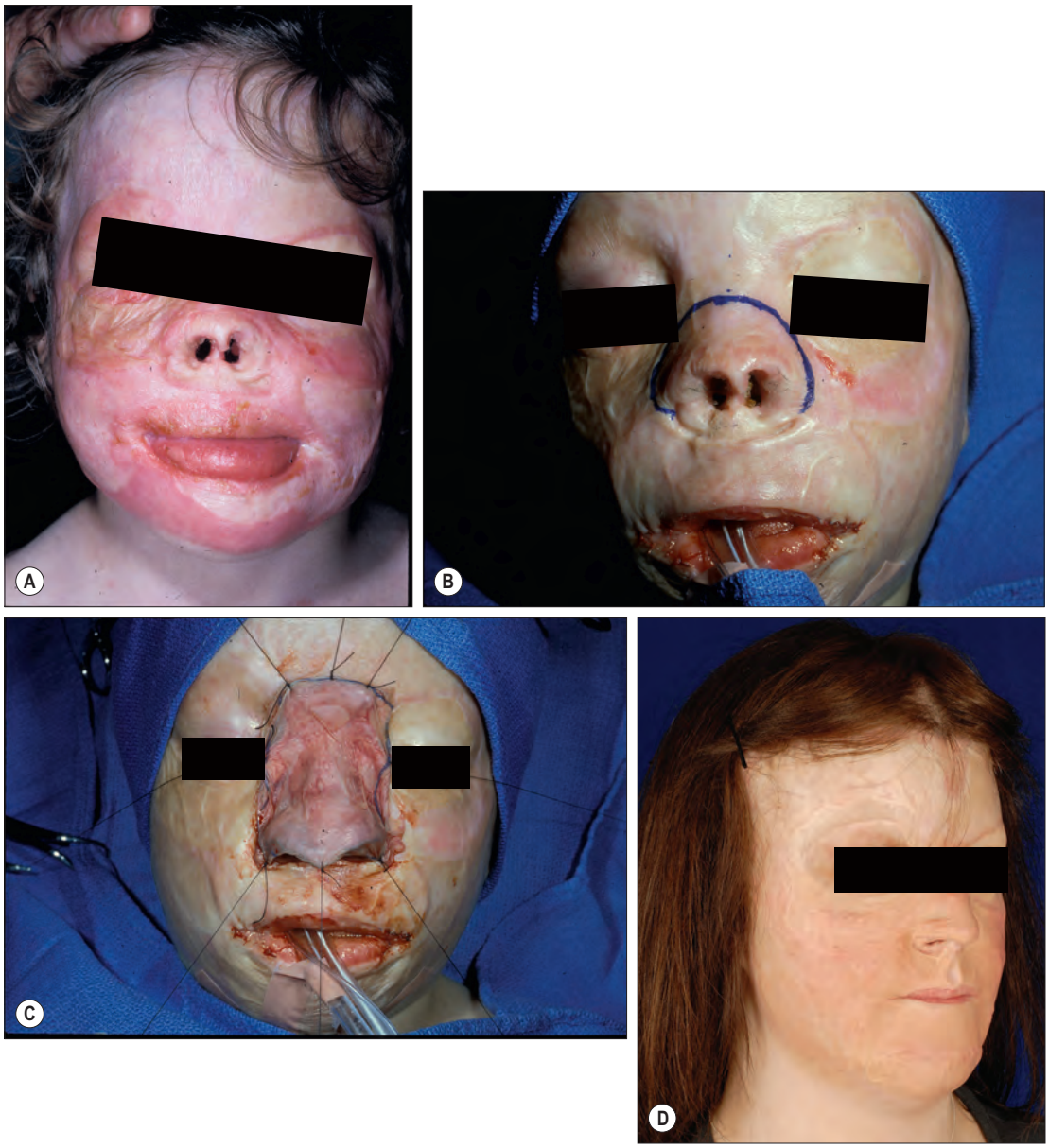

Fig. 50.23 **(A)** A 3-year-old female 10 months following severe facial burn with subtotal nasal amputation. **(B)** Intraoperative design of a nasal turn-down flap. **(C)** Split-thickness skin grafting to nasal dorsum following turn-down flap and contracture releases. **(D)** At 16 years following turn-down flap after second release and graft.

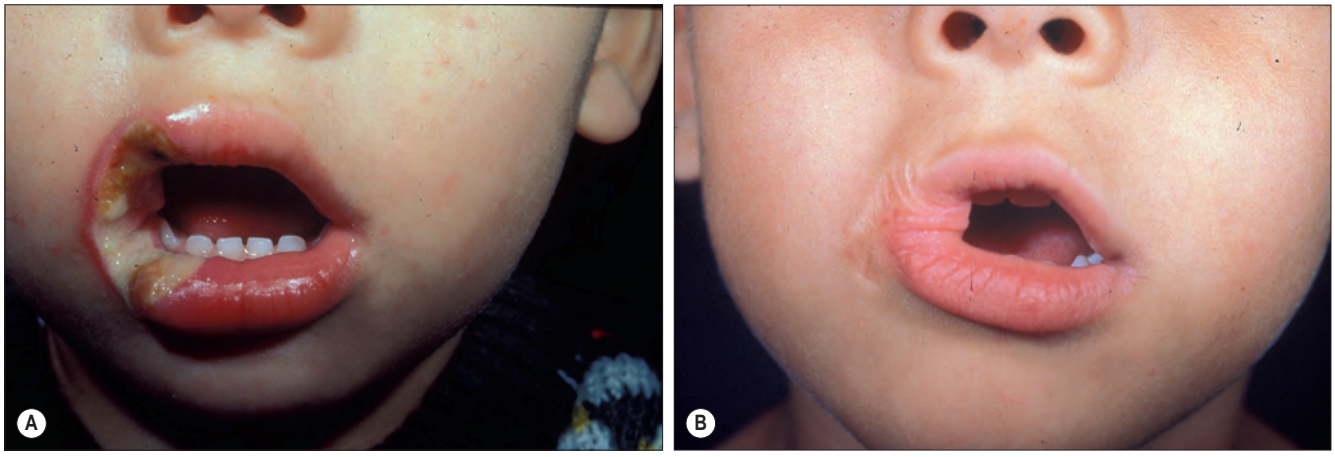

Fig. 50.24 **(A)** Severe oral commissure burns destroy vermillion, mucosa, muscle, and the skin of the lip and cheek. **(B)** Extensive contracture results with thickening of the leading edge of the commissure.

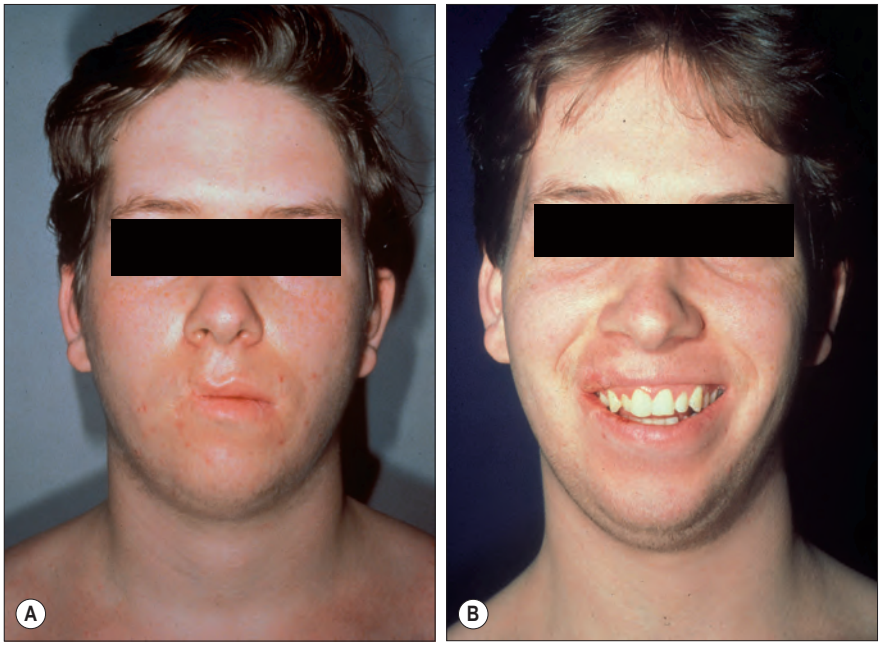

Fig. 50.25 (A) A 16-year-old male following devastating right oral commissure electrical burn. Some 40% of lip circumference is lost and the commissure is thick and immobile. **(B)** Following tongue flap reconstruction, the commissure is thin and mobile and facial expression is restored.

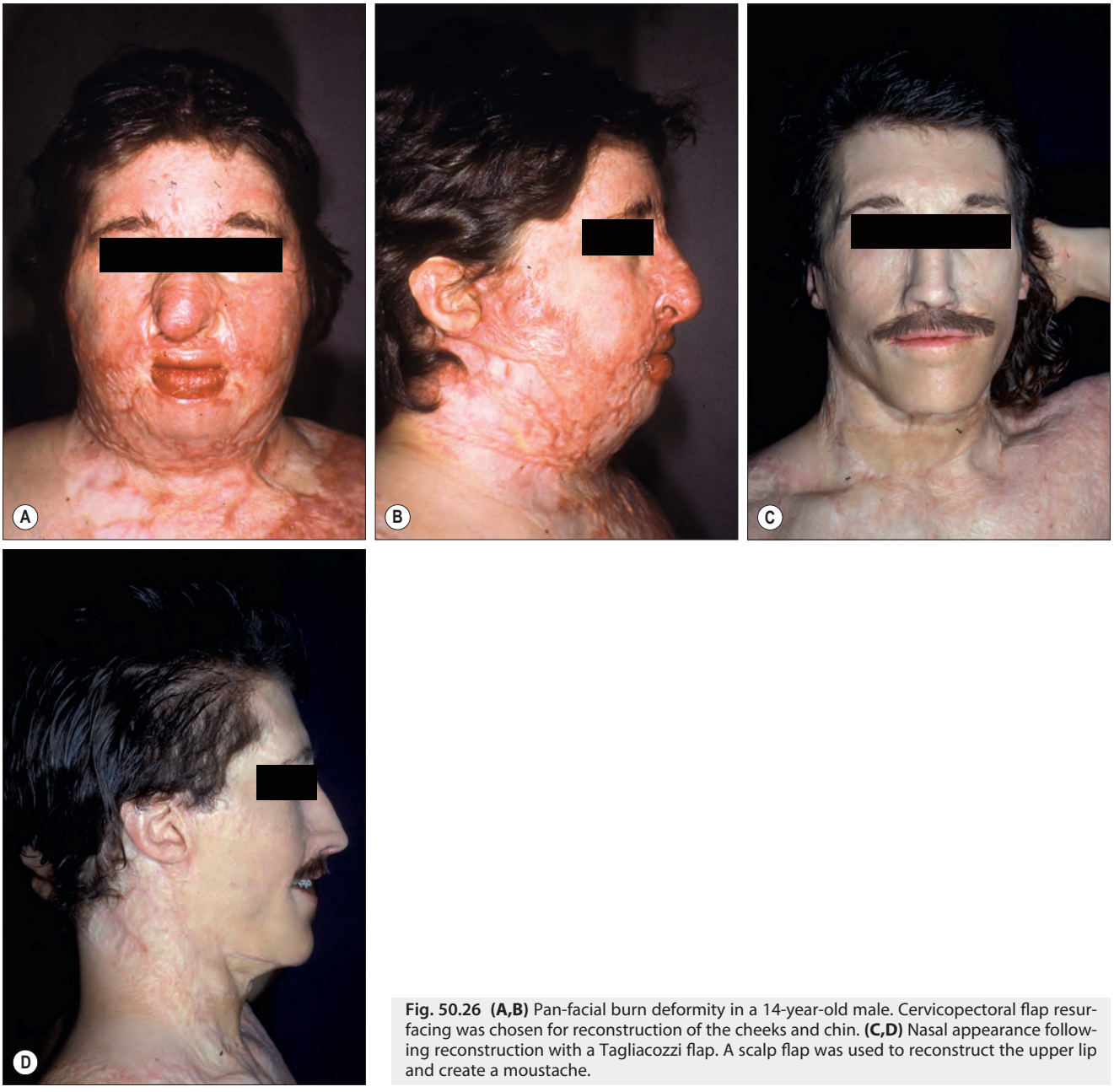

Fig. 50.26 (A,B) Pan-facial burn deformity in a 14-year-old male. Cervicopectoral flap resurfacing was chosen for reconstruction of the cheeks and chin. **(C,D)** Nasal appearance following reconstruction with a Tagliacozzi flap. A scalp flap was used to reconstruct the upper lip and create a moustache.

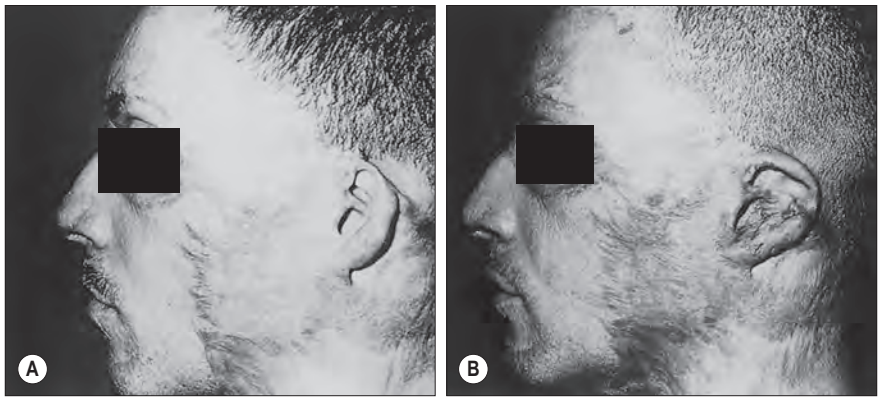

Fig. 50.27 (A) Typical post-burn pattern of peripheral helical loss. **(B)** Reconstructed ear following expansion with conchal transposition flap and skin grafts.

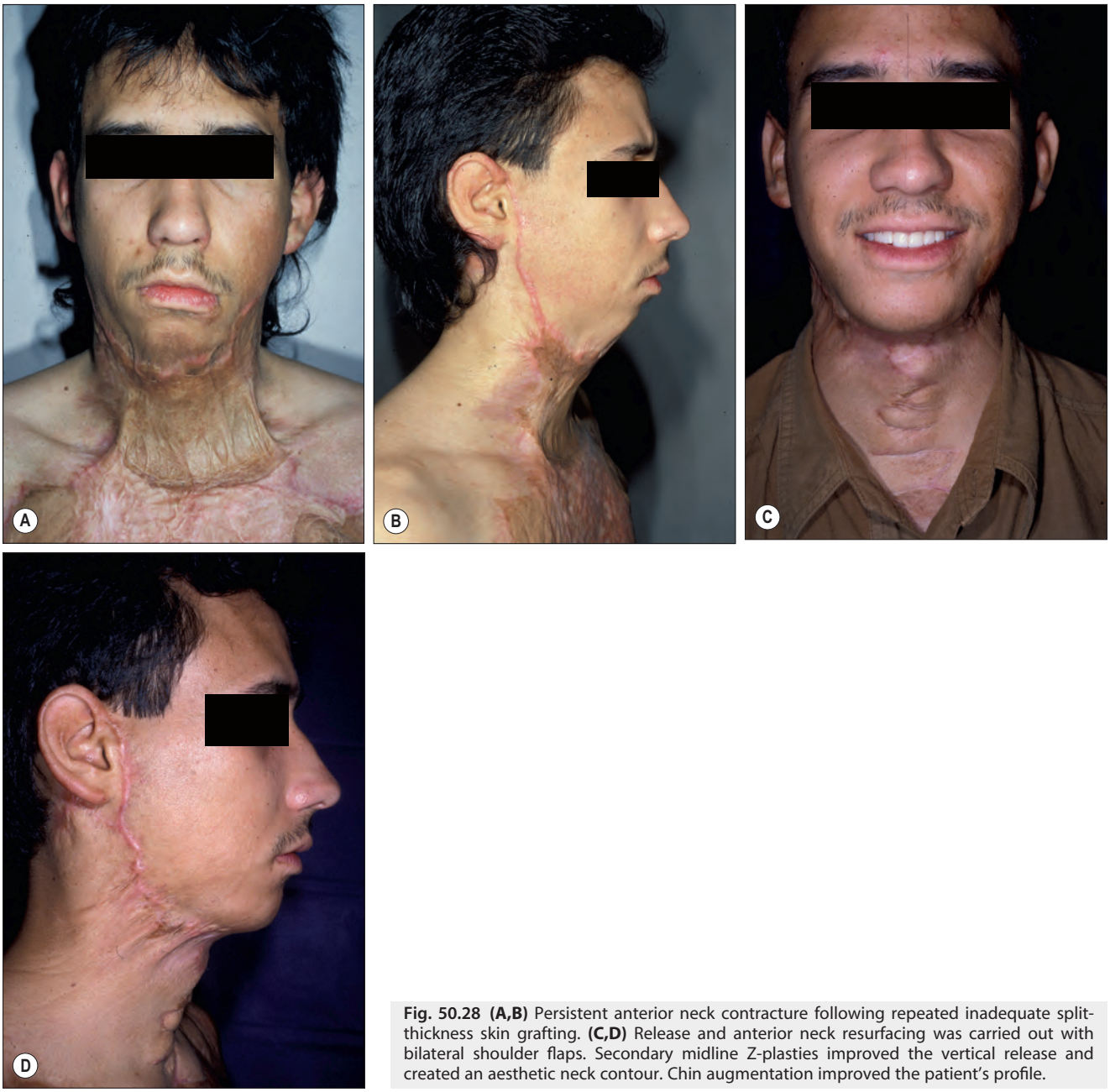

Fig. 50.28 (A,B) Persistent anterior neck contracture following repeated inadequate split-thickness skin grafting. **(C,D)** Release and anterior neck resurfacing was carried out with bilateral shoulder flaps. Secondary midline Z-plasties improved the vertical release and created an aesthetic neck contour. Chin augmentation improved the patient's profile.

affect the maturation of scars on the face. Preventive methods to minimize cervical contractures during the acute period as burn scars and grafted areas contract include splinting, physical therapy, neck collars, and the use of a three-quarter mattress to encourage neck extension.

RELEASE AND GRAFTING

The majority of anterior neck contractures can be satisfactorily treated with release and skin grafting. Extensive contractures usually require split-thickness skin grafting. Focal contractures can be appropriate for full-thickness grafting, which will result in a superior outcome from both a functional and an aesthetic standpoint. When neck contractures are extensive, the lower face and chest are usually a combination of healed skin graft and scar. Split-thickness skin grafts represent "like tissue" and will blend into the area (Fig. 50.17).

LOCAL FLAP RECONSTRUCTION

When split-thickness skin grafting is unsuccessful because of recurrent contracture or does not provide a satisfactory aesthetic result, local flap reconstruction of the anterior neck is an excellent technique if there is available tissue. Flaps can either be unilateral or bilateral. When bilateral flaps are available, midline Z-plasties secondarily can help to improve neck contour (Fig. 50.28). Donor site morbidity is usually minimal because the upper chest in these patients has frequently been disfigured to some degree by the burn injury.

DISTANT FLAP RECONSTRUCTION

Free flaps have been advocated for the treatment of anterior neck contractures.[60] Excellent outcomes can be obtained but require microsurgical technique and create the possibility of complete flap loss. Another potential negative of free flaps to the anterior neck is that they can be thick and bulky, requiring multiple defattings and secondary revisions. The free flap can also appear to be an island in the midst of a broad area of healed graft and burn scar.

Complete references available online at
www.expertconsult.inkling.com

Further Reading

Davis JS. The relaxation of scar contractures by means of the z-, or reversed z-type incision: stressing the use of scar infiltrated tissues. *Ann Surg*. 1931;94:871-884.

Donelan MB. Conchal transposition flap for postburn ear deformities. *Plast Reconstr Surg*. 1989;83:641-654.

Janzekovic ZA. New concepts in the early excision and immediate grafting of burns. *J Trauma*. 1970;10:1103-1108.

Longacre JJ, Berry HK, Basom CR, et al. The effects of Z plasty on hypertrophic scars. *Scand J Plast Reconstr Surg*. 1976;10:113-128.

Parrett BM, Donelan MB. Pulsed dye laser in burn scars: current concepts and future directions. *Burns*. 2010;36:443-449.

Pisarski GP, Mertens D, Warden GD, et al. Tissue expander complications in the pediatric burn patient. *Plast Reconstr Surg*. 1998;102:1008-1012.

References

1. Donelan MB. Facial burn treatment principles. In: McCarthy JG, Galiano RD, Boutros S, eds. *Current Therapy in Plastic Surgery*. Philadelphia: Elsevier; 2006:184-193.
2. McIndoe A. Total facial reconstruction following burns. *Postgrad Med*. 1949;6:187-200.
3. Engrav L, Donelan MB. Face burns: acute care and reconstruction. *Oper Tech Plast Reconstr Surg*. 1997;4:53-85.
4. Cope O, Langohr JL, Moore FD, et al. Expeditious care of full-thickness burn wounds by surgical excision and grafting. *Ann Surg*. 1947;125:1-22.
5. Jackson D, Topley E, Cason JS, et al. Primary excision and grafting of large burns. *Ann Surg*. 1960;152:167-189.
6. Janzekovic ZA. new concept in the early excision and immediate grafting of burns. *J Trauma*. 1970;10:1103-1108.
7. Engrav LH, Heimbach DM, Walkinshaw MD, et al. Excision of burns of the face. *Plast Reconstr Surg*. 1986;77:744-751.
8. Neale HW, Billmire DA, Carey JP. Reconstruction following head and neck burns. *Clin Plast Surg*. 1986;13:119-136.
9. Cole JK, Engrav LH, Heimbach DM, et al. Early excision and grafting of face and neck burns in patients over 20 years. *Plast Reconstr Surg*. 2002;109:1266-1273.
10. Achauer BM. Reconstructing the burned face. *Clin Plast Surg*. 1992;19:623-636.
11. Engrav LH, Heimbach DM, Walkishaw MD, et al. Acute care and reconstruction of facial burns. In: Mathes SJ, Hentz VR, eds. *Plastic Surgery. The Head and Neck*. Vol. 2. Philadelphia: Saunders Elsevier; 2006:45-76.
12. Feldman J. Facial burns. In: McCarthy JG, ed. *Plastic Surgery*. Philadelphia: WB Saunders; 1990:2153-2236.
13. Alster TS. Improvement of erythematous and hypertrophic scars by the 585-nm flashlamp-pumped pulsed dye laser. *Ann Plast Surg*. 1994;32(2):186-190.
14. Allison KP, Kiernan MN, Waters RA, et al. Pulsed dye laser treatment of burn scars. Alleviation or irritation? *Burns*. 2003;29:207-213.
15. Gonzalez-Ulloa M, Castillo A, Stevens E, et al. Preliminary study of the total restoration of the facial skin. *Plast Reconstr Surg (1946)*. 1954;13:151-161.
16. Ivy RH. Who originated the Z-plasty? (Charles Pierre Denonvilliers). *Plast Reconstr Surg*. 1971;47:67-72.
17. Davis JS. The relaxation of scar contractures by means of the z-, or reversed z-type incision: stressing the use of scar infiltrated tissues. *Ann Surg*. 1931;94:871-884.
18. Longacre JJ, Berry HK, Basom CR, et al. The effects of Z plasty on hypertrophic scars. *Scand J Plast Reconstr Surg*. 1976;10:113-128.
19. Wong VW, Akaishi S, Longaker MT, Gurtner GC. Pushing back: wound mechanotransduction in repair and regeneration. *J Invest Dermatol*. 2011;131(11):2186-2196.
20. Derdarian CA, Bastidas N, et al. Mechanical strain alters gene expression in an in vitro model of hypertrophic scarring. *Ann Plast Surg*. 2005;55(1):69-75.
21. Alster TS, Tanzi EL. Hypertrophic scars and keloids: etiology and management. *Am J Clin Dermatol*. 2003;4:235-243.
22. Engrav LH, Gottlieb JR, Millard SP, et al. A comparison of intramarginal and extramarginal excision of hypertrophic burn scars. *Plast Reconstr Surg*. 1988;81:40-45.
23. Ketchum LD, Robinson DW, Masters FW. Follow-up on treatment of hypertrophic scars and keloids with triamcinolone. *Plast Reconstr Surg*. 1971;48:256-259.
24. Tavares Filho JM, Belerique M, Franco D, et al. Tissue expansion in burn sequelae repair. *Burns*. 2007;33:246-251.
25. Donelan MB, Parrett BM, Sheridan RL. Pulsed dye laser therapy and z-plasty for facial burn scars: the alternative to excision. *Ann Plast Surg*. 2008;60:480-486.
26. Alster TS, Williams CM. Treatment of keloid sternotomy scars with 585 nm flashlamp-pumped pulsed-dye laser. *Lancet*. 1995;345:1198-1200.
27. Kuo YR, Wu WS, Jeng SF, et al. Activation of ERK and p38 kinase mediated keloid fibroblast apoptosis after flashlamp pulsed-dye laser treatment. *Lasers Surg Med*. 2005;36:31-37.
28. Reiken SR, Wolfort SF, Berthiaume F, et al. Control of hypertrophic scar growth using selective photothermolysis. *Lasers Surg Med*. 1997;21:7-12.
29. Smith CJ, Smith JC, Finn MC. The possible role of mast cells (allergy) in the production of keloid and hypertrophic scarring. *J Burn Care Rehabil*. 1987;8:126-131.
30. Parrett BM, Donelan MB. Pulsed dye laser in burn scars: current concepts and future directions. *Burns*. 2010;36:443-449.
31. Henderson DL, Cromwell TA, Mes LG. Argon and carbon dioxide laser treatment of hypertrophic and keloid scars. *Lasers Surg Med*. 1984;3:271-277.
32. Donelan M, Silverman RP. Full-thickness skin grafts for elective facial burn reconstruction; review of 237 consecutive cases. *J Burn Care Rehabil*. 2002;2:S68.
33. Friedman R, Ingram AE, Rohrich RJ, et al. Risk factors for complications in pediatric tissue expansion. *Plast Reconstr Surg*. 1996;98:1242-1246.
34. Neale HW, High RM, Billmire DA, et al. Complications of controlled tissue expansion in the pediatric burn patient. *Plast Reconstr Surg*. 1988;82:840-848.
35. Pisarski GP, Mertens D, Warden GD, et al. Tissue expander complications in the pediatric burn patient. *Plast Reconstr Surg*. 1998;102:1008-1012.
36. Barret JP, Dziewulski P, Wolf SE, et al. Outcome of scalp donor sites in 450 consecutive pediatric burn patients. *Plast Reconstr Surg*. 1999;103:1139-1142.
37. Cronin TD. The use of a molded splint to prevent contracture after split skin grafting on the neck. *Plast Reconstr Surg*. 1961;27:7-18.
38. Huang TT, Larson DL, Lewis SR. Burn alopecia. *Plast Reconstr Surg*. 1977;60:763-767.
39. McCauley RL, Oliphant JR, Robson MC. Tissue expansion in the correction of burn alopecia: classification and methods of correction. *Ann Plast Surg*. 1990;25:103-115.
40. Buhrer DP, Huang TT, Yee HW, et al. Treatment of burn alopecia with tissue expanders in children. *Plast Reconstr Surg*. 1988;81:512-515.
41. Ridgway EB, Cowan JB, Donelan MB, et al. Pediatric burn-related scalp alopecia treated with tissue expansion and the incidence of associated facial burn injuries. *J Burn Care Res*. 2010;31:409-413.
42. Brent B. Reconstruction of ear, eyebrow, and sideburn in the burned patient. *Plast Reconstr Surg*. 1975;55:312-317.
43. Pensler JM, Dillon B, Parry SW. Reconstruction of the eyebrow in the pediatric burn patient. *Plast Reconstr Surg*. 1985;76:434-440.
44. Sloan DF, Huang TT, Larson DL, et al. Reconstruction of eyelids and eyebrows in burned patients. *Plast Reconstr Surg*. 1976;58:340-346.
45. Conway H, Stark RB, Kavanaugh JD. Variations of the temporal flap. *Plast Reconstr Surg (1946)*. 1952;9:410-423.
46. Monks GH. The restoration of a lower eyelid by a new method. *J Burn Care Res*. 1998;139:385-387.
47. Liao EC, Driscoll DN, Donelan MB. Restoration of brow position and contour with tissue-expanded antegrade foreheadplasty. *Plast Reconstr Surg*. 2010;125:1263-1267.
48. Converse JM, McCarthy JG, Dobhovsky M, et al. Facial burns. In: Converse JM, ed. *Reconstructive Plastic Surgery*. Philadelphia: WB Saunders; 1977:1628-1631.
49. Schmid E. The use of auricular cartilage and composite grafts in reconstruction of the upper lip, with special reference to reconstruction of the philtrum. In: Broadbent TR, ed. *Transactions of the Third International Congress of Plastic Surgery*. Amsterdam: Excerpta Medica; 1964:306.
50. Gilles H, Millard DR Jr. *The Principles and Art of Plastic Surgery*. Boston: Little, Brown; 1957.
51. Converse JM. Technique of elongation of the oral fissure and restoration of the angle of the mouth. In: Kazanjian JM, Converse JM, eds. *The Surgical Management of Facial Injuries*. Baltimore, MD: Williams and Wilkins; 1959:795.
52. Kazanjian VH, Roopenian A. The treatment of lip deformities resulting from electric burns. *Am J Surg*. 1954;88:884-890.
53. Donelan MB. Reconstruction of electrical burns of the oral commissure with a ventral tongue flap. *Plast Reconstr Surg*. 1995;95:1155-1164.
54. Antia NH, Buch VI. Chondrocutaneous advancement flap for the marginal defect of the ear. *Plast Reconstr Surg*. 1967;39:472-477.
55. Brent B. Reconstruction of the auricle. In: McCarthy JG, ed. *Plastic Surgery*. Philadelphia: WB Saunders; 1990:2094-2152.
56. Davis J. *Aesthetic and Reconstructive Otoplasty*. New York: Springer-Verlag; 1987.
57. Donelan MB. Conchal transposition flap for postburn ear deformities. *Plast Reconstr Surg*. 1989;83:641-654.
58. Brent B, Byrd HS. Secondary ear reconstruction with cartilage grafts covered by axial, random, and free flaps of temporoparietal fascia. *Plast Reconstr Surg*. 1983;72:141-152.
59. Lynch JB, Pousti A, Doyle JE, et al. Our experiences with silastic ear implants. *Plast Reconstr Surg*. 1972;49:283-285.
60. Angrigiani C. Aesthetic microsurgical reconstruction of anterior neck burn deformities. *Plast Reconstr Surg*. 1994;93:507-518.

51 Management of Postburn Alopecia

RAJEEV B. AHUJA and PALLAB CHATTERJEE

Introduction

The importance of burn involvement of the scalp is due to its very visible location on the body. Deformities of the scalp may not always be easy to hide or camouflage, causing great distress to the individual. In large surface area burns, the scalp may be involved in 25–45% of cases.[1,2] Superficial burns of the scalp heal rapidly owing to the abundance of dermal epithelial structures. However in cases of deep dermal or full-thickness burns, the loss of dermal adnexa manifests as alopecia once healing is complete. As with anywhere else in the body, burns of the scalp that take more than 2 weeks to heal spontaneously are at a risk of developing increased scarring with accompanying cicatricial alopecia.[3]

Repeated split skin graft (SSG) harvesting from the scalp may also result in scalp alopecia. Although scalp, because of its thickness and high density of hair follicles, lends itself to reharvesting of SSG, Brou et al. reported a 61% incidence of alopecia if scalp was used to harvest skin grafts and had also sustained burns.[1] This is in contrast to only a 2.2% incidence of alopecia in patients without scalp burns who underwent harvesting of SSG from scalp.[4]

Spectrum of Postburn Alopecia

Burns of the scalp may purely involve the soft tissue or may also involve the underlying calvarium. While deeper partial-thickness burns may cause alopecia, full-thickness burns will inevitably lead to alopecia. A different dimension is added to the clinical problem if the calvarium also sustains burns, as is likely in an electrical injury. Optimal management of such an extensive injury has been a topic of discussion for a long time, with an evolving consensus for optimal management.

CLASSIFICATION OF SCALP BURNS

Harrison offered a classification to guide the treatment based on the depth of the injury:[5]

Type I: Total skin loss with intact pericranium
Type II: Total skin loss with involvement of pericranium
Type III: Total skin loss with involvement of outer table
Type IV: Total skin loss with involvement of both plates of the skull.

Patients with type I injuries typically require SSG for wound coverage in the acute stage, and later they present for alopecia reconstruction. Type II/III injuries require débridement until a vascular surface is reached, followed by immediate application of SSG; this may involve chiseling until reaching the underlying diploë. Alternatively, after soft tissue débridement multiple holes may be drilled in the outer cortex until reaching bleeding diploë. The wound is dressed for a few weeks until it is fully covered by healthy granulations and then split-skin grafted. Alopecia reconstruction is undertaken at 6–9 months after skin grafting. Immediate coverage with local flaps to obviate temporary alopecia is not warranted except in small wounds with normal surrounding scalp. In type IV injuries, because there is loss of calvarium, the exposed dura requires coverage with local flaps (for small defects) or a free flap.[6,7] Historically SSG has been applied directly to dura to cover defects in a strategy that is risky but may be the only option in a resource-constrained setting. The goal is to obtain an early wound closure and restore aesthetics as a secondary procedure. These patients may have more complex reconstructive needs other than simple alopecia reconstruction. It is not unusual in developing countries to see patients requesting coverage of exposed calvarium several months after the injury.

Surgical Correction of Alopecia

A whole gamut of reconstructive options is available to correct postburn alopecia. The surgical options include serial excision,[8] scalp reduction, bipedicle flaps, modified rotation flaps on a template design,[9,10] other local flaps (Juri flaps,[11–13] Elliot flaps,[14] or Orticochea flaps[15,16]), tissue expansion,[17] and hair grafting (micro- or minifollicles).[18] It is intuitive and expedient to surgically excise the alopecia patch (whether from scar, skin graft, or a nonhealing wound) and to close the defect directly or with a local flap. In practice, this approach works for small areas of involvement.[19,20] Scalp tissue characteristics and underlying galea make the skin less stretchable and therefore less amenable to direct closure. Large areas of alopecia need to take into account the size and location of the defect and the state of remaining scalp before planning any procedure.

SERIAL EXCISION

Huang et al., in 1977, proposed a classification of the extent of postburn alopecia to guide reconstruction.[8] They recommended that alopecia defects of less than 15% of entire hair-bearing scalp were suitable for excision and direct closure by two or three serial excisions.[8] Seemingly mathematical, it still is an empirical approach because such calculations are not exact guides to the extent that other stages of serial excision would be possible. For small to

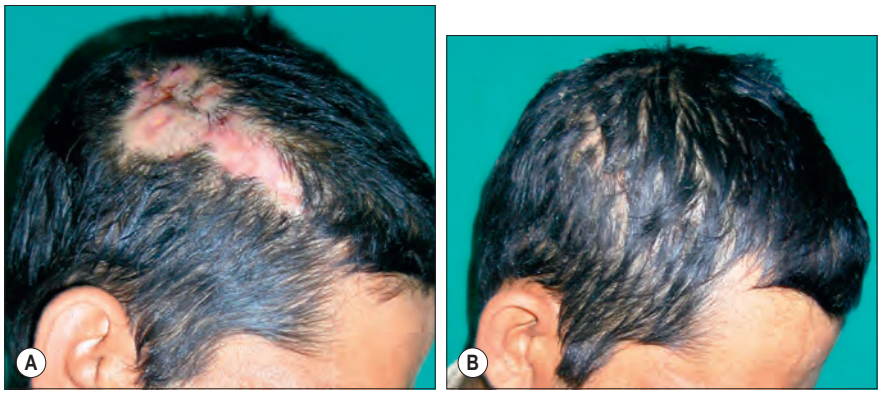

Fig. 51.1 (**A**) An 11 × 3-cm postburn alopecia patch in the right parietal area of a 30-year-old male patient. A 2.5-cm central ellipse of the scar was excised and primarily closed. (**B**) Postoperative result at 4 months. A second stage of excision was not necessary because the surrounding hair covered the residual scarred patch.

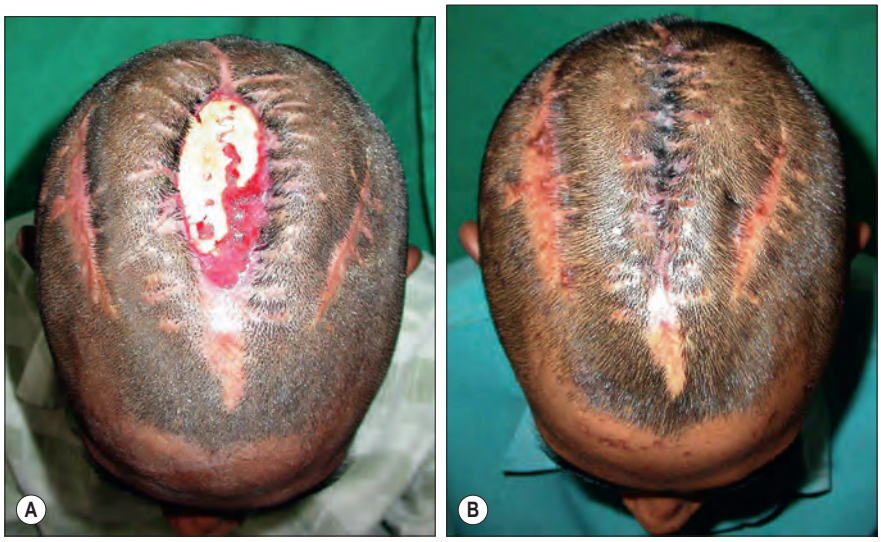

Fig. 51.2 (**A**) Long-standing exposed calvarium on the vertex of a 20-year-old male who suffered electrical burns. The outer table of the skull has sequestered, and attempts were made at drilling holes to generate granulations. There was also a previous unsuccessful attempt at moving bipedicle flaps to cover the wound. (**B**) After removal of the remaining sequestered bone, the anterior triangular alopecic area was excised and the same bipedicle flaps were mobilized to be sutured in the midline. The lateral raw areas were split-skin grafted (SSG), showing completely healed wounds at 1 month after surgery. The bald patch that would have resulted at the vertex with SSG has been eliminated, and the lateral areas covered with SSG are narrow and will not be visible after the hair lengthens.

moderate defects, it is much simpler to design local flaps on the rotation template principle,[9] as described below. The elliptical excision of the alopecia leaves an incision not much shorter in extent than a corresponding design on a rotation flap template. However no more than 2.5 cm scar width should be excised in one stage, or primary closure would become difficult (Fig. 51.1A and B). The second stage should be planned after 6–9 months to allow the scalp to adequately stretch and relax to permit another stage. Typically the scar width excised in the second stage is less than that in the first stage.

BIPEDICLE FLAPS

Quite similar to the principle of serial excision is the use of bipedicle flaps in scalp. Relaxing incisions on either side of the defect allow a slightly larger area to be excised and closed primarily (Fig. 51.2A). The donor areas are split-skin grafted, and these linear scars of alopecia are easily covered by surrounding hair (Fig. 51.2B).

LOCAL FLAPS AND THE ROTATION FLAP TEMPLATE

Ultimately the best tissue match is provided if alopecia reconstruction can be achieved by locally available tissue, either by serial excision or by a flap that leaves no donor defect or an insignificant defect requiring SSG that can be camouflaged by surrounding hair. Of historical significance are classical rotation flaps[9] where the defect was triangulated and the base of the triangle was a segment in the hemispherical incision of the rotation flap. The size of the rotation flap was never specific, and very large rotation flaps had to be designed to achieve the desired closure in the inextensible skin of the scalp. Often, design inadequacies were compensated for by making "back cuts" along the flap

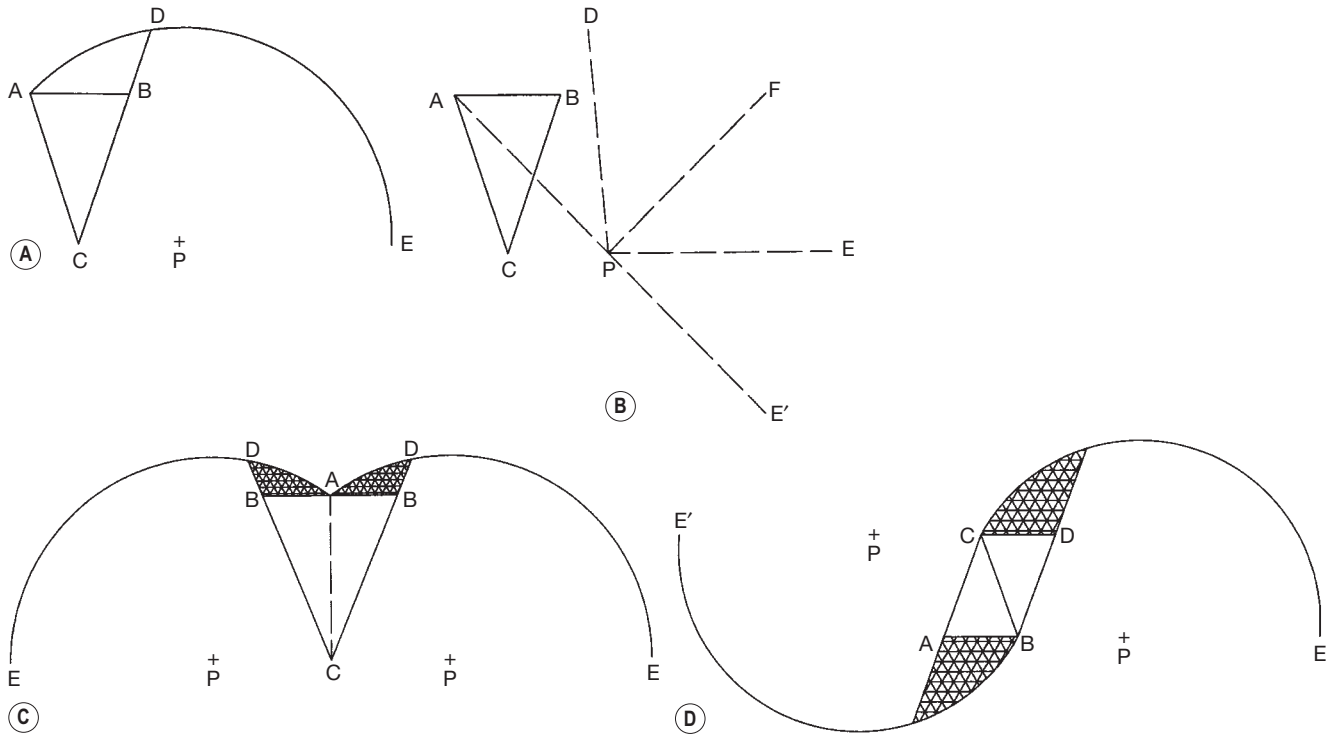

Fig. 51.3 (**A,B**) Line drawings to show the execution of a rotation flap template design for triangulated defects. An isosceles defect is created, with a less than 30-degree apical angle (A), and the pivot point (P) is selected so that CP is slightly longer than AB. With AP as the radius, an arc ADE is drawn. CDE is the rotation flap template. The incision can continue along the arc of rotation beyond E if CP = AB or slightly less due to anatomical constraints. This extension of incision beyond E is a design reserve and not a back-cut because it does not compromise the blood supply of the flap. The triangle ABD is geometrically shown to be excised, but only a small piece needs trimming after flap movement, and this helps in accommodating tension in large defects. (**B**) To design the arc ADE, strategic points can be marked using a thread, and these are joined in free hand. (**C,D**) Large defects may be excised maximally as an equilateral triangle that can be bisected to have a template flap on either side of the defect or as an appropriate rhomboid with flaps designed diagonally. Flap planning takes into account the available tissue, anatomic limitations, and minimal excision of normal tissue to fit a suitable geometry.

base to facilitate movement at the cost of compromising the blood supply. A paradigm change in geometry was proposed by Ahuja in 1988,[9] wherein a modified rotation flap was used clinically in scalp defects, and then subsequently a rotation flap template design was offered to logically explain the movement.[10] It became possible to primarily close moderate to large scalp defects in a single stage without "back cuts," thus obviating the requirement for serial excisions or tissue expansion in such cases. The technique has since been adopted in an algorithmic approach to scalp defects.[21] Rotation flaps planned on the template design can easily close defects up to 6.5 cm in width, something that was never possible using the classical rotation flap. Fig. 51.3(A–D) explains the execution of a rotation flap template design for triangulated defects. Figs. 51.4 to 51.6 illustrate clinical execution of a single template flap, bilateral template flaps, and two template flaps in an S-shaped design to cover large alopecia areas in a single stage.

To improve the extensibility of the scalp skin it is often useful to score the galea on the under surface of the flap perpendicular to the flap movement. Raposio et al. state that each galeatomy corresponds to a 40% reduction in scalp closing tension and a tissue gain of approximately 1.67 mm.[22] However this technique should always be a reserved move to lessen tension and should never be considered as a means to excise larger areas by making compromises in the design. Occasionally, at the limits of the flap design, if there is undue tension in flap closure it is better to place a small SSG at the extreme end of the donor area (Fig. 51.5D). Such small resultant defects generally are covered by surrounding hair but can also be excised after 9–12 months.

Quite often the alopecia patch is a large area of exposed calvarium. A dry, uninfected exposed calvarium need not be chiseled to create a bleeding surface because it will be well vascularized after a viable flap cover (Figs. 51.4 to 51.6). However if the outer table of calvarium is sequestered completely or partially, the complete outer table should be excised before flap coverage (Fig. 51.2). All flaps need to be provided suction drains for 3–4 days, even if the calvarium outer table has not been excised.

Although now of historic interest only for large vertex defects Orticochea introduced a four-flap technique[15] that was subsequently modified to a three-flap "banana peel" technique in 1971.[16] This was before the era of tissue expansion and the rotation template design. Although quite useful in the correction of moderately sized areas of alopecia, these techniques cause extensive blood loss and excessive scarring.

Juri et al.[11–13] and later Elliot[14] described a variety of innovative monopedicled scalp flaps to cover segmental areas of alopecia, especially to restore the frontal hairline and for the occipital region. However only small-sized alopecia segments that were located in favorable locations

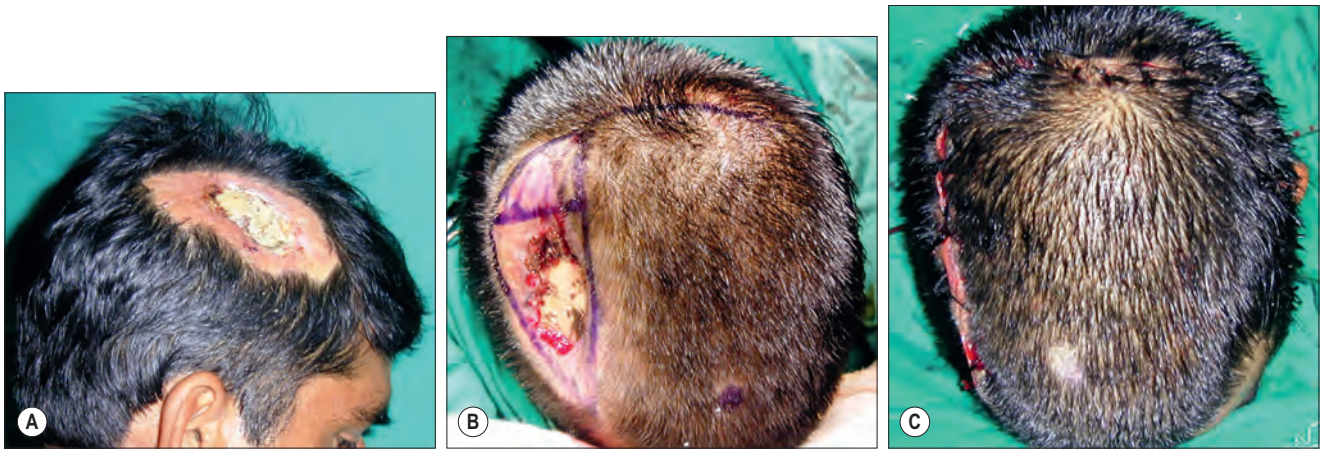

Fig. 51.4 (**A**) A 35-year-old patient with a 6 × 9.5-cm defect in the scalp following electrical injury. There is an alopecia patch with exposed calvarium. (**B**) Showing triangulation of the defect and markings for a rotation flap template. Note the area ABD has been marked in the defect that will be excised and not as a part of the triangulation. (**C**) Intraoperative picture showing primary closure of the large defect and complete correction of alopecia.

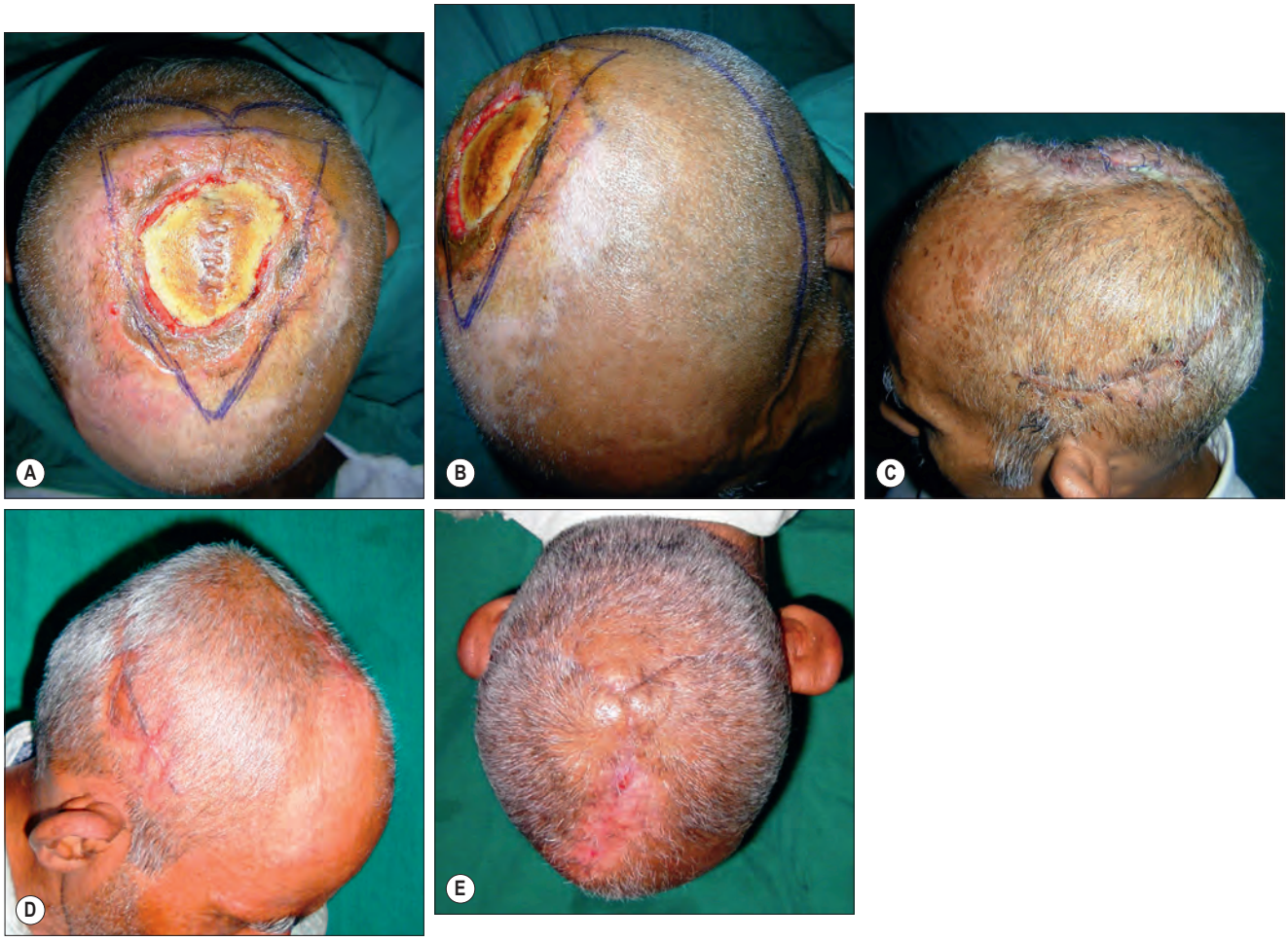

Fig. 51.5 (**A**) A 65-year-old patient with a long-standing defect on the scalp measuring 7 × 6 cm. Bilateral rotation flaps have been marked after proposed triangulation of the defect. (**B**) Left lateral view to show the extent of flap marking. (**C**) Left lateral view at the 10th postoperative day. The flaps were rotated over the exposed bone without chiseling of the outer cortex (bone was dry and noninfected). (**D**) Right lateral view at 6 weeks showing well-healed incisions. A small skin graft was placed to ease some tension because the defect was extremely large and closure was leading to some tension. (**E**) Showing primary healing of the flaps at midline with complete resurfacing and correction of alopecia.

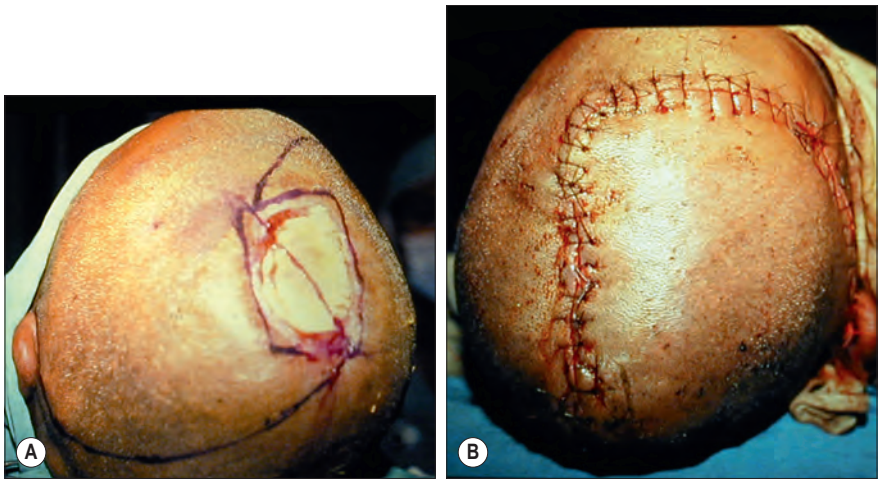

Fig. 51.6 (**A**) A 5.5 × 6.5-cm circular defect on the vertex of the scalp following electrical injury. Large rotation template flaps have been designed diagonally with proposed freshening of the defect as a rhomboid. (**B**) Immediate postoperative result showing complete closure of the scalp defect (as well as correction of alopecia).

could be corrected. Feldman increased coverage of patients with significant burn alopecia by combining horizontal scalp reduction with the Juri flap.[23]

TISSUE EXPANSION

Although the concept of soft tissue expansion using inflatable subcutaneous balloons was introduced in 1956 by Neuman,[24] Radovan is credited with its rediscovery and making it popular for clinical use in the 1980s.[25]

Briefly tissue expansion is the result of a constant mechanical stress load that leads to tissue regeneration.[26] The epidermis becomes thicker, with most of the mitotic activity occurring in the stratum spongiosum. The dermis thins out, with the greatest amount of thinning occurring in the papillary dermis.[27,28] The activation of a number of growth factors for epithelial and connective tissue growth may be responsible for this true tissue regeneration and not merely stretching of overlying tissue.[26]

McCauley et al. described the effective use of tissue expansion in the treatment of post-burn alopecia of the scalp in 1990.[17] This was at a time when the rotation flap template design was just introduced, so their classification of post-burn alopecia based on both pattern and extent of scalp involvement to guide treatment strategy included the option of tissue expansion only.[17] With our current approach, we propose a simplified treatment strategy to manage scalp alopecia by modifying the recommendation of McCauley et al. (Table 51.1). Despite the fact that tissue expansion has complication rates ranging from 15% to 20%[29–31] in scalp defects, it remains the best option and is the only option for defects of between 20% and 75% of hair-bearing scalp area. For defects larger than 75%, the only possibility is camouflage with a hairpiece.

Use of tissue expanders massively improved the outcomes for reconstruction of large alopecia patches. Losses between 50% and 75% will require placement of two expanders simultaneously or sequentially. Sequential expansion aims to achieve partial reconstruction from one expander; after a wait of several months, the second expander can be placed strategically to complete the reconstruction.

Table 51.1 Treatment Strategy Recommended for Alopecia Management

Alopecia Segment	Treatment Strategy
	SINGLE
<20% of the hair-bearing scalp	Rotation flap template
20–50% of the hair-bearing scalp	Single tissue expander
50–75% of the hair-bearing scalp	Two expanders placed simultaneously or sequential expansions
>75% of the hair-bearing scalp	Use hair piece (wig)
	TWO OR MORE
If amendable to tissue expansion	One/two expanders placed simultaneously or sequentially
Not amendable to tissue expansion	Use hair piece (wig)

Modified from McCauley RL, Oliphant JR, Robson MC. Tissue expansion in the correction of burn alopecia: classification and methods of correction. *Ann Plast Surg.* 1990;25:103–115.)

Tissue expansion generates a source of local skin that may be used as an advancement or a rotation template flap, and it permits direct closure of the donor site.[32] After proper planning of the desired flap movement following expansion, a suitably sized and shaped expander is chosen by measuring the dimensions of the recipient area. Although the literature is replete with several mathematical models in deciding the most appropriate size and shape of the expander,[33] the selection can be easily made clinically by recipient site requirements and the donor flap available for expansion. As a rule of thumb, the available donor skin before expansion should never be less than the recipient

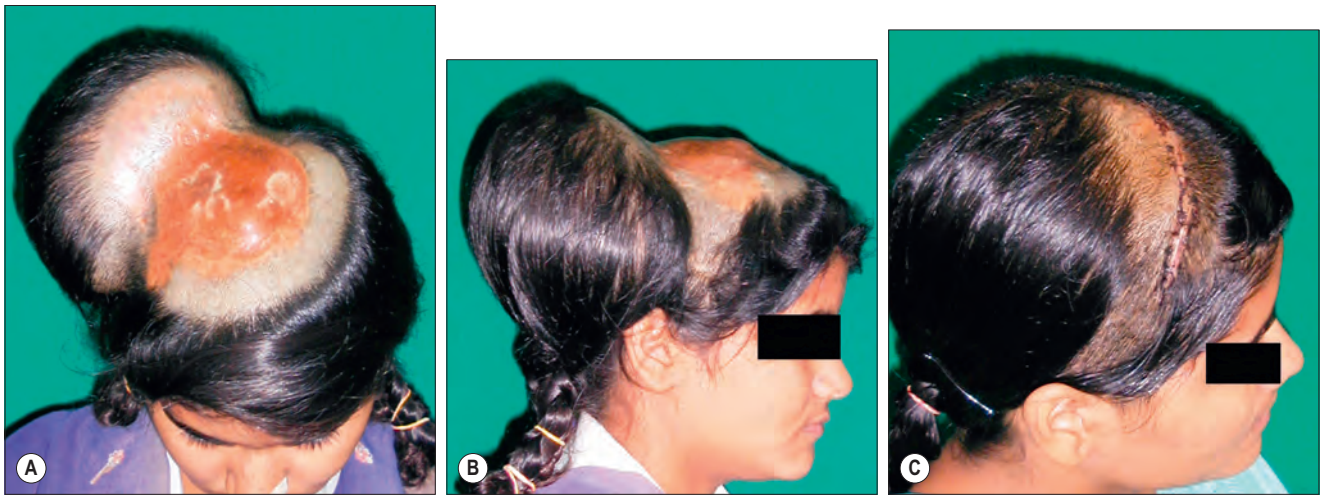

Fig. 51.7 A 21-year-old girl with a 10 × 10 cm alopecia patch on the vertex following thermal burns. A 500-mL crescent tissue expander was inserted through an incision just parallel to the edge of the defect. (**A**) Showing full expansion achieved in 3 months. (**B**) Lateral view to show the posterior extent of expansion. (**C**) The alopecia patch was excised and the expanded flap advanced into the defect. Postoperative view at 10 days.

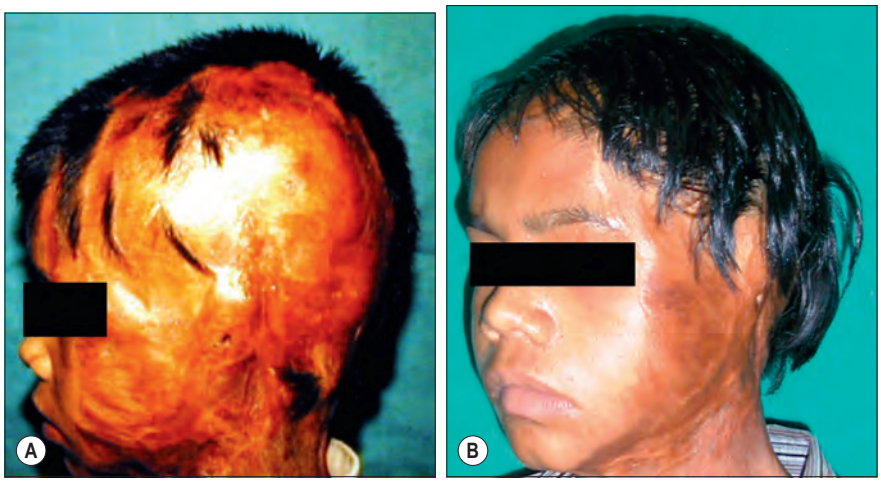

Fig. 51.8 (**A**) A laterally situated, extremely large alopecia patch on a 12-year-old boy following thermal burns. A single 800-mL, crescent-shaped expander was inserted and inflated over a 4-month period. The incision line gave way slightly after 3.5 months, but the expansion continued with an exposed implant for the next 10 days. (**B**) Five-year postoperative picture showing complete restoration of hair on the scalp by tissue expansion.

area for one-stage expansion. The minimum expander base should be a little more than the recipient area, although the largest expander possible should be selected. Expander volume is less of a clinical guide because overexpansion is always possible. Figs. 51.7 and 51.8 are illustrative clinical examples of tissue expansion for alopecia correction.

The inextensible skin of the scalp makes it a bit tougher to place the implant, and it is essential that an adequate pocket is created below the galea. It is hazardous to place tissue expanders above the galea in the subcutaneous tissue. A short incision parallel to the defect and about a centimeter into healthy skin is used for implant placement. The port of the expander is located at a short distance through another narrow pocket. Magnasite expanders are convenient but more expensive. They have an in-built port that can be detected under the skin with a magnet. The expansion is initiated 10–14 days after the insertion. Full expansion is achieved over 3–4 months, by weekly injections, as an outpatient procedure. The end point of injection is slight patient discomfort or blanching of the overlying skin, after which a few milliliters of fluid are withdrawn. The width of the expanded skin over the dome should at least equal two times the recipient area plus 30% (to allow for skin retraction). Hallock described the utility and safety of expander overexpansion very early in the evolving concept,[34] and nowadays overexpansion beyond the manufacturer's volume recommendations are routine. After complete expansion, the expander is removed through an incision that traces the proposed flap. Optimal mobilization of the flaps is accomplished by releasing the periphery of the capsule under the expanded tissue. Capsular scoring incisions should include galea, and they are made perpendicular to the direction of flap movement.[32]

Tissue expansion is painful and socially incapacitating for the patient during the expansion phase. In addition, it has a substantial complication rate from infection, exposure, or extrusion, ranging from 15% to 20%, which may require premature removal of the expander and abandonment of

the procedure.[30,31] Occasionally it may be possible to continue expansion with an exposed implant but only for a few days because each injection to inflate the implant also causes the skin gap to widen.

HAIR FOLLICLE GRAFTING

More recently Barrera has shown successful use of micro- and minigrafts in the correction of large alopecia segments in 32 burn patients.[18] Because of the small size of micrografts (1–2 hair follicles) and minigrafts (3–4 hair follicles), it is hypothesized that the metabolic demand is very low, thus allowing them to survive in scar tissue. This affords an important technique to provide coverage to irregular patches or to provide refinements to misaligned hairlines following various flap coverage techniques.

Conflict of Interest

None of the authors has any conflict of interest to report.

Complete references available online at
www.expertconsult.inkling.com

References

1. Brou JA, Vu T, McCauley RL, et al. The scalp as a donor site: revisited. *J Trauma*. 1990;30(5):579-581.
2. Burns BF, McCauley RL, Murphy FL, et al. Reconstructive management of patients with 80% TBSA burns. *Burns*. 1993;19(5):429-433.
3. Deitch EA, Wheelahan TM, Rose MP, et al. Hypertrophic burn scars: analysis of variables. *J Trauma*. 1983;23(10):895-898.
4. Barret JP, Dziewulski P, Wolf SE, et al. Outcome of scalp donor sites in 450 consecutive pediatric burn patients. *Plast Reconstr Surg*. 1999;103:1139-1142.
5. Harrison SH. Exposure of the skull from burns. *Br J Plast Surg*. 1952;4:279-292.
6. Spies M, McCauley RL, Mudge BP, et al. Management of acute calvarial burns in children. *J Trauma*. 2003;54(4):765-769.
7. Worthen EF. Regenerations of the skull following a deep electrical burn. *Plast Reconstr Surg*. 1971;48:1-4.
8. Huang TT, Larson DL, Lewis SR. Burn alopecia. *Plast Reconstr Surg*. 1977;60:763-767.
9. Ahuja RB. Geometric considerations in the design of rotation flaps in the scalp and forehead region. *Plast Reconstr Surg*. 1988;81(6):900-906.
10. Ahuja RB. Mechanics of movement for rotation flaps and a local flap template. *Plast Reconstr Surg*. 1989;83(4):733-737.
11. Juri J. Use of parieto-occipital flaps in the surgical treatment of baldness. *Plast Reconstr Surg*. 1975;55:456.
12. Juri J, Juri C, Arufe HN. Use of rotation scalp flaps for the treatment of occipital baldness. *Br J Plast Surg*. 1978;61:23.
13. Juri J, Juri C. Aesthetic aspects of reconstructive scalp surgery. *Clin Plast Surg*. 1981;8:243-254.
14. Elliott RA Jr. Lateral scalp flaps for instant results in male pattern baldness. *Plast Reconstr Surg*. 1977;60(5):699-703.
15. Orticochea M. Four flap scalp reconstruction technique. *Br J Plast Surg*. 1967;20:159-171.
16. Orticochea M. New three flap scalp reconstruction technique. *Br J Plast Surg*. 1971;24:184-188.
17. McCauley RL, Oliphant JR, Robson MC. Tissue expansion in the correction of burn alopecia: classification and methods of correction. *Ann Plast Surg*. 1990;25:103-115.
18. Barrera A. The use of micrografts and minigrafts for the treatment of burn alopecia. *Plast Reconstr Surg*. 1999;103:581-589.
19. Paletta C. Surgical management of the burned scalp. *Clin Plast Surg*. 1982;9:167.
20. Vallis CP. Surgical management of cicatricial alopecia of the scalp. *Clin Plast Surg*. 1982;9:179.
21. Leedy JE, Janis JE, Rohrich RJ. Reconstruction of acquired scalp defects: an algorithmic approach. *Plast Reconstr Surg*. 2005;116(4):54e-e72.
22. Raposio E, Santi P, Nordström RE. Effects of galeotomies on scalp flaps. *Ann Plast Surg*. 1998;41(1):17-21.
23. Feldman G. Post-thermal burn alopecia and its treatment using extensive horizontal reduction in combination with a Juri flap. *Plast Reconstr Surg*. 1994;93:1268-1273.
24. Neumann CG. The expansion of an area of skin by progressive distention of a subcutaneous balloon. *Plast Reconstr Surg*. 1957;19:124.
25. Radovan C. Tissue expansion in soft tissue reconstruction. *Plast Reconstr Surg*. 1984;74:491.
26. Takei T, Mills I, Arai K, et al. Molecular basis for tissue expansion: clinical implications for surgeons. *Plast Reconstr Surg*. 1998;102:247-258.
27. Pasyk KA, Argenta LC, Hasseh C. Quantitative analysis of the thickness of human skin and subcutaneous tissue following controlled expansion with a silicone implant. *Plast Reconstr Surg*. 1988;81:516.
28. Pasyk KA, Argenta LC, Austed ED. Histopathology of human expanded tissue. *Clin Plast Surg*. 1987;14:435-445.
29. Garavito E, McCauley RL, Verbitzky J. Reconstruction of the burned scalp. In: McCauley RL, ed. *Functional and Aesthetic Reconstruction of Burned Patients*. Boca Raton, FL: Taylor and Francis; 2005:217-226.
30. Neale HW, High RM, Billmire DA, et al. Complications of controlled tissue expansion in the pediatric burn patient. *Plast Reconstr Surg*. 1988;82:840-845.
31. LoGiudice J, Gosain AK. Pediatric tissue expansion: indications and complications. *J Craniofac Surg*. 2003;14(6):866-872.
32. Zide BM, Karp NS. Maximizing gain from rectangular tissue expanders. *Plast Reconstr Surg*. 1992;90(3):500-504.
33. Agrawal K, Agrawal S. Tissue regeneration during tissue expansion and choosing an expander. *Indian J Plast Surg*. 2012;45(1):7-15.
34. Hallock GG. Safety of clinical overinflation of tissue expanders. *Plast Reconstr Surg*. 1995;96(1):153-157.

52 Trunk Deformity Reconstruction

PETER DZIEWULSKI and JORGE LEON VILLAPALOS

Introduction

Burn injuries to the trunk may have functional and cosmetic consequences.

The torso, abdomen, and back connect anatomically with the shoulder girdle and the axilla laterally, with the neck superiorly, and with the groin tissue and the lower limbs inferiorly. This means that burn injuries to the trunk may cause damage primarily to three areas:

a. Damage to soft tissue layers including skin, subcutaneous tissue, fascia, muscle, and internal organs
b. Damage to the trunk boundaries, causing potential contracture and functional deficit to the neck, axillae, and groin areas
c. Damage to specialized body parts within the trunk, specifically the breast.

Even though the initial acute management of any extensive burn injury is relatively universal and subjected to well-recognized protocols of trauma resuscitation, the extensive total body surface area (TBSA) that can potentially be involved when the whole of the trunk is injured—up to 36% TBSA—may have devastating consequences: skin, muscle and visceral damage, breast and nipple-areolar destruction, and potential development of life-changing burn scar contractures in the vicinity of the neck, axillae, and groin areas.

It is then easy to understand the potential complexity of the reconstructive challenges that trunk tissue damage may require. Superficial damage may leave minimal functional deficit and barely noticeable cosmetic embarrassment that may not need difficult or lengthy reconstruction, but deeper damage may require the use of multiple reconstructive procedures of ascending order of complexity in several subzones of the trunk: excision of scars, use of split-skin grafts (SSG) with or without the support of dermal matrices, full-thickness grafts, tissue rearrangement procedures based on the z-plasty principle, tissue expansion surgery, and local, regional, distant, or free flaps.

Complex reconstruction will require maximum complicity and collaboration of the burn patient with the multidisciplinary team, specifically with the scar management and physical rehabilitation teams to ensure restoration of anatomy and return of the patient to his normal life and society environment.

The impact of appropriate acute management in subsequent reconstruction cannot be understated. The principles of prompt trauma management, judicious resuscitation, early débridement with a dermal preservation approach and soft tissue cover, and a strong rehabilitation approach impact greatly on the subsequent approach to reconstruction.

Any deep damage to the tissues of the trunk at those levels may cause simultaneously deep soft tissue loss, damage that affects body parts such as the breast, or a burn scar contracture either primarily or secondarily by involvement of those important joint mobile areas.

Recently published International Society for Burn Injuries (ISBI) practice guidelines for burn care[1] supported by best evidence and research established recommendations for optimum acute management of the burn wound.

Those most relevant to successful reconstruction of the trunk are:

- Thermally injured patients should be evaluated using a systematic approach that first seeks to identify the greatest threat to life.
- Evaluation of burns should estimate TBSA utilizing a standardized method and delineate characteristics that require immediate attention from a designated burn center.
- Appropriate resuscitation should be initiated promptly and tailored based on patient parameters to avoid over- and underresuscitation.
- Adult patients with burns greater than 20% TBSA and pediatric patients with burns greater than 10% TBSA should be formally resuscitated with salt-containing fluids; requirements should be based on body weight and percentage burn.
- Abdominal escharotomy should be performed when circumferential or near circumferential eschar is associated with evidence of intraabdominal hypertension (IAH) or signs of abdominal compartment syndrome (ACS).
- Early surgery for small to moderate-sized deep burns (less than approximately 20% TBSA) speeds recovery, might improve outcome, and is cost-effective.
- Tangential excision is the standard method of burn wound excision. Fascial excision may be indicated in very deep burns and high-voltage electrical conduction injuries.
- Burn wound excision and grafting can be undertaken without undue blood loss by using some or all the following: subcutaneous infiltration of burn wound and donor site or topical application of epinephrine solutions, or both; tourniquets for limb surgery; fascial-type excision using electrocautery; other topical hemostatic agents such as thrombin and fibrinogen; prevention of hypothermia; compression dressings; limb elevation; and staged burn excision.
- After excision or débridement of the deep burn wound, it is essential that the wound is covered with autograft skin or an appropriate skin substitute.
- Deep dermal burns (wounds that heal in >3 weeks) require aggressive and monitored scar prevention

therapies augmented with appropriate pain relief and combined with early positioning regimens and physiotherapy for joint mobilization to prevent hypertrophic scarring and joint contractures.
- All extensive hypertrophic burn scars should receive pressure therapy with silicone therapy as the first line of treatment. Restraint should be applied in opting for the surgical modality before scar maturation unless the scar is functionally limiting because of a developing contracture.

Therefore, four clear burn care phases are ultimately considered:

- Initial evaluation and resuscitation
- Wound excision and initial skin cover
- Definitive skin closure and rehabilitation
- Reconstruction and reintegration to society.

Appropriate implementation of these recommendations in a staged fashion ensures the survivability of the burned patient, but also of the quality of the reconstruction.[2]

Reconstruction of the Trunk Soft Tissue Layers

Even though the late effects of burn injury in the tissue layers of the abdomen, torso, and back may be less problematic than in other anatomical areas, the consequences of abnormal scarring and tissue derangement may still cause functional problems such as pain, itching, limitations in activities of daily living, and cosmetic embarrassment.

The torso protects the thoracic cavity and upper abdomen and assists in the process of respiration. The abdominal wall, with its multilayered structure, protects the abdominal viscera and assists in position, breathing, and visceral function.[3] The clinical consequences of the burn injury to this part of the trunk in an acute setting may be relatively mild or utterly devastating if full-thickness soft tissue loss occurs.

ACUTE RECONSTRUCTIVE MANAGEMENT OF THE TRUNK SOFT TISSUE LAYERS

In the acute setting, superficial skin loss may be treated in a relatively conservative fashion with standard dressings or with the application of dermo-protective matrices such as Biobrane or Suprathel. A recent Cochrane review[4] aiming to assess the effects of burn wound dressings on partial-thickness burns suggested that dressing selection should be based on their effects on healing but that other parameters such as ease of application and removal, dressing change requirements, cost, and patient comfort should also be considered. Their conclusion was that, following analysis of a total of 30 randomized controlled trials (RCTs), traditional dressings containing silver sulfadiazine (SSD) were consistently associated with poorer healing outcomes than were biosynthetic (skin substitute) dressings, silver-containing dressings, and silicon-coated dressings.

Dermo-protective skin substitutes are characteristically used to aid reepithelialization in the acute management of partial-thickness burns until full healing occurs.[5] Biobrane is a bi-layered semi-permeable biosynthetic wound dressing with an outer silicone layer, a nylon-net in the middle layer, and an inner porcine collagen type I layer. Suprathel is a synthetic wound dressing consisting of a copolymer-foil of D,L-laktidtrimethylencarbonate and e-caprolakton.

A study comparing both dressings showed satisfying comparable clinical results in the use of both types of prosthetic material.[6]

In the acute setting, extensive burns and injudicious fluid resuscitation may lead to ACS, defined by the presence of organ dysfunction because of increased abdominal pressure or IAH.

Patients with severe burns are at risk for developing ACS due to the large volume of resuscitation fluid that is infused, abdominal wall compliance, and capillary leakage due to increased permeability.[7] This subsequently reduces blood flow to the abdominal viscera and may lead to bowel ischemia, multiorgan failure, and death if not properly addressed.[8]

When decompressive laparotomy is necessary, the complications due to an open abdomen add to those due to the extent of the burn.[9]

Decompressive laparotomy may help in the survival of burn patients, but the mortality can still be up to 50% and introduce a serious physiological and reconstructive challenge.[10]

Recently updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome state that decompressive laparotomy is the standard surgical method to treat severe IAH/ACS despite considerable potential mortality even after decompression.[11] Taking into consideration that the longer the abdomen remains open, the greater the potential complications, this forum of experts established several recommendations significant for the reconstructive strategies of the open abdomen following decompressive laparotomy for IAH:

- Prevent visceral adhesions, loss of soft tissue coverage, lateralization of the abdominal musculature and its fascia, malnutrition, and enteric fistulae.
- Aim to achieve same-hospital-stay closure of the open abdomen.
- Consider the use of negative pressure wound therapy (NPWT) for temporary abdominal closure after decompressive laparotomy.
- Consider component separation to facilitate early fascial closure of the open abdomen.
- Bioprosthetic meshes should not be routinely used in the early closure of the open abdomen compared to alternative strategies.

Several temporizing options using external devices have been suggested to aid the closure of the abdomen following decompressive laparotomy.[12,13]

The use of techniques that apply to the closure of large hernia defects can be used to close large decompressive laparotomy defects as well. The technique of component separation is not contraindicated in the burn patient, even in large burns with a deep pattern of injury.[14]

In this series, fascial access was obtained by raising burned skin flaps at the level of the costal margin from the anterior superior iliac spine inferiorly to the ribs superiorly. These skin flaps were then excised to facilitate grafting of

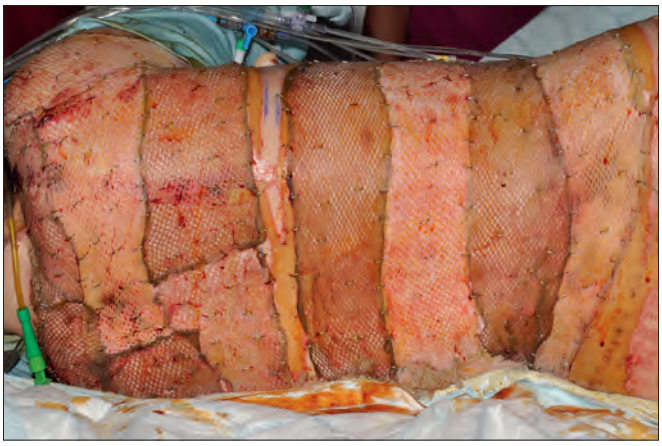

Fig. 52.1 Allograft cover of the back of an 80% total body surface area (TBSA) burn.

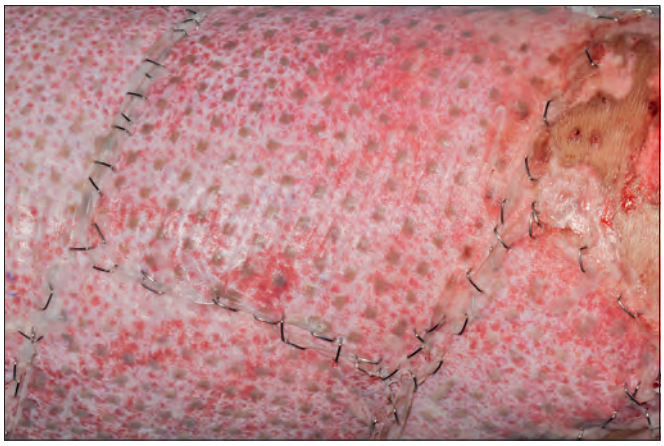

Fig. 52.2 Acute Meek autografting covering back skin following 80% total body surface area (TBSA) burn.

the abdominal wall. The fascial release that facilitated abdominal closure was made, in standard fashion, lateral to the rectus sheath through the aponeurosis of the external oblique muscle.

The acute reconstruction of trunk soft tissue loss related to the direct effects of the burn injury follows the steps applied to other parts of the body. Following stabilization, resuscitation, and débridement, acute soft tissue cover methods are decided based on the depth and extent of the burn, the availability of suitable donor sites, and the microbiology and nutritional status of the patient.

Extensive burns may destroy the skin layers and their blood supply to the extreme of making impossible self-healing and regeneration following a conservative approach. There are occasions in which the paucity of autologous skin or concerns regarding the infection control status of the recipient site recommends the use of temporizing techniques such as xenografts or allografts (Fig. 52.1) until definitive skin cover is achieved. Characteristically split-thickness autografting has been the standard method to address soft tissue loss during this period. A recent expert panel white paper on the surgical management of the burn wound and use of skin substitutes[15] clearly establishes the differences between skin substitute—a commercial biomaterial, engineered tissue, or combination of materials and cells or tissues that can be substituted for skin autograft or allograft in a clinical procedure—from a skin replacement, which is a tissue or graft that permanently replaces lost skin with healthy skin.

Skin grafts are usually meshed to a desired level of expansion; split-thickness grafts are frequently used if the wound bed exhibits appropriate vascularity and the donor skin is available in appropriate quantities. As every burns surgeon is aware, expansion of the SSG is associated with small areas of the wound healing by secondary intention and a poorer scar outcome.

In cases of extreme paucity of donor sites, the use of micrografting (Meek) techniques with or without dermal regeneration templates may represent a suitable form of reconstruction in the acute period[16,17] (Figs. 52.2 and 52.3).

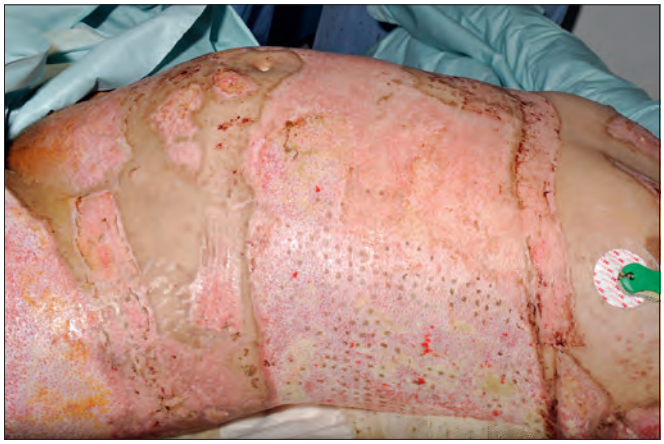

Fig. 52.3 Healing of trunk burn wounds following Meek autografting.

Tissue engineering options have expanded the possibilities of reconstruction for the burned trunk. The ideal tissue engineering device needs to be rapidly available, autologous, site-matched, possess reliable wound adherence and express minimal donor site morbidity, be clinically manageable, improve the quality of scar, and be affordable.[18]

Some of the techniques currently available involve the use of dermal scaffolds such as Integra (Integra Life Sciences Corporation, Plainsboro, NJ), Matriderm (MedSkin Solutions, Dr. Suwelack, Germany), or Pelnac (Gunze Ltd., Japan) and the use of confluent and nonconfluent keratinocyte culture techniques such as Recell (Avita Medical, UK).

A deeper pattern of injury may require the use of more complex steps of the reconstructive ladder. The chest and abdomen, due to their anatomic proximity, are injured together frequently in flame, scald, or electrical injuries. In these situations, in which deep visceral structures may become exposed, the use of large flaps such as the omentum, latissimus dorsi, rectus abdominis, or deltopectoral may be indicated.[19–22]

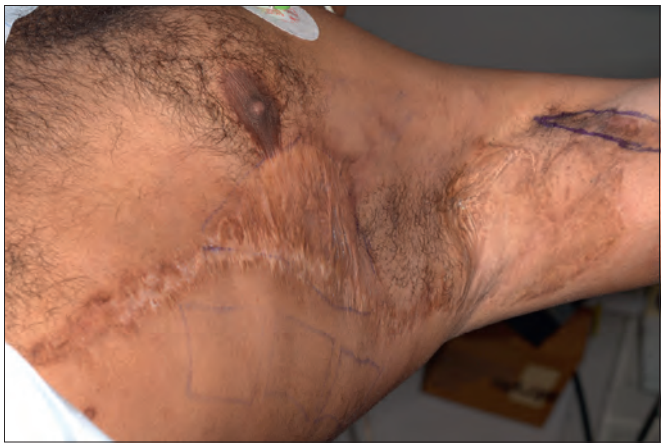

Fig. 52.4 Hyperpigmented scar on the left side of the chest following electrical injury.

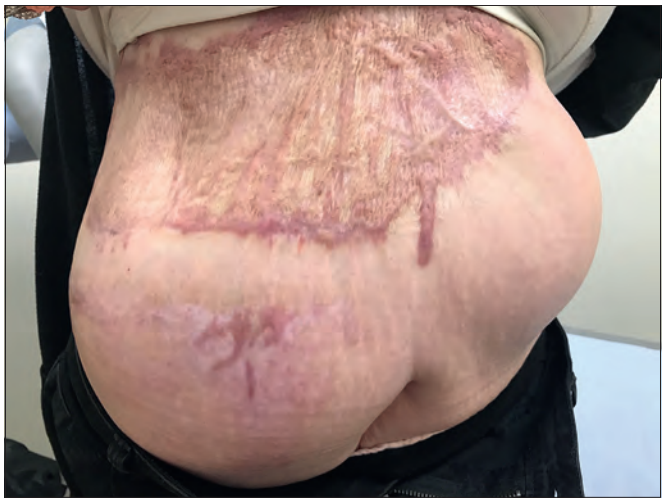

Fig. 52.5 Hypertrophic scar on the abdomen following flame burn.

LATE RECONSTRUCTIVE MANAGEMENT OF THE TRUNK SOFT TISSUE LAYERS

The late reconstruction of the soft tissue layers addresses the impact of abnormal scarring on the cosmetic and functional integrity of the trunk. Reconstruction due to scars in the boundaries of the trunk that alter the functionality of the neck, axillae, and groin area and reconstruction of specific body parts such as the breast will be addressed later in the chapter.

The reconstruction of the soft tissue layers of the trunk is simultaneous with recognized protocols of scar management such as massaging, moisturizing, and sun-protecting the scar; application of compression garments; and physical therapy. These are beyond the scope of this chapter and will not be addressed here.

The wise use of recognized surgical techniques in the acute phase of scar maturation diminishes the complexity of reconstructive needs. These include the use of darts in escharotomies when crossing joints, placing the seams of the skin grafts following skin tension lines, using sheet grafts when possible, placing grafts transversely over joints, applying early pressure therapy, and implementing an early ambulation and exercise regimen.[23]

The skin layers of the trunk may be affected by abnormal pigmentation, hypervascularity, hypertrophic and keloid scars, texture abnormalities in both the reconstructed and the donor site (Figs. 52.4 to 52.6), by the presence of contractures that can be well defined or diffuse, and by the presence of unstable tissue (Figs. 52.7 and 52.8) with a tendency to breaking down.[24] The approach to the management of these abnormalities is to always prioritize function over cosmesis, have a realistic approach to reconstruction, and appropriately time any surgical procedure to avoid interfering with the maturation of scars.

Selective scar resection and direct closure of the subsequent defect may be used in the trunk providing that sufficient skin laxity and tension-free closure exists.[25]

The skin of the abdomen, with its natural laxity and the possibility of redundant tissue, allows the use of recognized techniques of reconstruction such as abdominoplasty and liposuction to become valid options of soft tissue cover after scar excision.[26,27]

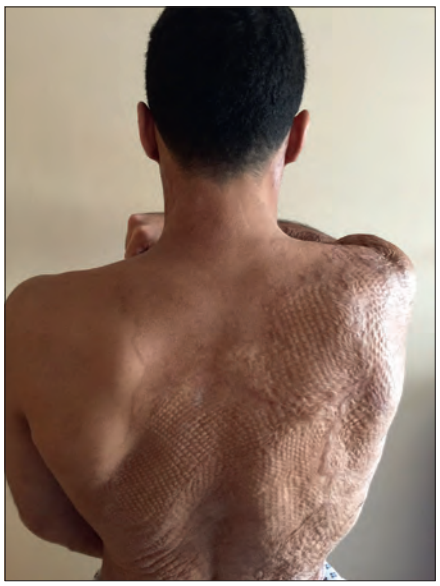

Fig. 52.6 Extensive mesh pattern on the back following grafting.

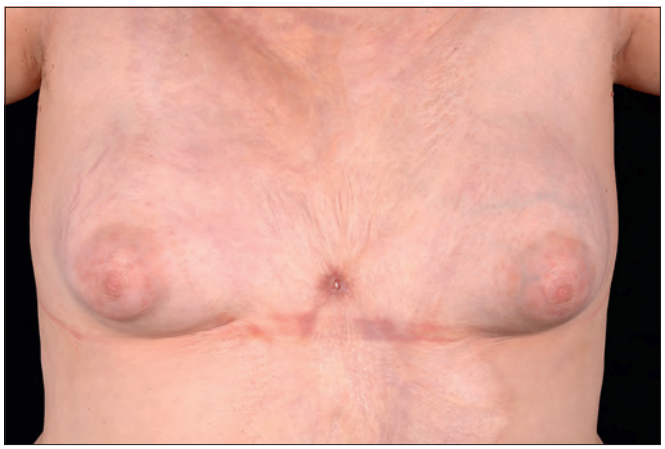

Fig. 52.7 Unstable scar in the center of the chest after flame burns treated conservatively.

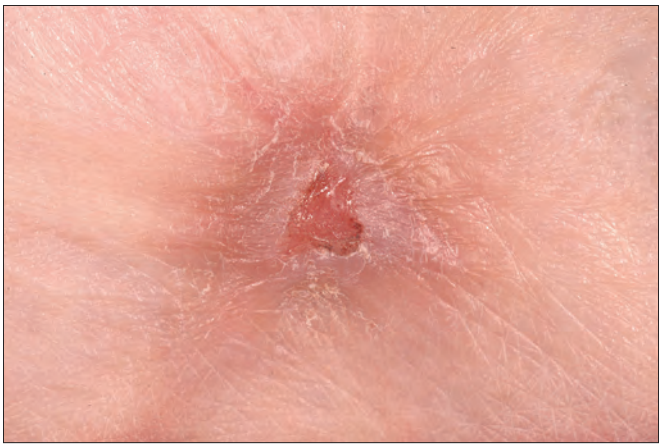

Fig. 52.8 Unstable scar on the center of the chest after flame burns treated conservatively. Close-up.

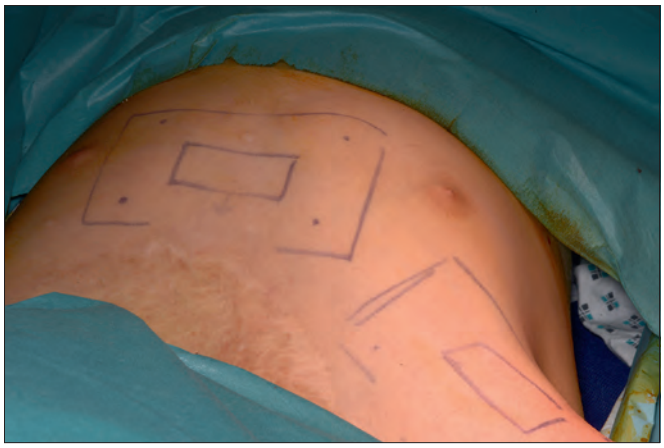

Fig. 52.9 Insertion of osmotic tissue expanders for reconstruction of chest burn scarring: skin markings.

The use of full-thickness grafts or dermal regeneration templates constitutes the next stage in the resurfacing and reconstruction of elective scar revision surgery. They provide the patient with a reconstruction of improved pliability[28,29] that has been proved to withstand even the natural skin tension resulting from a pregnancy.[30]

In cases of cosmetically disfiguring scars that exhibit lack of pliability, the use of tissue expansion techniques either on their own or combined with flap techniques[31] in the trunk offers the possibility of providing reconstruction with autologous skin following a two-stage procedure. The first stage introduces the expanders in a pocket near the scar. Once appropriate expansion has been achieved, including overexpansion,[32] the scar is excised and the subsequent defect covered with a flap of expanded skin usually using a technique of advancement, transposition, or rotation. It has been postulated that the insertion of the largest possible expander, a rectangular shape, and the method of advancement provides the largest amount of expanded tissue available.[33] Traditional tissue expanders are connected to a tubing system and a port that is placed usually over a bony prominence distant to the implant itself. Recently the use of osmotic tissue expanders has introduced a new option for reconstruction and resurfacing of defects after scar excision by avoiding the need for repeated injections. This is especially useful when dealing with pediatric patients.[34]

The insertion of osmotic tissue expanders requires careful dissection of an appropriately sized pocket to place the prosthesis. This is an important issue in the learning curve of the early user of this technique because the osmotic tissue expander tends to grow relatively quickly during the first 2 weeks of insertion.

Insertion of the expander too close to the scar to be reconstructed will increase the potential for implant extrusion. A sequence for the insertion of osmotic tissue expanders can be seen in Figs. 52.9 to 52.14. Following insertion, our protocol is to review the patient weekly for the first month post insertion to review the wound and assess for breakdown or dehiscence. We then follow the patient monthly until the second stage of reconstruction. This stage includes expander removal, scar excision, and reconstruction of the defect usually by advancement (Figs. 52.15 to 52.18).

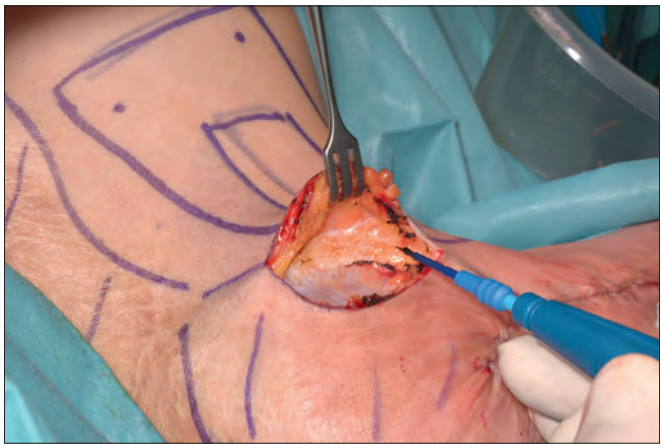

Fig. 52.10 Insertion of osmotic tissue expanders for reconstruction of chest burn scarring: pocket dissection.

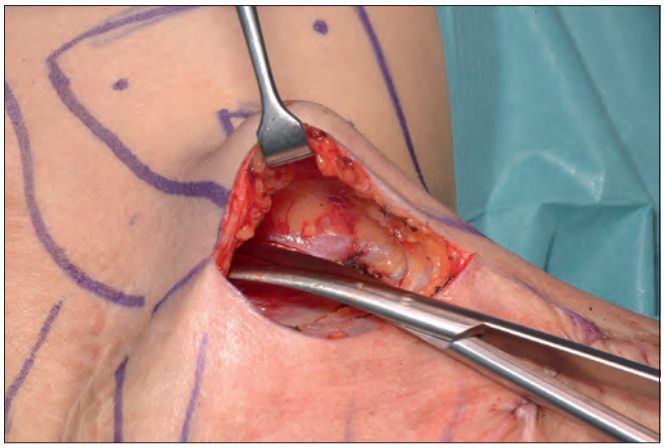

Fig. 52.11 Insertion of osmotic tissue expanders for reconstruction of chest burn scarring: pocket dissection.

Reconstruction of the Trunk Boundaries

Primary reconstruction of the neck, axillae, and groin areas will be described in a different chapter. Scarring in the trunk

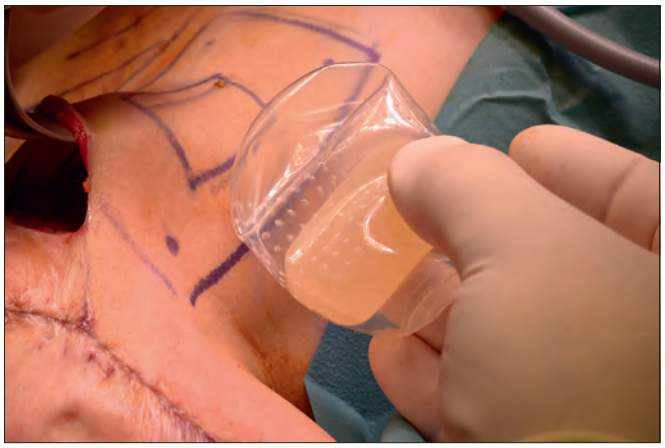

Fig. 52.12 Insertion of osmotic tissue expanders for reconstruction of chest burn scarring: insertion of expander into pocket.

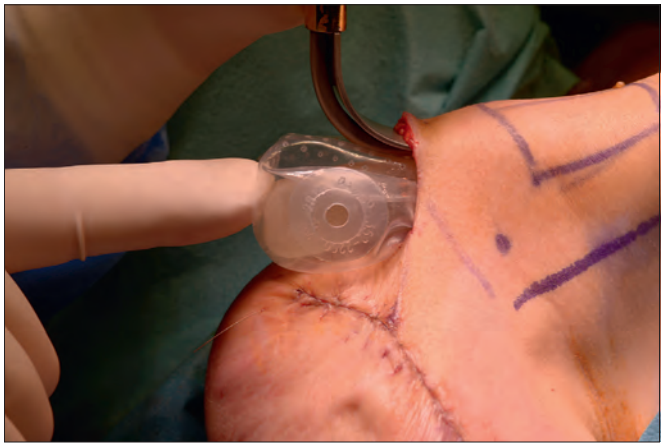

Fig. 52.13 Insertion of osmotic tissue expanders for reconstruction of chest burn scarring: insertion of expander into pocket.

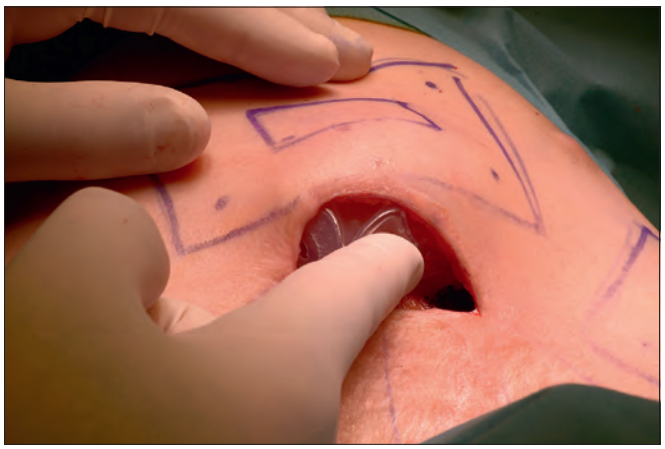

Fig. 52.14 Insertion of osmotic tissue expanders for reconstruction of chest burn scarring: insertion of expander into pocket.

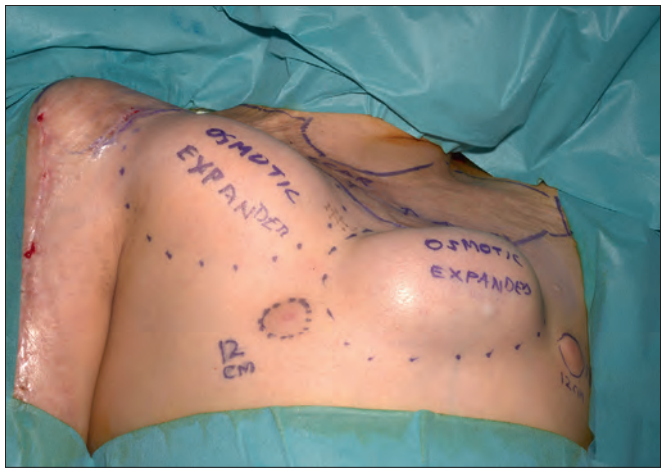

Fig. 52.15 Expanders after 2 months and prior to removal and reconstruction.

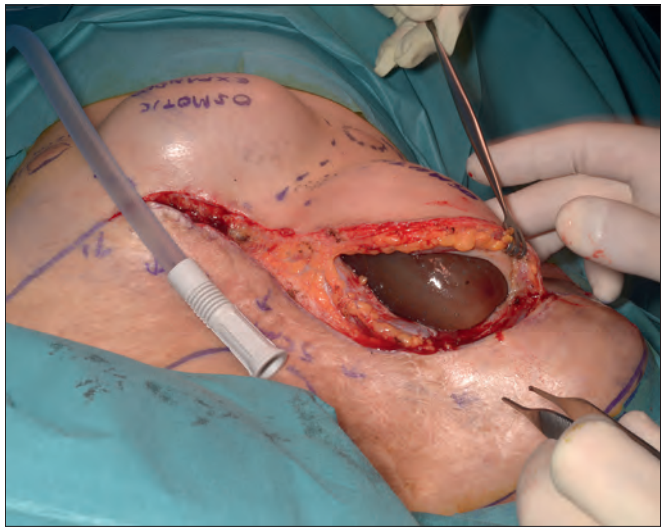

Fig. 52.16 Removal of expanders.

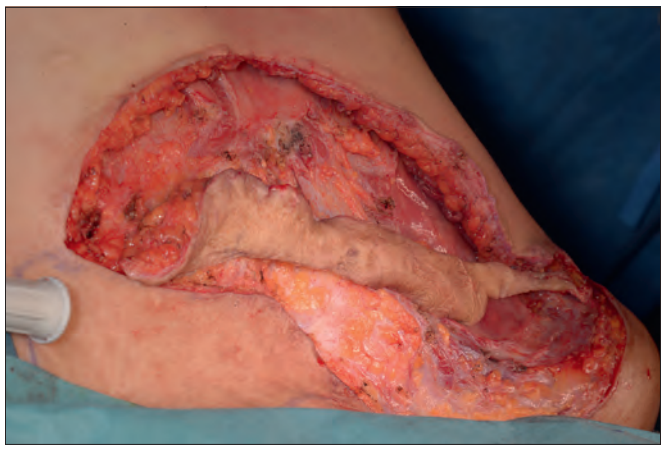

Fig. 52.17 Scar excision.

bordering these areas may cause contractures requiring reconstruction. The management of these involve the use of known principles of reconstruction, such as tissue rearrangement techniques like z-plasties or the introduction of additional tissue with skin grafts, dermal templates, or flaps.

The following clinical case illustrates these techniques. A 21-year-old who suffered 40% TBSA burns 4 years ago presented to our office complaining of tightness in the right flank, right axilla, and neck due to burns in the torso (Fig. 52.19).

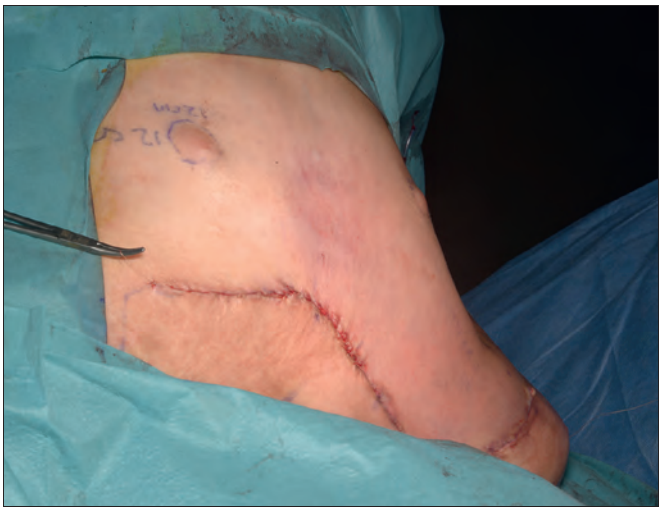

Fig. 52.18 Expanded skin flap advancement, reconstruction and closure.

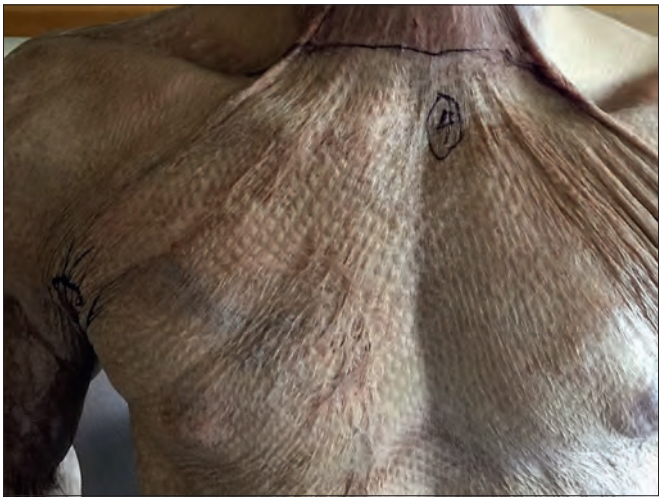

Fig. 52.19 Extensive chest scarring in a 40% total body surface area (TBSA) burned patient.

The scar contracture in the neck was addressed with the use of a dermal substitute (Matriderm) and a thin skin graft. An area of tightness in the right flank was treated with a long releasing z-plasty (Fig. 52.20). The tightness in the right axilla was addressed with a standard z-plasty for the anterior axillary fold and a five-flap plasty for the posterior shoulder area (Figs. 52.21 and 52.22).

The symptoms, once healing of the wounds was completed, were largely resolved by these procedures.

Reconstruction of the Breast

The management of the burned breast is a special and unique part of trunk reconstruction. The specific stages of the surgical techniques used to reconstruct the breast correspond to the distinct developmental stages it goes through. Due to this, reconstruction is particularly important in the prepubescent young girl because absence of a nipple is a noticeable concern.

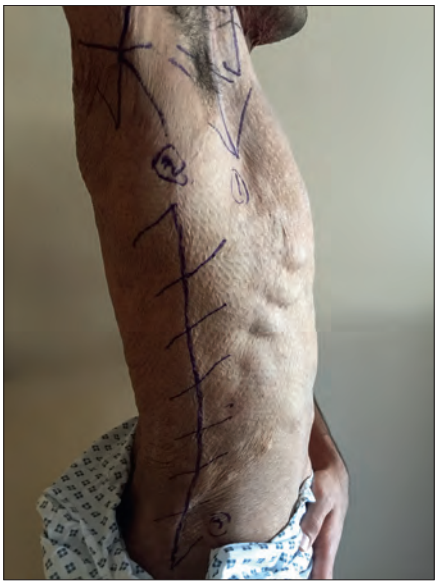

Fig. 52.20 Z-plasty designed along right flank linear burn scar contracture.

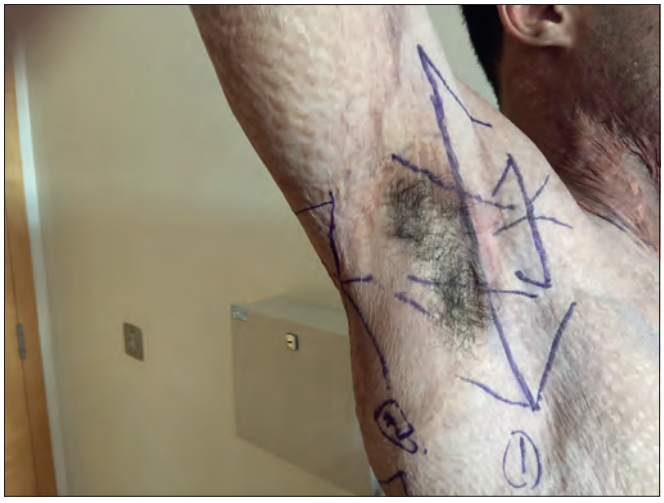

Fig. 52.21 Z-plasty designed in right axillary linear burn scar contracture.

Once disfigurement and deformity are established, accurate assessment, characterization, and planning are crucial to timely and successful reconstruction.[35,36]

Abnormal burn scarring during puberty results in compromised breast growth and displacement of the nipple-areolar complex (NAC), the breast mound, and the inframammary fold.[37]

It is important to avoid excision of the breast bud in order to preserve the development of the breast in prepubescent girls.[38]

Burns during pregnancy and lactation are usually addressed with tangential excision and split-thickness skin grafts to facilitate healing of the wounds, allow breastfeeding, and reduce potential compromise to mother and fetus. The use of bromocriptine in the lactating woman ceases lactation and induces breast involution, allowing tissue cover as soon as possible.[39]

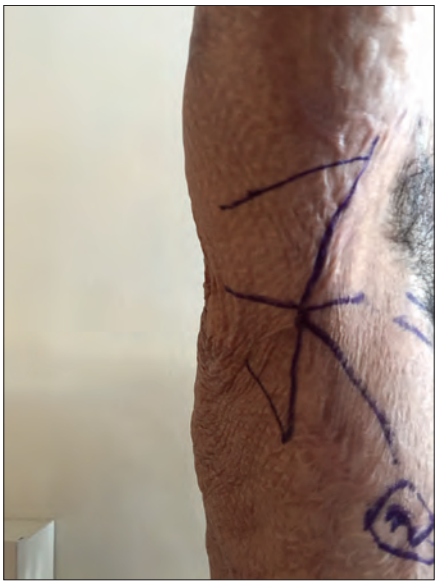

Fig. 52.22 Five-flap plasty designed in right posterior shoulder area.

Table 52.1 Classification of Postburn Breast Deformity

Location	Unilateral Bilateral
Extent	Total Subtotal
Anatomical	Breast mound NAC Inframammary fold
Deformity	Contracture: Intrinsic/extrinsic Hypoplasia Aplasia
Symmetry	

Postburn breast sequelae can be classified according to the descriptions in Table 52.1.

The burned breast can suffer scar contractures that can be intrinsic or extrinsic. Burn scars crossing the inframammary fold show both loss of definition and flattening of this area. When the breast mound is involved, breast growth can be compromised, and hypoplasia or aplasia ensues. The resulting asymmetry will cause distress and a perceived loss of femininity.

PRINCIPLES OF BREAST RECONSTRUCTION

Reconstruction of the burned prepubescent breast is best achieved once breast maturity is attained. Generally scar maturation is awaited, and reconstruction is performed during early adulthood. Appropriate timing of the contracture release is fundamental to avoid a hypoplastic-looking breast during postpubertal development. Staged reconstruction throughout puberty may be required to optimize the aesthetic result.

It is fundamental to document on examination the quality of the skin and scar, the type of scar contracture (intrinsic or extrinsic), the NAC position, the sternal notch to nipple distance, the breast base size, and any differences between the breasts in terms of symmetry, shape, and size. In addition it is important to note what tissues are left and what parts are missing.

It is also important to document what sort of donor sites are available: areas for harvesting both full- and split-thickness skin grafts, the back to examine the latissimus dorsi donor site, and all areas where potential flaps can be harvested for free tissue transfer such as the lower abdomen (deep inferior epigastric perforators [DIEP] flap), inner thigh (transverse upper gracilis [TUG] flap), and the buttock (superior gluteal artery perforator [SGAP] flap). In addition areas of fat deposition on flanks, buttocks, and upper abdomen must also be examined as potential sites of fat harvest for autologous fat transfer.

The reconstructive techniques to improve the burned breast appearance include the principles outlined earlier for reconstruction of the trunk such as skin grafts and tissue rearrangement techniques through z-plasties. Specific breast procedures include nipple reconstruction, implant-based breast augmentation, autologous fat transfer to improve breast volume, free tissue transfer, and reduction of the contralateral unburned breast to match the underdeveloped burned breast. The principles used to reconstruct the burned breast are described in Box 52.1.

Box 52.1 Principles of Postburn Breast Reconstruction

Release scar contracture
Resurface unsightly or painful scar
Replace missing parts including breast mound and NAC
Reestablish symmetry

RELEASE AND SCAR RESURFACING

This is addressed by contracture release to expand breast skin surface and split-thickness skin grafting combined or not with dermal regeneration templates, specifically at the inframammary fold, periareolar area, sternal area, and anterior axillary line. This helps to improve shape and volume (Fig. 52.23).

Expansion of breast skin may be achieved by standard tissue expansion or the use of distal or free flap tissue options.[40]

Reconstruction of the inframammary fold can also be performed by a release and advancement flap through expanded reverse abdominoplasty techniques.[41]

REPLACEMENT OF MISSING PARTS: BREAST MOUND RECONSTRUCTION

Volume replacement can be achieved by prosthetic implant-based reconstruction and autologous tissue reconstruction. The burn scar can be stretched to obtain volume, using tissue expanders inserted either in an open or endoscopic fashion (Fig. 52.24).[42]

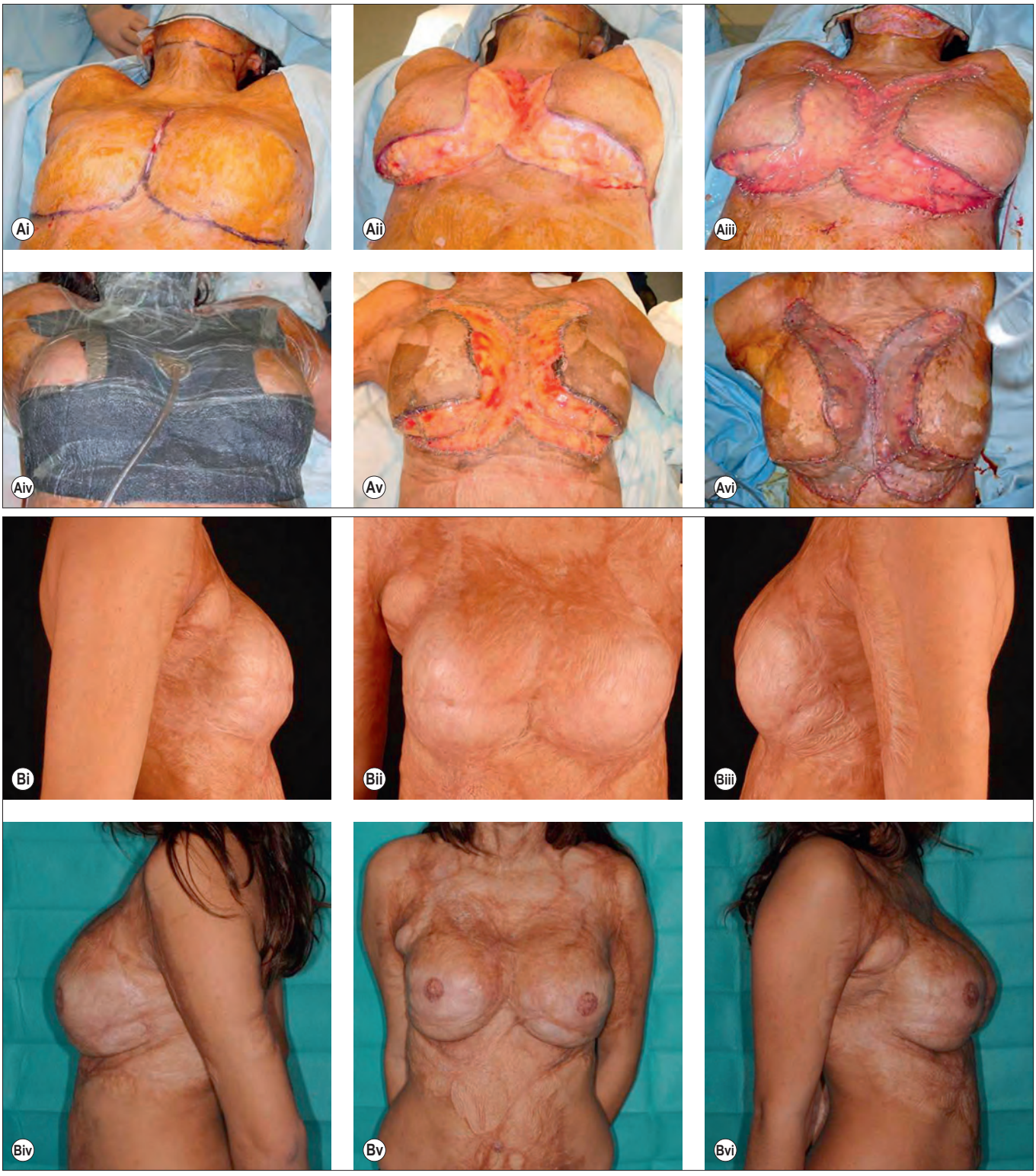

Fig. 52.23 Breast contracture release. (Ai) Planned release of symmastia and inframammary fold contractures to release breast mound. (Aii) Following incisional release; note skin deficit. (Aiii) Resurfacing with dermal template. (Aiv) Use of topical negative pressure to secure dermal template and prevent shearing. (Av) Dermal template ready for autografting. (Avi) Second-stage resurfacing of dermal template with sheet autograft. (Bi–Biii) Preoperative views. (Biv–Bvi) Postoperative views following nipple-areolar complex reconstruction showing improvement in projection, cleavage, inframammary fold.

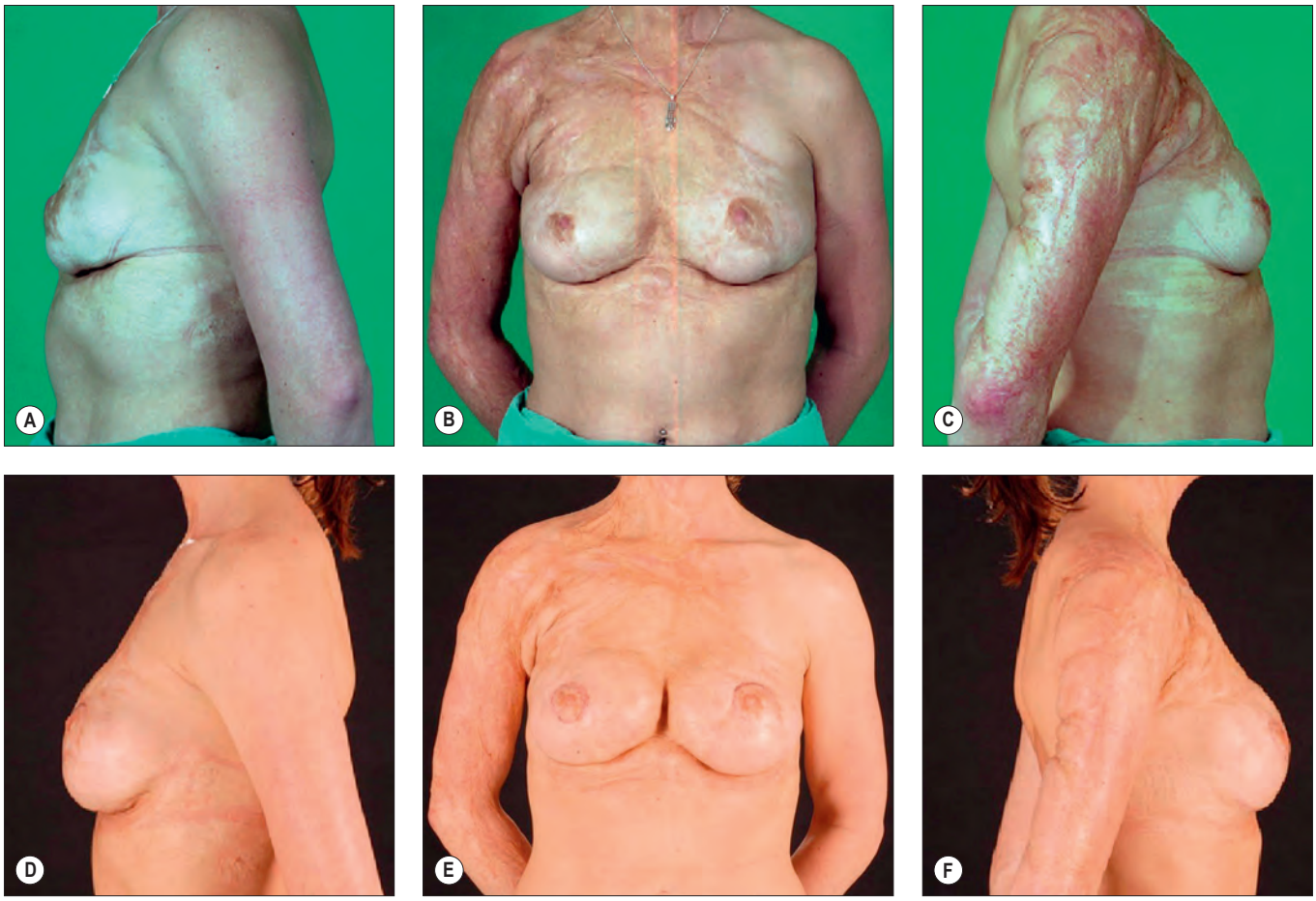

Fig. 52.24 Postburn breast mound reconstruction using tissue expanders. (A–C) Preoperative views showing characteristic flattening of breast, ptosis, and poor definition of cleavage. (D–F) Five-year postoperative insertion of bilateral tissue expanders showing improved projection, cleavage, and volume.

To prevent exposure and extrusion of the implant, submuscular placement and potential flap cover with a pedicle latissimus dorsi flap may be necessary.

Staged use of dermal templates (Integra) followed by tissue expansion appears to be a reliable technique to correct breast hypoplasia:[43]

- *First stage*: Scar release, expander submuscular insertion, and coverage of the anterior chest wall with Integra
- *Second stage, 1 month later*: Grafting of Integra, gradual expander overinflation
- *Third stage*: Expander removal and replacement with a permanent silicone implant.

Total breast reconstruction will be required in cases of breast aplasia. This is addressed with submuscular implants if the skin envelope is appropriate or with an array of flaps in cases of breast bud destruction. This will usually involve replacement of both skin and breast volume through submuscular tissue expansion, pedicle (latissimus dorsi) or free flap (DIEP, SGAP, TUG),[44,45] or a combination of both (Fig. 52.25).[46] Fat transfer provides options both for reconstruction and for scar modulation.[47,48]

NIPPLE-AREOLA COMPLEX RECONSTRUCTION

Reconstruction of the NAC is usually performed at a second stage once breast mound volume and shape have been addressed. The process can be divided into subtotal or total depending on how much of the NAC is preserved following burn injury. Subtotal reconstruction is usually addressed with release and skin grafting.

Total NAC reconstruction characteristically uses local flaps such as the skate or C-V flap but may be limited by the lack of pliability of scarred skin and by lack of projection of the reconstruction.

The areola can be reconstructed by using full-thickness skin grafts or tattooing techniques (Fig. 52.23 Bi–Bvi).

ASYMMETRY

Symmetrization procedures performed on the contralateral breast include breast augmentation or reduction and shaping using mastopexy/reduction techniques. Even though caution is warranted, concerns with reduction mammoplasty due to potential devascularization of the skin graft or NAC have proved warrantless because

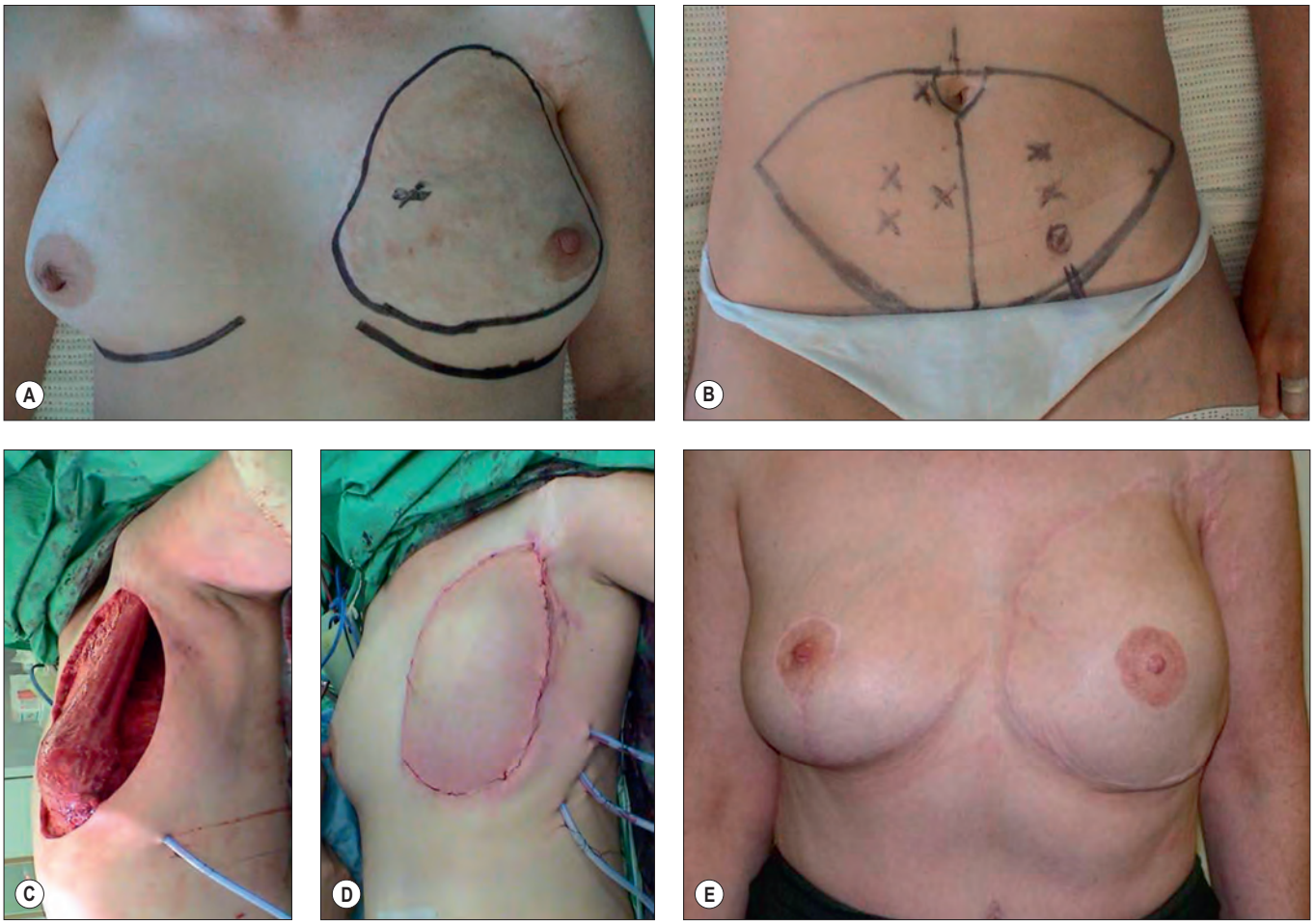

Fig. 52.25 Reconstruction of breast with DIEP flap. (A) Isolated burn scar on left breast in woman requiring mastectomy for breast cancer. (B) Markings for DIEP, including perforators. (C) Following mastectomy, subpectoral implant placement. (D) DIEP flap in place for skin cover. (E) Postoperative appearance following nipple-areolar complex reconstruction and contralateral mastopexy for symmetrization. (Case courtesy of Mr V Ramakrishnan FRCS [Plast] Consultant Plastic and Reconstructive Surgeon, St. Andrews Centre for Plastic Surgery, Chelmsford, Essex, UK.)

reduction mammoplasty in this group of patients is safe and carries minimal risk.

Conclusion

Initial care of the burned breast follows the general principles of burn management for the rest of the trunk, including resuscitation and judicious wound débridement with dermal and NAC preservation. This minimizes postburn deformity and maximizes reconstructive potential. Breast reconstruction principles include preservation and restoration of shape, volume symmetry, inframammary fold, NAC, and breast symmetry. Soft tissue cover applies reconstructive ladder principles of ascending complexity including symmetrization procedures.

Complete references available online at
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References

1. ISBI Practice Guidelines Committee. ISBI practice guidelines for burn care. *Burns*. 2016;42:953-1021.
2. Sheridan RL. Burns. In: Vincent JL, Abraham E, Moore FA, et al, eds. *Textbook of Critical Care*. New York: Saunders; 2011.
3. Townley WA, Hofer S. Abdominal wall reconstruction. In: Cugno S, Bultrode N, Ross D, eds. *Plastic and Reconstructive Surgery: Approaches and Techniques*. New York: Wiley-Blackwell; 2015.
4. Wasiak J, Cleland H, Campbell F, et al. Dressings for superficial and partial thickness burns. *Cochrane Database Syst Rev*. 2013;(3): CD002106.
5. Hubik DA, Wasiak J, Paul E, et al. A retrospective analysis of outcomes at a specialist adult burns centre. *Burns*. 2011;37:594-600.
6. Rahmanian-Schwarz A, Beiderwieden A, Willkomm LM, et al. A clinical evaluation of Biobrane W and Suprathel in acute burns and reconstructive surgery. *Burns*. 2011;37:1343-1348.
7. Oda J, Yamashita K, Inoue T, et al. Resuscitation fluid volume and abdominal compartment syndrome in patients with major burns. *Burns*. 2006;32:151-154.
8. Markell K, Renz E, White C, et al. Abdominal complications after severe burns. *J Am Coll Surg*. 2009;208(5).
9. Hershberger RC, Hunt JL, Arnoldo BD, et al. Abdominal compartment syndrome in the severely burned patient. *J Burn Care Res*. 2007;28(5):708-714.
10. Hobson KG, Young KM, Ciraulo A, et al. Release of abdominal compartment syndrome improves survival in patients with burn injury. *J Trauma Acute Care Surg*. 2002;53(6):1129-1134.
11. Kirkpatrick AW, Roberts DJ, De Waele J, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med*. 2013;39(7):1190-1206.
12. Heimes J, Carlton E, McDonnell J, et al. Use of an abdominal reapproximation anchor (ABRA) system in a patient with abdominal compartment syndrome after severe burns: a case report. *Burns*. 2013;39(4):e29-e33.
13. Keramati M, Srivastava A, Sakabu S, et al. The Wittmann patch as a temporary abdominal closure device after decompressive celiotomy for abdominal compartment syndrome following burn. *Burns*. 2008;34:493-497.
14. Poulakidas S, Kowal-Vern A. Component separation technique for abdominal wall reconstruction in burn patients with decompressive laparotomies. *J Trauma*. 2009;67(6):1435-1438.
15. Kagan R, Peck M, Ahrenholz D, et al. Surgical management of the burn wound and use of skin substitutes: an expert panel white paper. *J Burn Care Res*. 2013;34(2):e60-e79.
16. Papp A, Harma M. A collagen based dermal substitute and the modified Meek technique in extensive burns: report of three cases. *Burns*. 2009;29:167.
17. Medina A, Riegel T, Nystad D, et al. Modified Meek micrografting technique for wound coverage in extensive burn injuries. *J Burn Care Res*. 2016;37(5):305-313.
18. Wood F. Tissue engineering of skin. *Clin Plast Surg*. 2012;39(1):21-32.
19. Bhatia Y, Menon P, Bhavsar M. Coverage of chest wall defect in a case of electric burns by pedicled omental flap. *J Burn Care Res*. 2014;35(4): e262-e264.
20. Honda T, Yamamoto Y, Mizuno M, et al. Successful treatment of a case of electrical burn with visceral injury and full-thickness loss of the abdominal wall. *Burns*. 2000;26(6):587-592.
21. Nnabuko N, Anyanwu C, Ezinwa C, et al. Reconstructive challenges in full thickness left anterior chest wall defect following electrical burn: a case report demonstrating the use of extended reverse double turnover deltopectoral flap. *Burns*. 2011;37(5):e37-e40.
22. Li Y, Min L, Huang J, et al. Successful treatment of a case of severe electrical burns with heart and lung injuries. *J Burn Care Res*. 2007;28: 762-766.
23. Barret JP. Burns reconstruction. *BMJ*. 2004;329(7460):274-276.
24. Cartotto R, Cicuto BJ, Kiwanuka HN, et al. Common postburn deformities and their management. *Surg Clin North Am*. 2014;94(4):817-837.
25. Leon-Villapalos J, Kaniorou-Larai M, Dziewulski P. Full thickness abdominal burn following magnetic resonance guided focused ultrasound therapy. *Burns*. 2005;31(8):1054-1055.
26. Maguina P, Busse B, Emelin J. Mini-abdominoplasty in burn reconstruction. *J Burn Care Res*. 2012;33(2):e39-e42.
27. Ma G, Lei H, Chen J, et al. Reconstruction of large hypertrophic scar on trunk and thigh by means of liposuction technique. *Burns*. 2010;36(2):256-260.
28. Leffler M, Horch RE, Dragu A, et al. The use of the artificial dermis (Integra) in combination with vacuum assisted closure for reconstruction of an extensive burn scar–a case report. *J Plast Reconstr Aesthet Surg*. 2010;63(1):e32-e35.
29. Shelley OP, Van Niekerk W, Cuccia G, et al. Dual benefit procedures: combining aesthetic surgery with burn reconstruction. *Burns*. 2006; 32(8):1022-1027.
30. Kakagia D, Kyriopoulos E, Zapandioti P, et al. Natural expansion of artificial dermal template by successful full-term pregnancy. *J Burn Care Res*. 2012;33(3):e166-e168.
31. Lykoudis EG, Seretis K, Ziogas DE. Tissue expansion and latissimus dorsi transfer for arm-thorax synechia reconstruction. *J Burn Care Res*. 2011;32(2):e15-e20.
32. Di Mascio D, Castagnetti F, Mazzeo F, et al. Overexpansion technique in burn scar management. *Burns*. 2006;32(4):490-498.
33. Hudson D, Grob M. Optimising results with tissue expansion: 10 simple rules for successful tissue expander insertion. *Burns*. 2005;31(1):1-4.
34. Chummun S, Addison P, Stewart KJ. The osmotic tissue expander: a 5-year experience. *J Plast Reconstr Aesthet Surg*. 2010;63:2128-2132.
35. Maxwell GP, Gabriel A. Breast reconstruction. In: Aston SJ, Steinbrech DS, Walden JL, eds. *Aesthetic Plastic Surgery*. Philadelphia: Elsevier; 2009.
36. Muller M, Gahankari D, Herndon DN. Operative wound management. In: Herndon DN, ed. *Total Burn Care*. 3rd ed. London: Saunders Elsevier; 2007:193.
37. Ogilvie MP, Panthaki ZJ. Burns of the developing breast. *J Craniofac Surg*. 2008;19:1030.
38. Armour AD, Billmire DA. Pediatric thermal injury: acute care and reconstruction update. *Plast Reconstr Surg*. 2009;124:117.
39. Giele HP, Nguyen H, Wood F, et al. Management of full thickness burns to lactating breasts. *Burns*. 1994;20:278.
40. Grishkevich VM. Restoration of the shape, location and skin of the severe burn-damaged breast. *Burns*. 2009;35:1026.
41. Haik J, Grabov-Nardini G, Goldan O, et al. Expanded reverse abdominoplasty for reconstruction of burns in the epigastric region and the inframammary fold in female patients. *J Burn Care Res*. 2007; 28:849.
42. Levi B, Brown DL, Cederna PS. A comparative analysis of tissue expander reconstruction of burned and unburned chest and breasts using endoscopic and open techniques. *Plast Reconstr Surg*. 2010; 125:547.
43. Shariff Z, Rawlins JM, Austin O. Burned breast reconstruction by expanded artificial dermal substitute. *J Burn Care Res*. 2007;28:929.
44. Granzow JW, Levine JL, Chiu ES, et al. Breast reconstruction with gluteal artery perforator flaps. *J Plast Reconstr Aesthet Surg*. 2006;59(6):614-621.
45. Arnez ZM, Pogorelec D, Planinsek F, et al. Breast reconstruction by the free transverse gracilis (TUG) flap. *Br J Plast Surg*. 2004;57(1):20-26.
46. Figus A, Canu V, Iwuagwu FC, et al. DIEP flap with implant: a further option in optimising breast reconstruction. *J Plast Reconstr Aesthet Surg*. 2009;62(9):1118-1126.
47. Elfadl D, Garimella V, Mahapatra TK, et al. Lipomodelling of the breast: a review. *Breast*. 2010;19(3):202-209.
48. Locke M, Feisst V, Dunbar PR. Concise review: human adipose-derived stem cells: separating promise from clinical need. *Stem Cells*. 2011;29(3):404-411.

53 Management of Contractural Deformities Involving the Shoulder (Axilla), Elbow, Hip, and Knee Joints in Burned Patients

KAREL D. CAPEK, RAMON ZAPATA-SIRVENT, and TED T. HUANG

Introduction

Burn injuries, regardless of the etiology, rarely involve a joint itself. However the joint function is often impaired because of burns. The joint problems and joint deformities noted in burn patients are mostly due to physical inactivity combined with limitation of joint movement because of scar contracture. The consequences of joint dysfunction are usually left for reconstruction later in the course of burn convalescence.

Contractural Deformities of the Shoulder (Axilla), Elbow, Hip, and Knee Observed in a Burned Patient

THE FACTORS LEADING TO FORMATION OF CONTRACTURAL DEFORMITIES

Folding bodily joints in flexion, a so-called posture of comfort, is a characteristic body posture seen commonly in a distressed individual. Although the exact reasons are not entirely clear, contraction of muscle fibers at rest and contractile force difference between the flexor muscle and the extensor muscle play an important role in the genesis of this body posture. The magnitude of joint flexion, furthermore, increases as an individual loses voluntary control of muscle movement, as frequently occurs in a burn victim (Fig. 53.1). A prolonged period of physical inactivity associated with burn treatment and scar tissue contraction around the joint structures as the recovery ensues further impedes joint mobility.

A subtype of joint problem seen with major burn injuries is heterotopic ossification. This may affect any joint, although the elbow is by far the most frequently affected. Its initial symptoms are markedly increased pain with motion and hyperemia/swelling. A high index of suspicion is needed to differentiate this problem from background post-burn pain.[1–3] The splinting and exercise/range-of-motion (ROM) care of patients with heterotopic ossification differ from standard burn rehabilitation, as noted later.

INCIDENCE OF BURN CONTRACTURE INVOLVING THE SHOULDER (AXILLA), ELBOW, AND KNEE JOINTS

Burn treatment that requires a long period of bed confinement and physical inactivity as well as restriction of joint movement will lead to joint dysfunction. Consequently every bodily joint (i.e., the vertebral, mandibular, shoulder, elbow, wrist, finger, hip, knee, ankle, and toe) is susceptible to changes. Of various bodily joints involved, the contractural deformities of the shoulder (axilla), elbow, hip, and knee are relatively common. Factors such as a wide range of joint movement and asynchronous muscular control are characteristic features of these joints, and, when combined with a high vulnerability to burn injuries, are the probable reasons accounting for the high incidence encountered. A review of the records of 1005 patients treated at the Shriners Burns Hospital in Galveston, Texas, over 25 years, indicated that the elbow was the joint most commonly affected. There were 397 patients with elbow joint deformity followed by 283 knee contractures. There were 248 axillary deformities. Hip joint contracture was the deformity least encountered and was noted in only 77 patients (Table 53.1).

EFFICACY OF SPLINTING IN CONTROLLING BURN CONTRACTURES OF SHOULDER (AXILLA), ELBOW, AND KNEE JOINTS

Although Cronin in 1955 demonstrated that the neck splint was effective in preventing recurrence of neck contracture following surgical release,[4] the routine use of splinting for burn patients did not become a part of the regimen of burn wound care in Galveston until 1968, when Larson, the former Surgeon-in-Chief and Willis, the former Chief Occupational Therapist at the Shriners Burns Institute, began to fabricate splints with thermoplastic materials to brace the neck and extremities.[5–8]

For more than three decades, a neck brace, a three-point extension splint, and a molded brace fabricated from thermoplastic materials—prototypes of devices used to splint the neck, elbow, and knee joints—were used in the management of burn patients at the Shriners Burns Hospital and

Table 53.1 The Distribution of Joint Deformities

Joint Involved	*n*
Shoulder (axilla)	248
Elbow	397
Hip	77
Knee	283
Total	1005

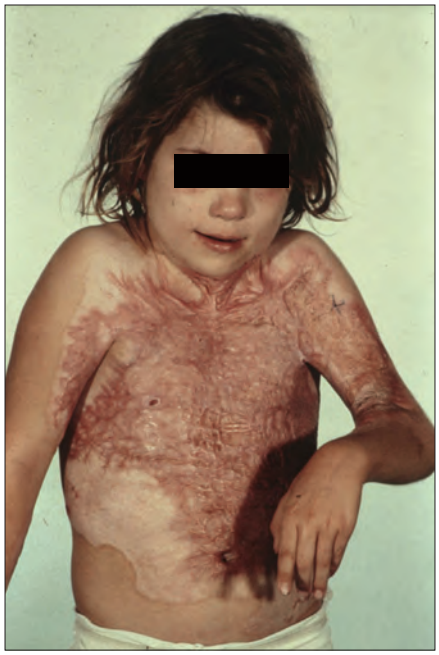

Fig. 53.1 The posture of comfort characterized by flexion of shoulder (axilla) and elbow joints, plus hip and knee joints, is assumed by patients under distress, as in burn patients.

the University of Texas Medical Branch Hospitals in Galveston, Texas. An "airplane splint" similarly made of thermoplastic materials was also used to splint the axilla when the use of other splinting and bracing techniques, such as a "figure-of-eight" bandage, were not feasible.

A study was conducted in 1977 to determine the efficacy of splinting across large joint structures such as the elbow, axilla, and knee by reviewing the records of 625 patients. There were 961 burns over these joints in this group of patients. Of these, 356 had involved the axillae, while 357 and 248 involved the elbow and knee joints, respectively. The incidence of axillary contractural deformities without splinting was 79%; with splinting this decreased to 26%. The subgroup able to wear splints for longer than 6 months had the lowest incidence of contracture at 15%, whereas discontinuation of splinting before 6 months identified a subgroup at high risk for splint failure, with 80% incidence (similar to a no-splint group). At the elbow, the incidence of contracture was 55% without splinting, decreasing to 12% with splinting, and further decreasing to 6% if splint usage was maintained for more than 6 months. At the knee, the incidence of contracture was 37% without splinting, decreasing to 3% with splinting, and further decreasing to 1% if splint usage was maintained for more than 6 months (Table 53.2). Although splinting and bracing were shown to be effective in minimizing joint contracture, it was not entirely clear if restriction of joint movement would affect the quality of scar tissues formed across the joint surface. The effects were assessed by determining the frequency of secondary surgery performed in this group of patients. More than 90% of 219 individuals who did not use splinting/bracing required reconstructive surgery. In contrast, the need for surgical reconstruction in individuals who wore splints was 25%.[9]

Table 53.2 The Incidence of Contractures Across the Shoulder (Axilla), Elbow, and Knee Joints

		WITH SPLINT	
	Without Splint	**<6 months**	**>6 months**
Shoulder			
Severe/moderate	137	24	23
Mild/none	37	6	129
Elbow			
Severe/moderate	75	17	10
Mild/none	61	33	161
Knee			
Severe/moderate	26	4	2
Mild/none	45	16	155

Management During the Acute Phase of Recovery

It is believed that inadequate physical exercise and lack of joint splinting and bracing, although allowing a patient to assume the posture of comfort, are the main factors responsible for the genesis of contractural deformities seen in patients during the acute phase of recovery from burn injuries. The deformities, furthermore, are made worse because of skin involvement and burn scar contracture. To minimize this undesirable consequence of burn injuries, proper body positioning and splinting of the joint structures must be incorporated into the regimen of burn treatment. The treatment should be implemented as soon as the patient's condition allows.

BODY POSITIONING AND JOINT SPLINTING

Body Position

Although a supine position is preferred, the patient may be placed in a lateral decubitus position while confined in bed. The head should be placed in a neutral position with the neck slightly extended. For a patient placed in a supine position, neck extension is achieved by placing a small pad between the scapulae to facilitate scapular traction. A neck brace may be used if a patient is placed in other body positions.

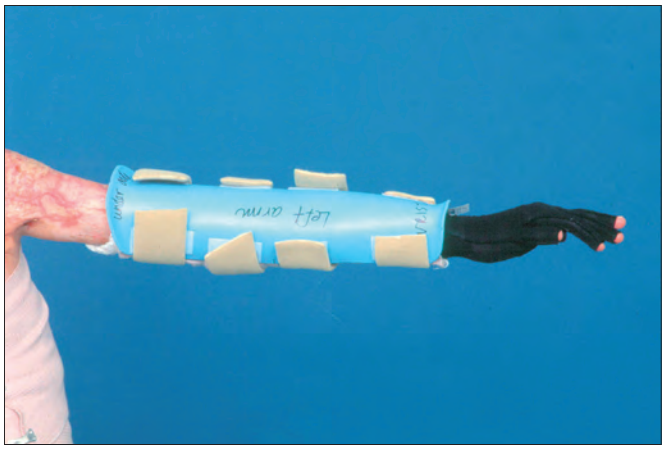

Fig. 53.2 A splint made of thermoplastic material is used to limit joint flexion.

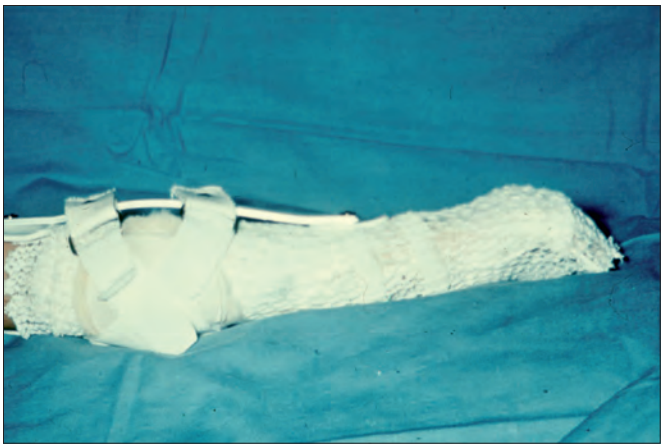

Fig. 53.3 A three-point extension splint manufactured similarly to an orthotic device is used either to extend a contracted elbow joint or immobilize the joint in full extension.

Shoulder (Axillary) Joint. The shoulder joint is kept at 90–120 degrees of abduction and 15–20 degrees of flexion. The position is not only useful in protecting the brachial plexus from traction injury but also effective in maintaining the stability of the glenohumeral joint. The position is best kept with the use of foam wedge, trough, and/or airplane splints. A figure-of-eight wrapping over a pad around the axilla, more frequently used for patients during the intermediate phase of recovery from injury, is effective in maintaining shoulder abduction. It is also useful in preventing excess shoulder flexion.

Elbow Joint. Elbow flexion is commonly seen in a distressed patient. Rigid flexion contracture of the elbow is a common sequela if the elbow is left unattended. With burns of the skin around the olecranon, exposure of the elbow joint is a common sequela if the elbow is allowed to contract freely. Maintaining the elbow in full extension therefore is essential. An extension brace (Fig. 53.2) or a three-point extension splint across the elbow joint is effective for this purpose (Fig. 53.3). If concern for heterotopic ossification develops, the elbow splint should be expediently changed to a functional position (around 90 degrees flexion) to avoid fusion of this joint in extension.

Wrist Joint. A contractural deformity involving a wrist joint is relatively common in individuals with hand burns that were not splinted properly. A cock-up hand splint should be applied to maintain a 30-degree wrist extension (Fig. 53.4).

Hip Joint. A contractural deformity of the hip is relatively uncommon unless the hip joint is allowed to remain flexed for a long period of time. Hip extension can be achieved by placing the patient in a prone position. In a supine position, 15–20 degrees of abduction is maintained with the use of a brace or anklet.

Knee Joint. Flexion of the knee is another posture commonly assumed by a burned victim. Similar to the elbow, uncontrolled flexion of the knee joint will lead to exposure of the joint structure, especially in instances where the injuries involved the patella surface. Maintenance of the knee in full extension is, in this sense, an essential component of therapeutic regimen. This is accomplished by means of a knee brace or a three-point extension splint to assure a full extension of the knee joint (Fig. 53.5).

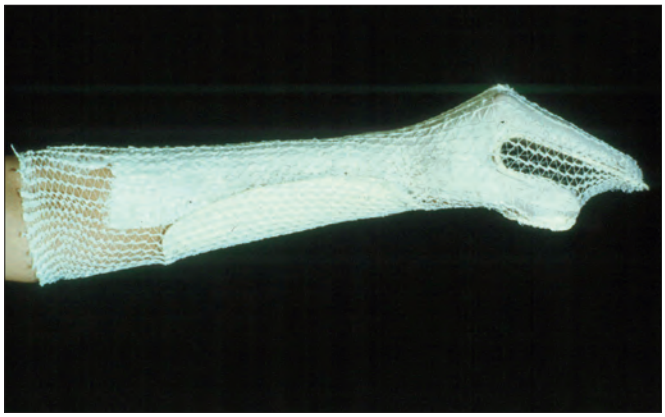

Fig. 53.4 A hand splint that will maintain the DIP-PIP joints at full extension and MCP joints at 70 degrees while keeping the wrist joint at 30 degrees extension (i.e., the hand in a position of "safety").

EXERCISE

Although exercising a burned victim is an integral part of burn therapy, it is seldom implemented until the resuscitative measures are completed and the condition of the patient is considered stable. The primary goal of exercise is to maintain the functional integrity of joint structures and muscle strength. This is attained by, in most instances, moving the joint manually and the muscles passively. Frequency and intensity of an exercise regimen, however, may vary depending on the magnitude of injury and the extent of joint involvement. The treatment, if possible, should be intensive and rendered as frequently as possible.

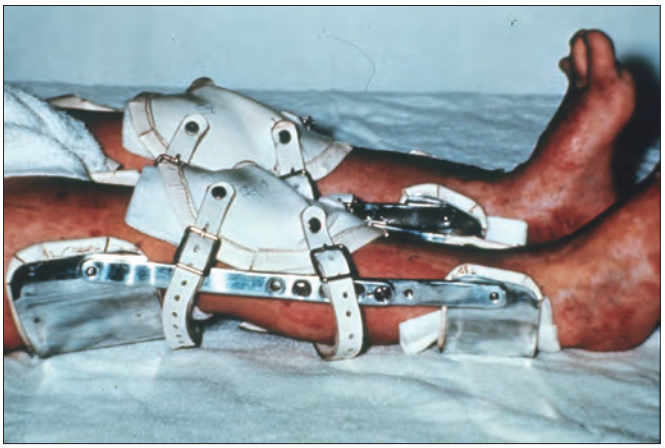

Fig. 53.5 A three-point extension splint can be also used to manage the flexion contractures of a knee joint.

Management During the Intermediate Phase of Recovery

A period starting from the second month following injury through the fourth month is considered the intermediate phase of recovery from burn injuries. The burn victims typically will have full recovery of physiologic functions with integument integrity restored. The cicatricial processes at the injured sites, on the other hand, are physiologically active, even though healing of the burned wound is considered satisfactory. This process is characterized by, in addition to a maximal rate of collagen synthesis, a steady increase in the myofibroblast fraction of the fibroblast population in the wound,[10,11] a cellular change believed to account for contraction of the scar tissues. Continuous use of splinting and pressure to support joints and burned sites is, in this sense, essential to control changes caused by ensuing scar tissue formation and scar contracture.

BODY POSITIONING AND JOINT SPLINTING

Joint splinting and body positioning are similar to the regimen used during the acute phase of burn recovery. That is, the shoulder is kept at 15–20 degrees of flexion and 80–120 degrees of abduction. A figure-of-eight wrapping over an axillary pad is used to maintain this shoulder joint position (Fig. 53.6). The elbow and knee joints are maintained in full extension by means of a three-point extension splint or brace. A pressure dressing or garment is incorporated into the splint. In instances where the use of figure-of-eight bandages or pressure dressings and/or garments is not feasible because of recent surgery, devices such as an airplane splint (Fig. 53.7) or a three-point extension splint may be used to splint the axilla, elbow, and knee joints.

PRESSURE DRESSING

A compression dressing, originally incorporated in the treatment of burned wounds of the upper and lower extremities at the Shriners Burns Hospital in 1968 as a means to provide mechanical support to healing wounds,

Fig. 53.6 An elasticized bandage is used to wrap around the shoulder (axilla) joints in a figure-of-eight fashion to extend and abduct the shoulder joints. An axillary pad is included in the wrapping to increase pressure upon the axillary fold.

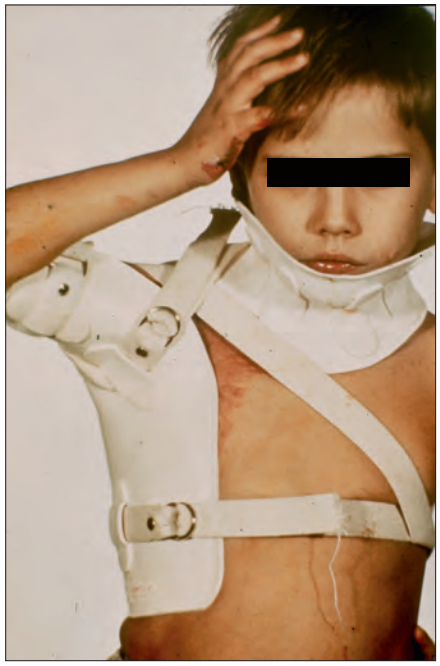

Fig. 53.7 An airplane splint made of thermoplastic materials is used to maintain shoulder abduction. The angle of separation may be increased as the joint becomes more mobile.

is effective in reducing tissue swelling and in promoting softening of a burned scar. Compression of a burn wound even while healing is still in progress is most easily achieved by wrapping the extremity with an elasticized bandage. Wrapping of the extremity should begin at the hand or foot. The bandage is moved cephalad in a criss-cross fashion. The splint is reapplied over the bandage. It is important to rewrap the extremity three to four times daily. Wrapping an extremity with an elasticized bandage can produce a pressure gradient of 10–25 mm Hg.[6,12] The use of a pressure dressing should be continued for 12–18 months.

Management of Established Contractural Deformities

Contraction of the shoulder, elbow, hip, and knee joints can occur despite proper splinting and intensive physical therapy. Surgical reconstruction of contractural deformities, in this sense, remains an essential component of patient care and patient rehabilitation. The task of deciding the timing of surgical intervention, however, can be difficult and requires detailed evaluation of the patient and the deformity. The following are ascertained before surgery:

a. The causes of joint immobility
b. The extent and availability of nearby tissues that could be used for reconstruction
c. The extent of maturation of scar tissues that surround the joint.

PATIENT EVALUATION

Numerous factors will affect joint movements in burn patients. Although hypertrophy and contraction of scar tissues and/or contracted skin graft around a joint are the most common causes of joint impairment, changes in the ligamentous structures or the joint itself due to burn injuries could also limit joint mobility. Detailed examination that may include radiographic assessment of the joint structures is essential in order to formulate a definitive treatment plan.

NONOPERATIVE OR MINIMALLY INVASIVE APPROACH TO CORRECT A CONTRACTED AND/OR STIFF JOINT

Restoration of movements in a contracted and/or stiff joint may be attained by minimally invasive or nonsurgical means.[5–9,13] "Pushing" and "pulling" of an extremity that, in turn, stretches contracted scars and tissues around an affected joint is the principle behind this modality of managing a contracted and/or stiff joint. The treatment is found to be especially effective in mobilizing a contracted joint caused by a long period of physical inactivity and, in some instances, by scar contracture.

Although the morbidities associated with this modality of treatment are minimal, breakdown of the skin due to pressure and/or friction resulting from pushing and pulling can occur.

Shoulder (Axillary) Contracture

Tight scars formed across the shoulder joint, usually in the area along the axillary folds, often limit joint movement. The joint stiffness caused by scar contracture may be further aggravated by physical inactivity, especially if the patient is allowed to remain in the posture of comfort.

Two nonsurgical methods are commonly used to mobilize a contracted shoulder (axilla) joint. One is the figure-of-eight compression dressing technique and the other an airplane splinting technique.

Figure-of-Eight Compression Dressing. An elasticized bandage is wrapped over a pad placed in the axillary fold and around the shoulder joint in a figure-of-eight fashion to extend and abduct the shoulder. The dressing must be worn continuously, and it is removed only for cleansing. Continuous wearing of the dressing for a period of 3–6 months is necessary to obtain release. The mobility of the joint increases as the scar tissues across the axilla soften. The extent of release may be limited if the scar is thick and unyielding to pressure (Fig. 53.8).

Airplane Splint. This splint is fabricated with a thermoplastic material. The spreading angle of the splint is conformed to the extent of the shoulder (axilla) joint held at maximum abduction plus 10–15 degrees of extension. Abduction and extension of the joint (i.e., elevation of the arm) will be maintained by pushing the arm away from the upper thorax. Care is needed to protect the skin over the inner aspect of the arm and the side of the chest. The splint is changed regularly as the angle of joint abduction increases. To achieve the needed release, in most instances 1–3 months of continuous use of this device is usually necessary (Fig. 53.7).

Elbow and Knee Contracture

Flexion contracture is the most common deformity encountered in these two joints. The scar formed across the antecubital and the popliteal fossae frequently aggravates the magnitude of contractural problems in these joints. The following techniques are frequently utilized before surgery to obtain joint movement and joint extension.

Three-Point Extension Splint. The three-point extension splint is assembled similarly to a prosthetic/orthotic device. Two sidebars hinged at the middle are connected with a bracing trough at the end. A cap pad is attached at the mid-section of the sidebar to fit over the elbow or kneecap. The splint is placed across the antecubital fossa or popliteal fossa. Fitting of the splint is adjusted with Velcro straps (Figs. 53.2 and 53.3).

The amount of extension achieved by the joint is determined by the extent of preexisting joint stiffness. The angle of extension is initially determined by the angle of joint contracture. The magnitude of extension is controlled by tightening the olecranon or patellar pad. Extension is increased gradually as the joint gains its mobility. Problems encountered with the use of a three-point extension splint are uncommon; however breakdown of the skin can occur. Leverage attainable from three-point pressure application may be limited in a young individual because of short limb

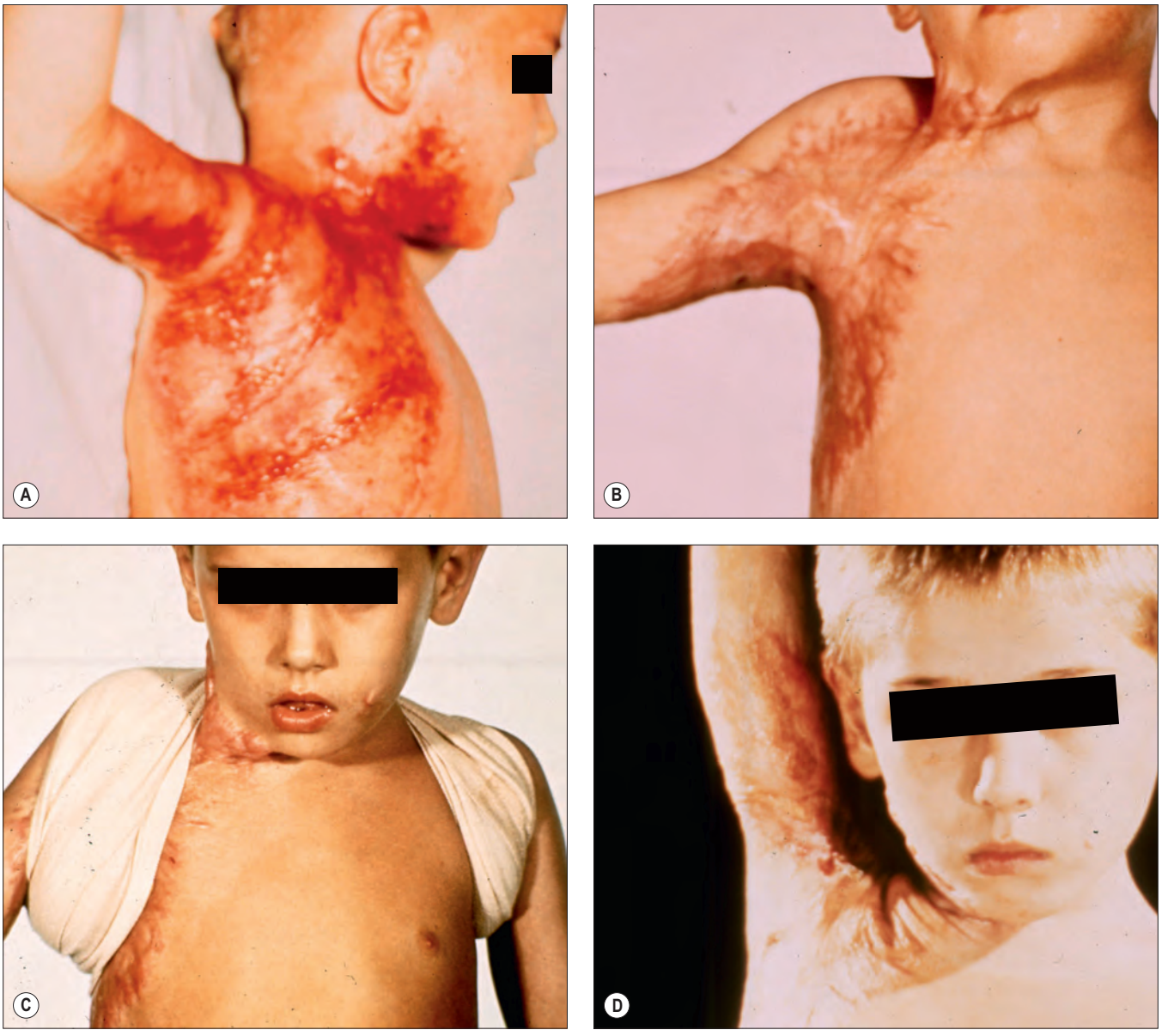

Fig. 53.8 **(A)** A 6-year-old boy sustained burns to the right side of his body extending from the lower neck to the upper thorax that included the axillary crease. **(B)** He experienced difficulty in extending both the neck and the right arm because of ensuing contraction of scar tissues around the neck and the axilla. **(C)** A figure-of-eight dressing was used to maintain the shoulder extension and abduction. The dressing was used for 12 months. **(D)** He regained shoulder extension and mobility with the use of pressure dressing.

length. In such instances, the skeletal traction technique may be used.

Skeletal Traction Technique. Utilizing a skeletal traction technique to restore movements in a contracted joint typically requires percutaneous insertion of a Steinmann's pin through the radius for the elbow joint and the tibia for the knee joint. The pin is inserted through both cortices at the junction of the proximal two-thirds and the distal third of the radius or tibia. A contracted joint can be mobilized by continuous and constant "pull" on the long bone utilizing the gravitational force generated by 10–15 pounds of weight hung with a pulley device.

For a flexion deformity of the elbow, the patient is placed in supine position. The pulley traction device will provide a horizontal and then a vertically downward pull (Fig. 53.9).

Instead of a skeletal traction device, a weight placed around the ankle, with the patient placed in prone position, may be used to pull the foreleg to loosen a contracted knee. This technique is especially useful in treating individuals with a limited knee flexion contracture. Traction is continued for a period of time and is repeated several times a day (Fig. 53.10).

Although morbidities due to infection are uncommon, the continuous and constant force of pull can cause

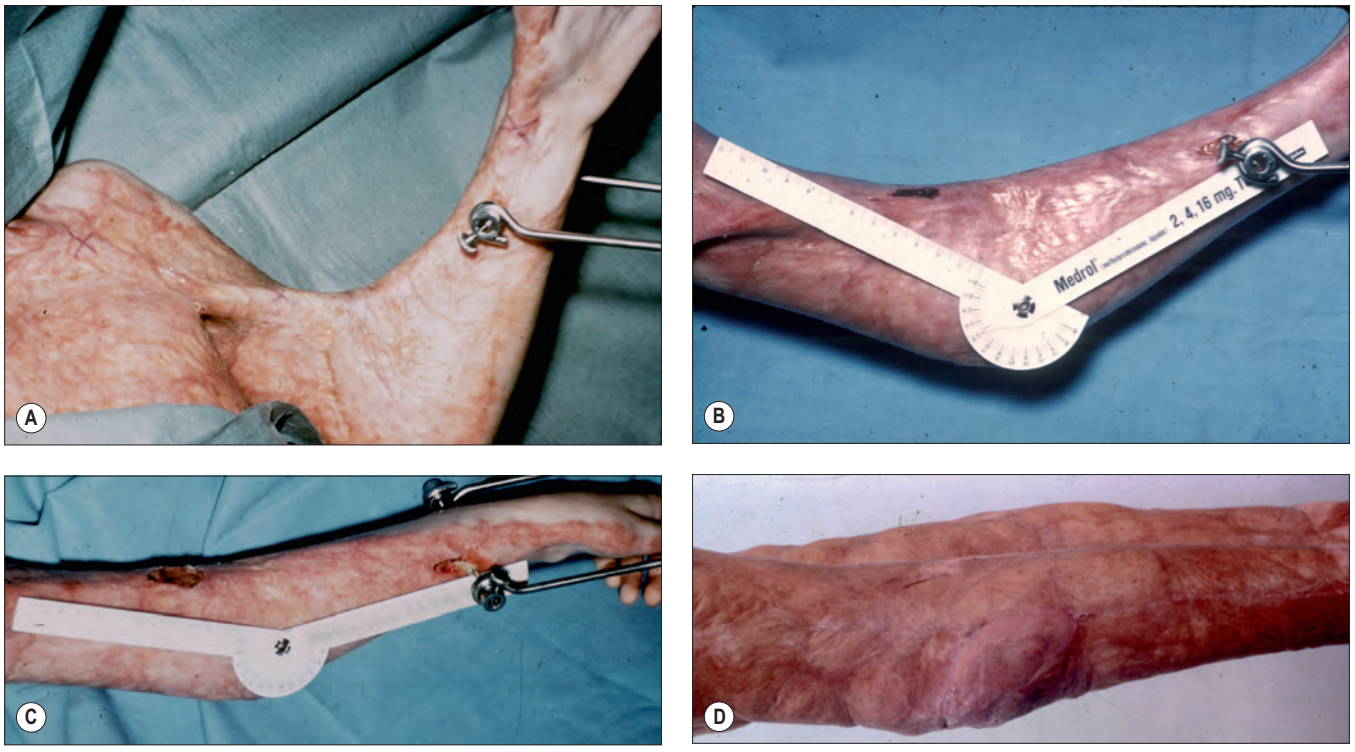

Fig. 53.9 A contractural deformity had developed involving the left elbow joint, even though there were no direct injuries involving the joint. A Steinmann's pin was inserted through the distal third of the radius for traction. A 500-g weight was used. A full extension of the contracted elbow joint was completed in 3–4 days.

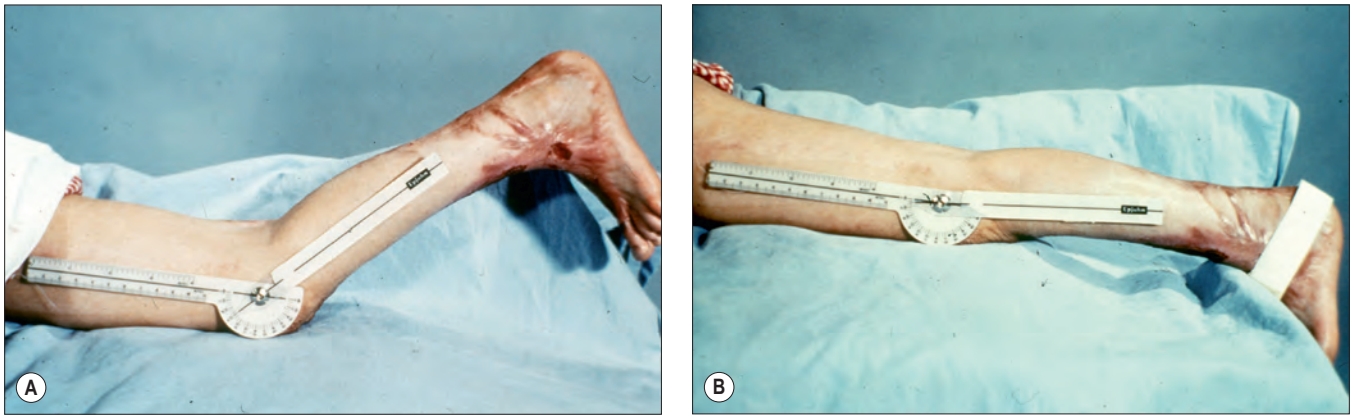

Fig. 53.10 A knee contracture developed in an 8-year-old boy due to improper positioning and immobilization of the knee joint. There were no direct injuries involving the knee area. With the patient being placed in a prone position, the ankle was strapped with a 10- to 15-pound weight. The flexion contracture was relieved in 3 days.

breakdown of the skin, typically located in the area across the joint surface. The wound can be temporarily covered with a surgical or biological dressing. Closure of the wound is contemplated once the joint contracture is fully corrected.

SURGICAL TREATMENT OF A CONTRACTED JOINT

Surgical treatment of a contracted joint is contemplated in individuals in whom the use of nonsurgical treatment is ineffective and where functional integrity of a joint is at jeopardy.

Presurgical Evaluation

The patient is seen and the involved joint is examined before surgery. The following features are assessed:

- *The extent of joint contracture* is determined and the passive and active range of joint motion is assessed. Radiographic evaluation may be obtained to delineate the structural integrity of the joint.

- *The magnitude of scarring and scar thickness* is assessed. The scar is usually thickest across the joint surface.
- *The location and size of uninjured skin* are delineated. The availability of uninjured skin frequently determines the technique of reconstruction. Skin graft and skin flap donor sites are also ascertained.
- *The point and axis of joint rotation* are located. The line of incisional release is in alignment with the axis of joint movement.

Techniques of Joint Contracture Release

Despite detailed examination before surgery, the exact cause of joint stiffness can only be delineated with surgery. In practice, contraction of the scar tissues across the joint structure is the most common cause of contractural joint deformities.

Release of Joint Contracture by Incising the Scarred Tissue. A contracted joint is freed by making an incision in the scar across the joint surface. The incision is placed in line with the axis of joint rotation. The incision is confined within the width of the scar initially and is lengthened as necessary to achieve the intended release. Prior infiltration of the area with lidocaine containing epinephrine in 1 : 400 000 concentration is useful in obtaining hemostasis and later pain control. The incision must be made with caution to avoid injuring major vessels and nerves. This is achieved by using a pushing instead of a slicing motion with a surgical blade to free the scarred tissues. The extent of release is assessed by the improvement of joint motion gained as the scarred tissue is severed.

In rare instances, cicatricial changes could involve the joint capsule. Then, reconstruction of the capsular structure will be necessary.

Z-Plasty Technique. A contracted area can be lengthened by use of the z-plasty technique.[9] The technique utilizes the principle that a contracted wound is lengthened by interposing two triangular skin flaps mobilized from an unburned area immediately adjacent to the area of release. The lengthening of the wound is maximally attained by interposing two triangular flaps of 60-degree angles. While the z-plasty technique is an excellent means to ameliorate the problem of wound contracture, it is not feasible if the amount of uninjured skin adjacent to the wound is limited.

Wound Coverage

There are six basic techniques of wound coverage. Namely:

a. Primary closure of the wound
b. A full-thickness or partial-thickness skin graft
c. An interposition skin flap mobilized from the area adjacent
d. Combination of an interposition skin flap and skin grafting
e. A muscle or skin-muscle flap mobilized from the adjacent area
f. A free skin or skin-muscle flap harvested from a distant site and transferred via a microsurgical technique.

Primary Closure of the Wound. Wound closure *per primum* following burn scar excision is difficult if not entirely impossible. Inelasticity of the skin surrounding the wound and an inadequate amount of uninjured skin available for mobilization and closure preclude the use of this method of wound closure. Closure of a resultant wound following release, in practice, would defeat the original objective of contractural reconstruction.

Skin Grafting Technique. The use of a skin graft, full or partial thickness, to cover a wound is the most fundamental technique of wound coverage; it is technically simple and has minimal morbidities.

OPERATIVE TECHNIQUE. A *partial-thickness skin graft* of 15/1000th to 20/1000th inch in thickness is harvested from an unburned area using a dermatome. The scalp, lower abdomen, and the anterior surface of the upper thigh are common donor sites.

A *full-thickness skin graft* can be harvested from the lower abdomen, above the suprapubic or inguinal area, without leaving unsightly donor site defects. The subdermal fatty tissues are removed but attempts should be made to preserve the subdermal capillary plexus (Fig. 53.11). The donor defect is usually closed primarily.

The graft is cut to fit the defect and the edges are anchored with 3-0 silk sutures. The ends are left sufficiently long to tie over a bolster to immobilize the graft. Several anchoring mattress stitches using 4-0 or 5-0 chromic catgut sutures may be placed in the center of the graft to immobilize the skin graft against the base. Hemostasis around the recipient site is essential. Hematoma formed underneath the graft will hinder the "take" of the graft.

AFTER-CARE. The bolster is usually removed 4–5 days after the procedure. Bodily fluid or blood elements accumulated underneath the graft (i.e., seroma and/or hematoma) are evacuated. This is achieved by making a small nick in the graft with a pair of surgical scissors. The fluid is "rolled" out with a cotton tip applicator. The joint is immobilized immediately, and a pressure dressing is used to minimize the consequence of contracture. Physical exercise is resumed 3 weeks after the surgery.

Interposition Flap Technique. This technique, known by various names such as the three-quarter z-plasty technique or the banner flap interposition technique, is the most useful method of wound coverage following a releasing procedure for a contracted joint. The technique is based on the principle that an open wound consequential to surgical release may be covered with a skin flap mobilized from an adjacent area. While the flap design is technically simple, it requires an area of movable tissue containing as little scar as possible adjacent to the released wound. Smaller defects can be treated with flaps of skin and subcutaneous tissue, although most functionally significant contractures require adjunctive measures to provide effective and durable release. We have found that an interposition flap, with its width tapering at its distal extent, can be fabricated with a length-to-width ratio as high as 5 : 1 by carrying the subjacent fascia with the rotation flap; this flap is the mainstay of our treatment of axillary contractures.[14,15]

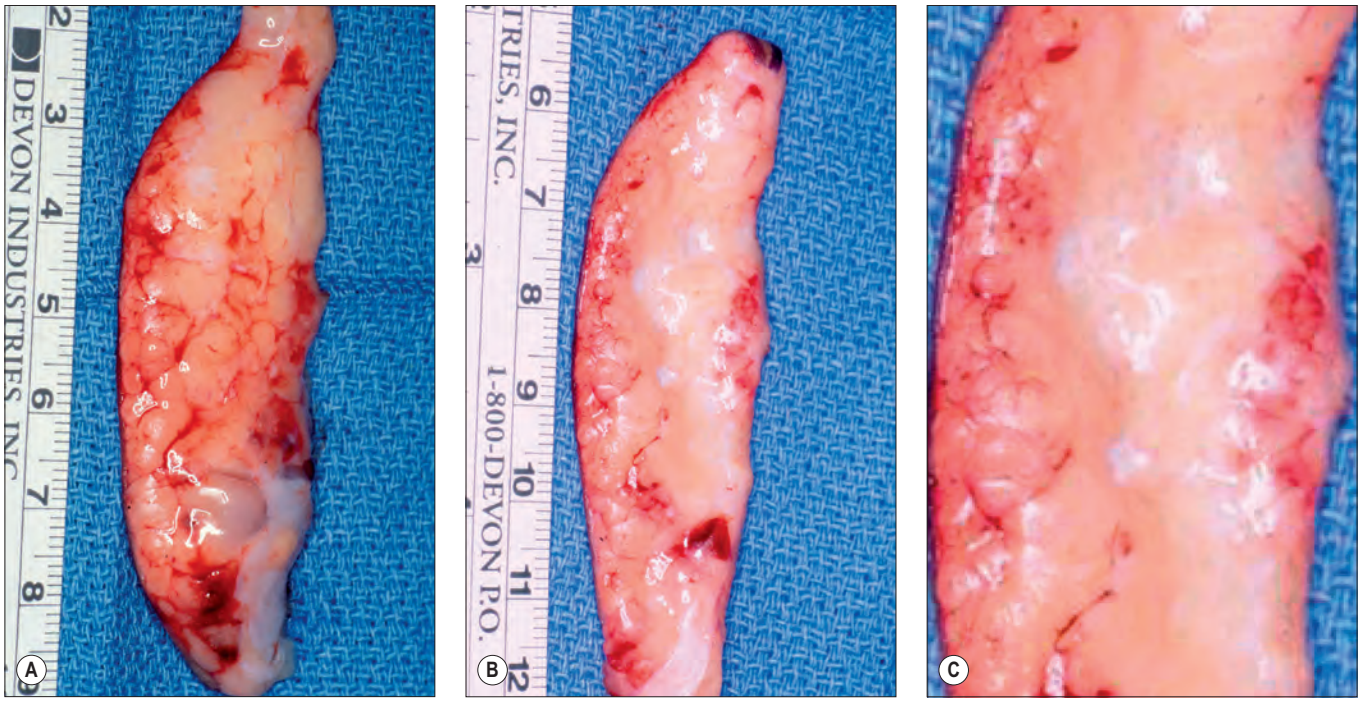

Fig. 53.11 **(A)** A piece of skin with subcutaneous tissues is removed from the abdomen and will be used as a full-thickness skin graft. **(B)** The subcutaneous fatty tissues were sharply removed with a pair of fine scissors. The capillaries were left undisturbed. **(C)** A close-up view to show the capillaries that are left in the graft.

OPERATIVE TECHNIQUE. A triangular skin flap is designed in an unburned area adjacent to the wound following release. A vertical limb of the flap begun at the end of released wound edge is set at a 90-degree angle to the end of the wound. The limb length is equal to the wound length. A triangular flap is formed by making the width of flaps at mid-section the same as the wound width. The flap can be based either proximally or distally depending on the direction of the triangular flap designed. The flap is dissected out and rotated 90 degrees to cover the defect. The flap donor defect is closed primarily. Healing of the wound is usually uneventful (Fig. 53.12).

The width of flap may be narrow in instances where the size of unburned skin is not enough to fabricate a triangular skin flap sufficiently wide to cover the wound. The flap, in such an instance, is anchored in the middle of the wound. The two sides not covered by the flap are closed with a skin graft (Fig. 53.13). For larger or wider defects requiring longer flaps, a fasciocutaneous flap is employed. This flap is designed as above, but the tissue to be mobilized is sharply dissected free "straight-down" to incorporate the outer leaf of the subjacent fascia. It is important to preserve the microcirculatory connections between the fascia and the skin. Occasionally we place a temporary suture between the edge of the fascia and its skin edge above while the flap is mobilized. A 5 : 1 or greater length-to-width ratio is possible using this technique. Superficial epidermolysis of the most distal aspect of the flap may occur but rarely is of clinical significance and resolves with local wound care over the course of 1–3 weeks.

AFTER-CARE. The wound edges are kept clean with antibiotic ointment. Sutures may be removed in 10 days. Splinting of the joint may be resumed within 4–5 days and joint exercise in 10–14 days.

Muscle Flap or Skin-Muscle Flap Technique. The technique is utilized in instances where the resultant defect following release is so extensive that coverage of the wound with a skin flap or a skin graft is not feasible.

While the latissimus dorsi muscle harvested either as a muscle flap or as a musculocutaneous flap may be used to cover the axillary defect, the soleus muscle flap or the gastrocnemius muscle-skin flap may be used to cover the wound around the knee joint (Fig. 53.14). A fasciocutaneous flap may similarly be fabricated to cover a tissue defect consequential to surgical release of a contracted joint (Fig. 53.15).

Use of a Free Flap or Muscle Flap. Although most of the major joint deformities could be reconstructed with the techniques described, the use of microsurgical technique may be occasionally necessary to transfer a segment of soft tissue from a distant donor site.

Of the varieties of flap available, we prefer the use of an anterior lateral thigh (ALT) perforator flap.[16,17] The vascular supplies to the skin around the anterior section of the upper thigh are consistent, so preparation of a flap is therefore technically simple. While the morbidities attributable to flap harvest are generally minimal, the flap can be bulky; secondary procedures to thin down a flap are often necessary (Fig. 53.16). Instead, a muscle flap may be used. The tissue bulkiness may be curtailed by using a skin graft (Fig. 53.17).

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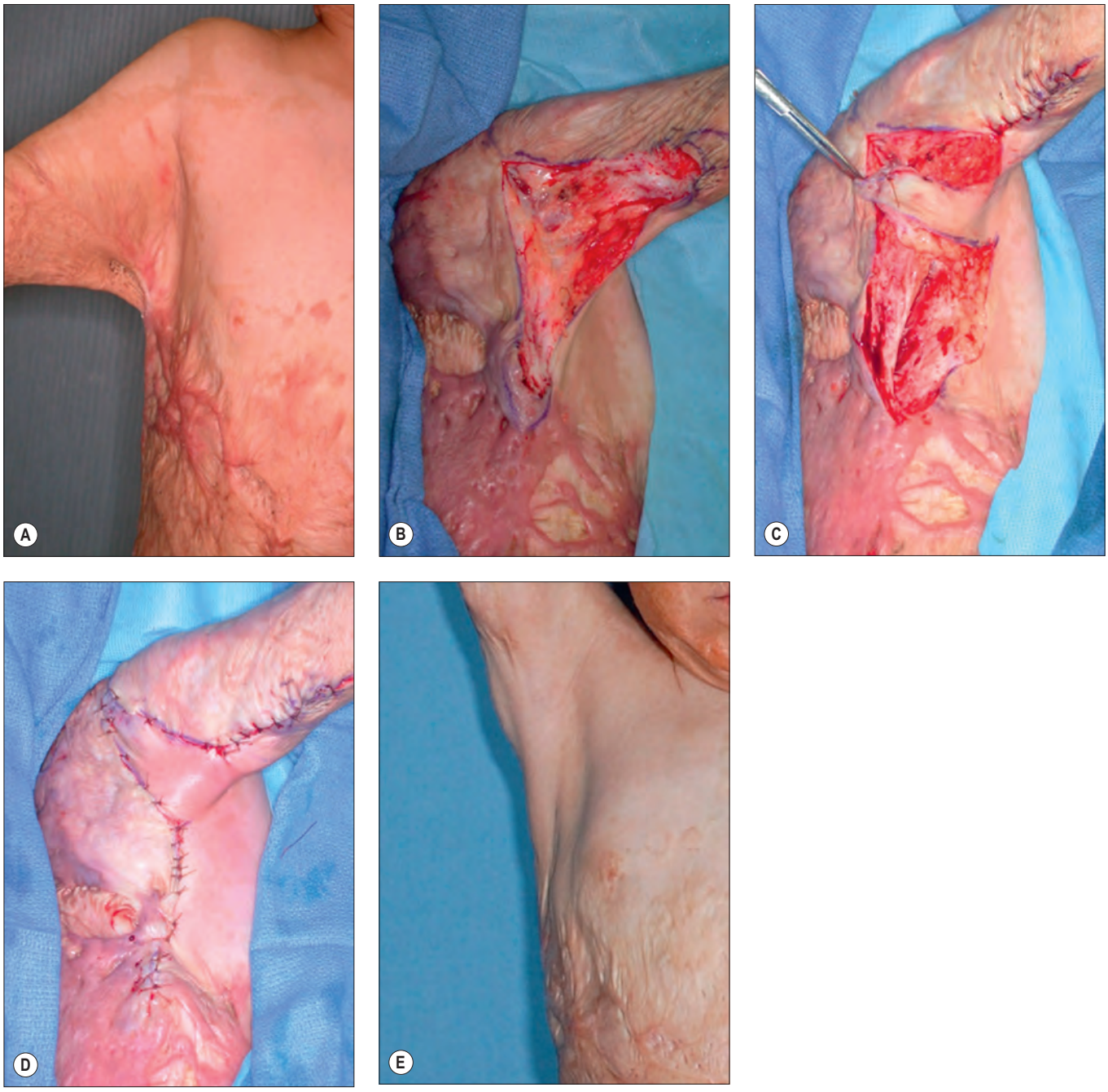


Fig. 53.12 **(A)** An interpositional skin flap technique (i.e., a modified z-plasty technique) is useful in reconstructing a flexion/adduction deformity around the joint, as seen in this 12-year-old individual who had sustained burn injuries around the right axilla. **(B)** An incision made across the area with maximal contraction resulted in a large tissue gap of 12 × 5–6 cm. **(C)** A triangular skin + fascia flap was mobilized from the lateral upper chest area and was rotated 90 degrees posteriorly to cover the wound. **(D)** The donor site was closed primarily. **(E)** The appearance of the wound 2 years following reconstruction.

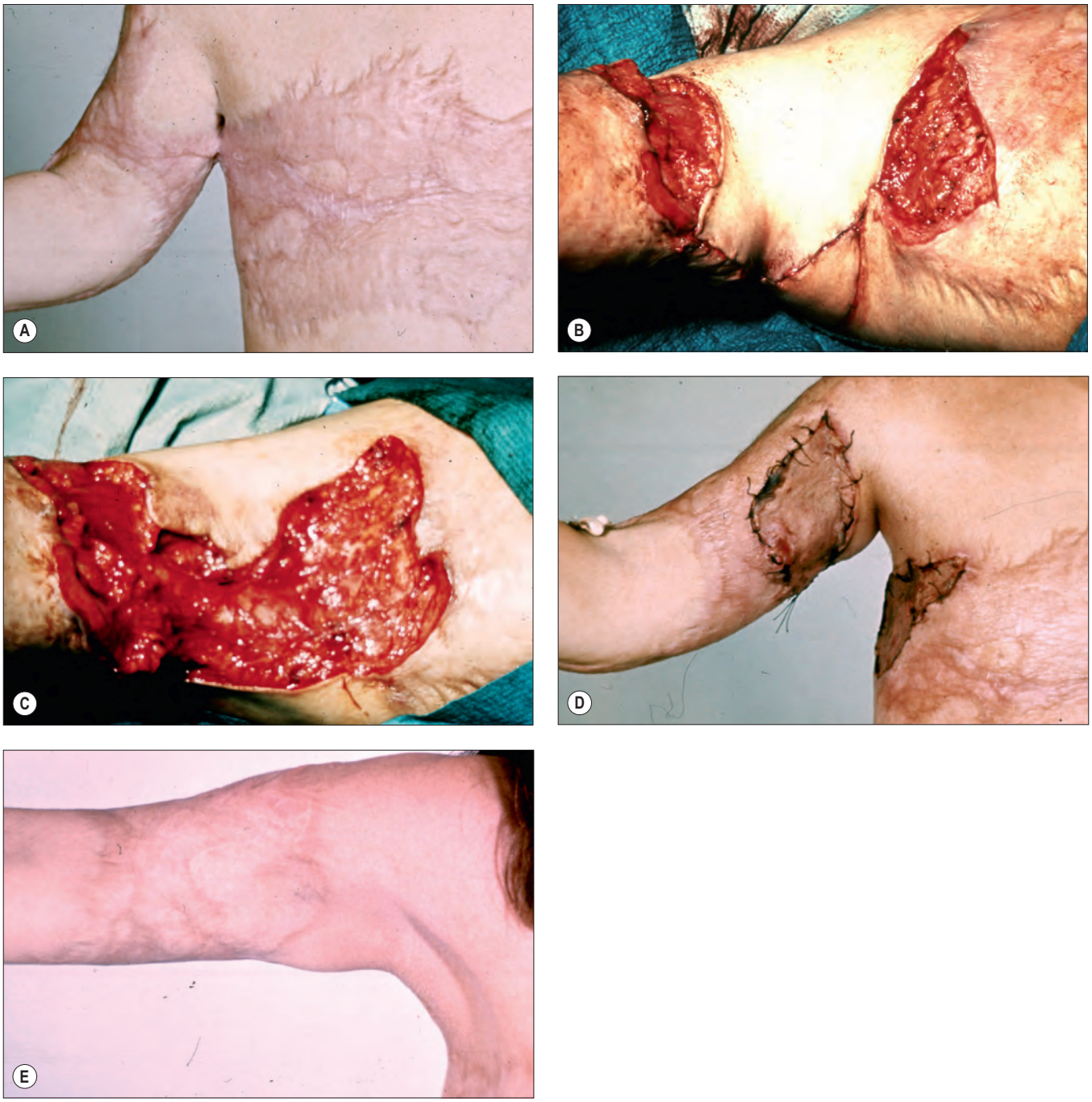


Fig. 53.13 **(A)** An interpositional skin flap technique of wound closure may be modified, as in this 5-year-old girl who had sustained burns around the right axilla that caused contracture of the axillary joint. **(B)** The skin defect was so extensive that it could not be covered completely with a single flap. **(C)** The uninjured skin raised as a flap was transferred to the middle of the wound, leaving the areas proximal and distal to the flap to be covered with skin grafts. **(D)** The appearance of the wound 10 days following the surgery. **(E)** The appearance of the wound 10 years after surgery. The flap placed in the middle of the wound had increased in size because of body growth and stretching of the scar tissues.

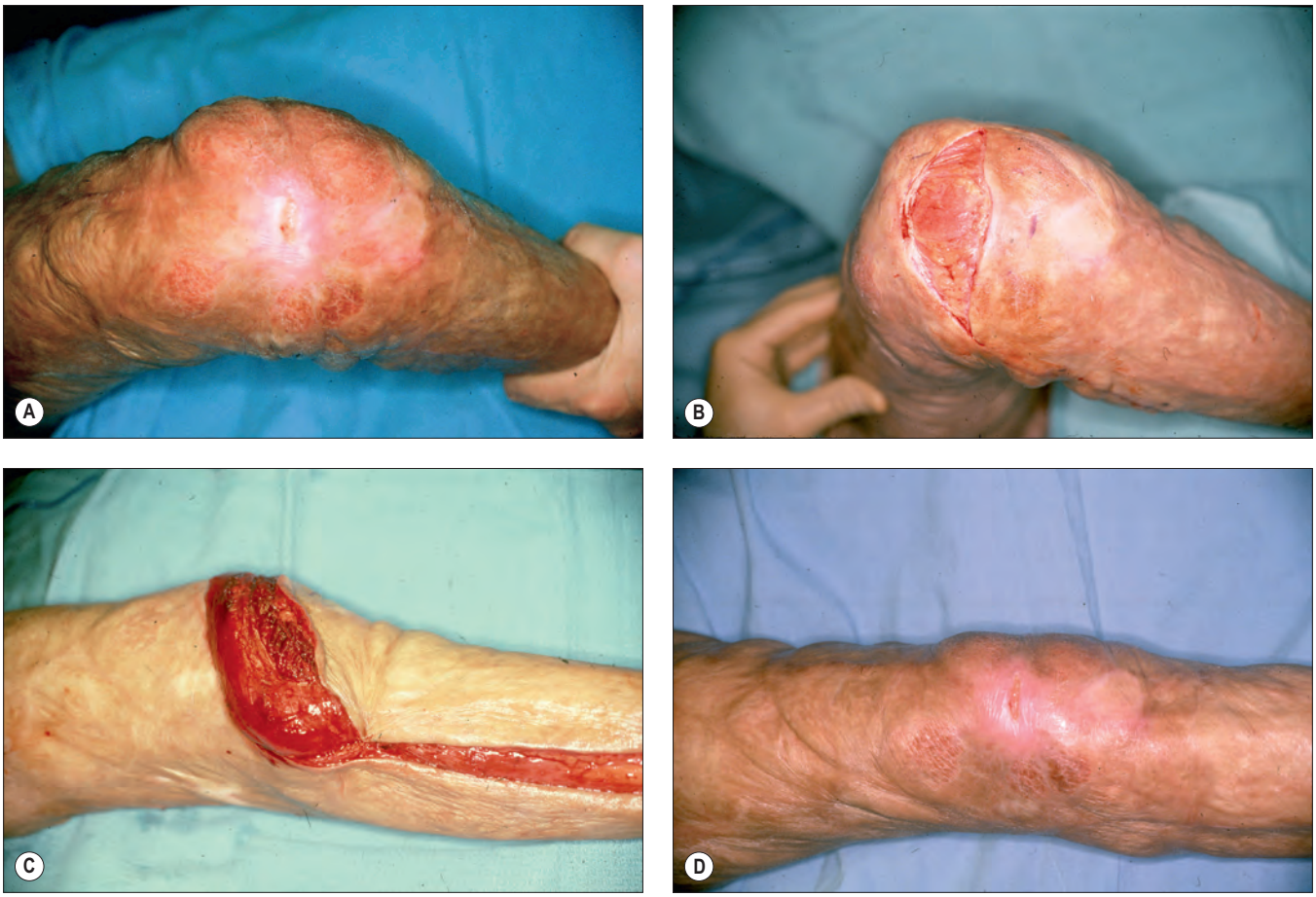


Fig. 53.14 (A) Flexion of the knee was limited because of tight scars around the patella. **(B)** An incisional release of the tight area across the patella provided relief of knee contracture. However, it resulted in an open wound of 4–5 cm in size. **(C)** A medial segment of the soleus muscle was used to cover the defect. **(D)** The appearance of the knee area 3 months following the procedure.

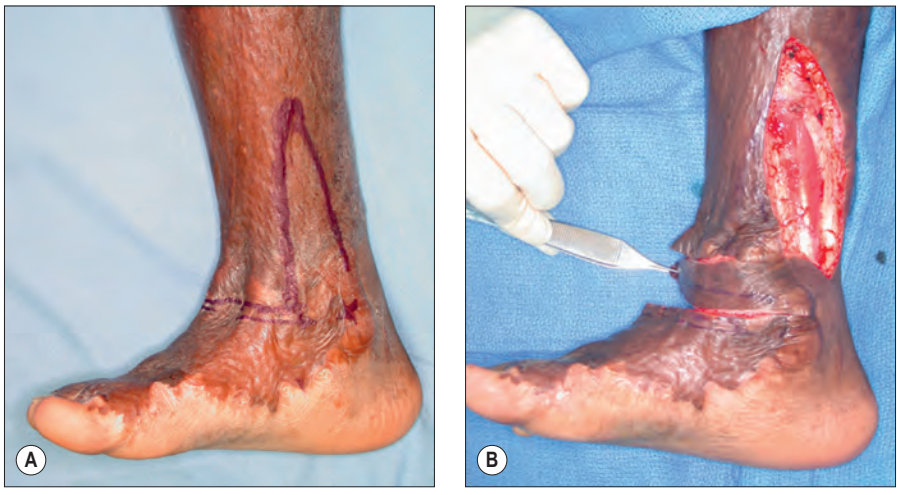


Fig. 53.15 (A) A moderate degree of dorsiflexion contracture involving the right ankle of a 6-year-old boy required release. A triangularly shaped skin + fascia flap was marked over the medial side of the lower leg. **(B)** A fasciocutaneous flap was fabricated and rotated 90 degrees anteriorly to cover a tissue defect consequential to contractural release.

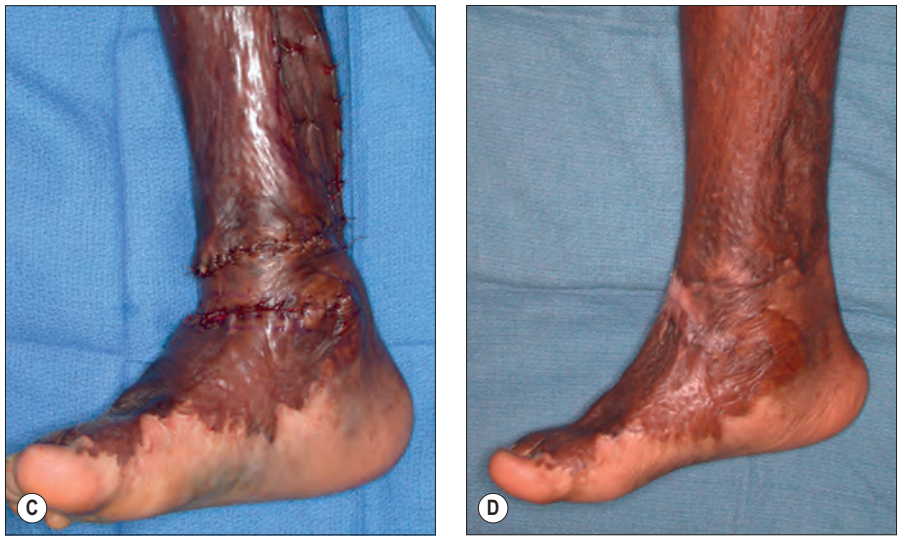


Fig. 53.15, con'd (C) The closure of the flap donor site required the use of a skin graft. Healing was uneventful. **(D)** The appearance of the right ankle area 18 months following surgery.

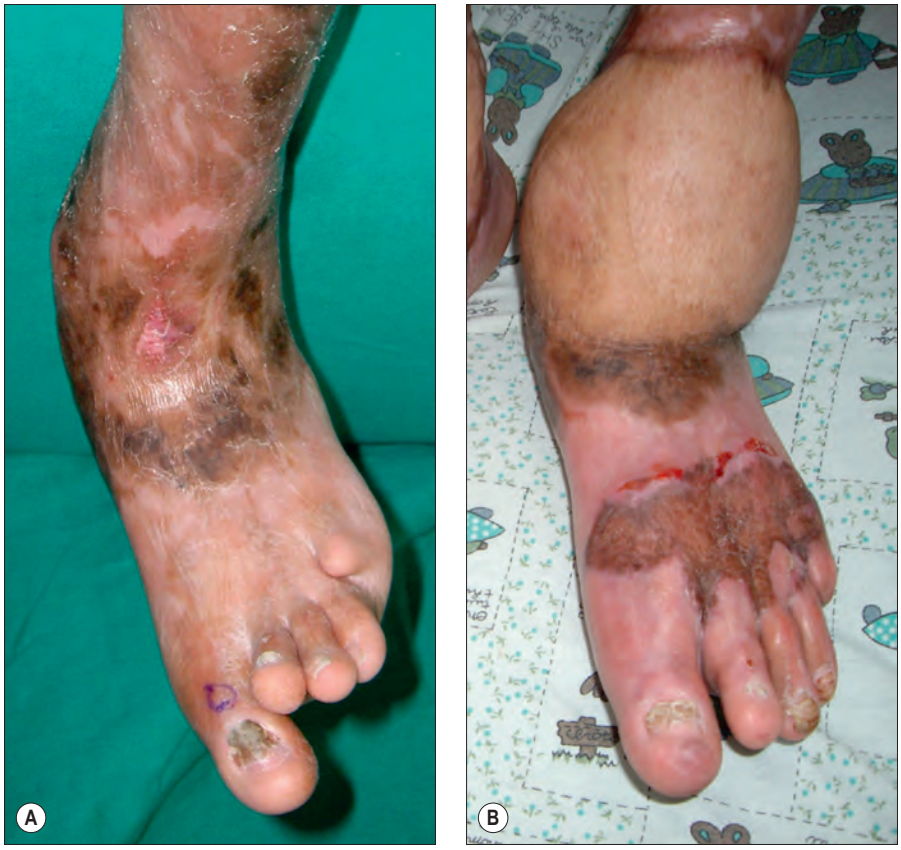


Fig. 53.16 (A) An anterior lateral thigh (ALT) perforator flap was used to reconstruct an ankle contracture deformity. **(B)** While wound coverage was achieved, the tissue was noted to be bulky, requiring secondary debulking procedures.

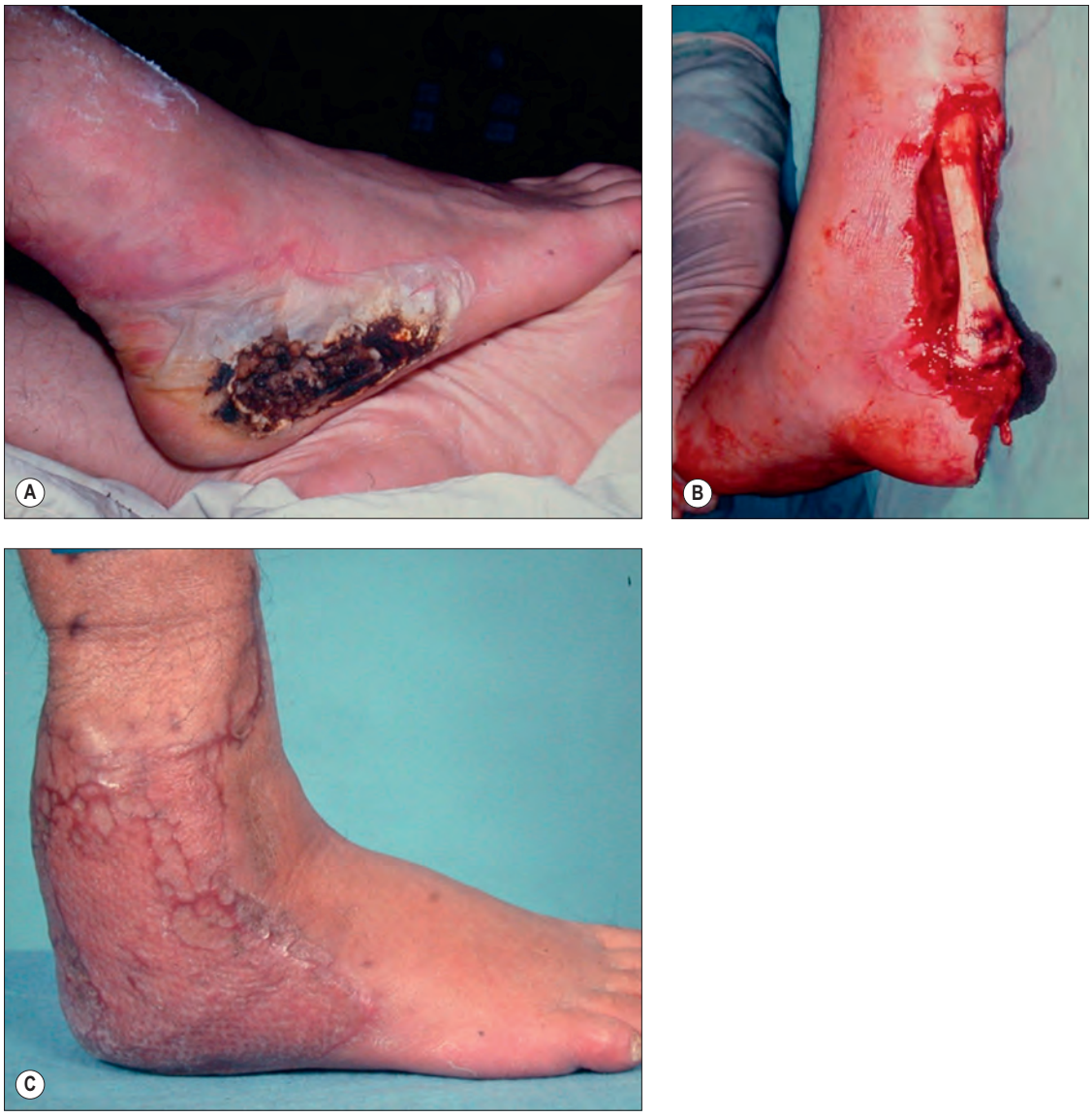


Fig. 53.17 **(A)** The patient had sustained electrical burns resulting in tissue loss over the right heel area. **(B)** Wound débridement resulted in a large soft tissue deficit exposing the Achilles tendon. A muscle flap was transferred via microsurgical means to cover the wound. The muscle was covered with a skin graft. **(C)** Healing was uneventful.

Conclusion

Contractural deformities of the shoulder (axilla), elbow, hip, and knee joints are commonly encountered after burn injuries. Although the injury involving limbs and joint structures could alone account for the deformities encountered, lack of proper positioning and inadequate physical exercise while recovering from injuries exacerbates these problems.

The use of braces, splinting, and pressure dressing is important in minimizing such an undesirable consequence of burn injuries. The treatment for an established joint deformity, on the other hand, requires surgical release of the contracted skin and scars. In this chapter, various methods of reconstruction have been described to manage the problems encountered and to outline the approach of managing contractural deformities involving the shoulder (axilla), elbow, hip, and knee joints. The interposition of an intact "integumentary functional unit" comprising epidermal, dermal, adipose, and fascial tissues with native nervous, vascular, and lymphatic connections allows release of the intrinsic tissue tension driving scar hypertrophy and contraction. Accumulating cellular evidence indicates that this mechanically transduced signal may lead to myofibroblast apoptosis and more rapid resolution of scar hypertrophy (Figs. 53.18 and 53.19).[18,19]

Complete references available online at www.expertconsult.inkling.com

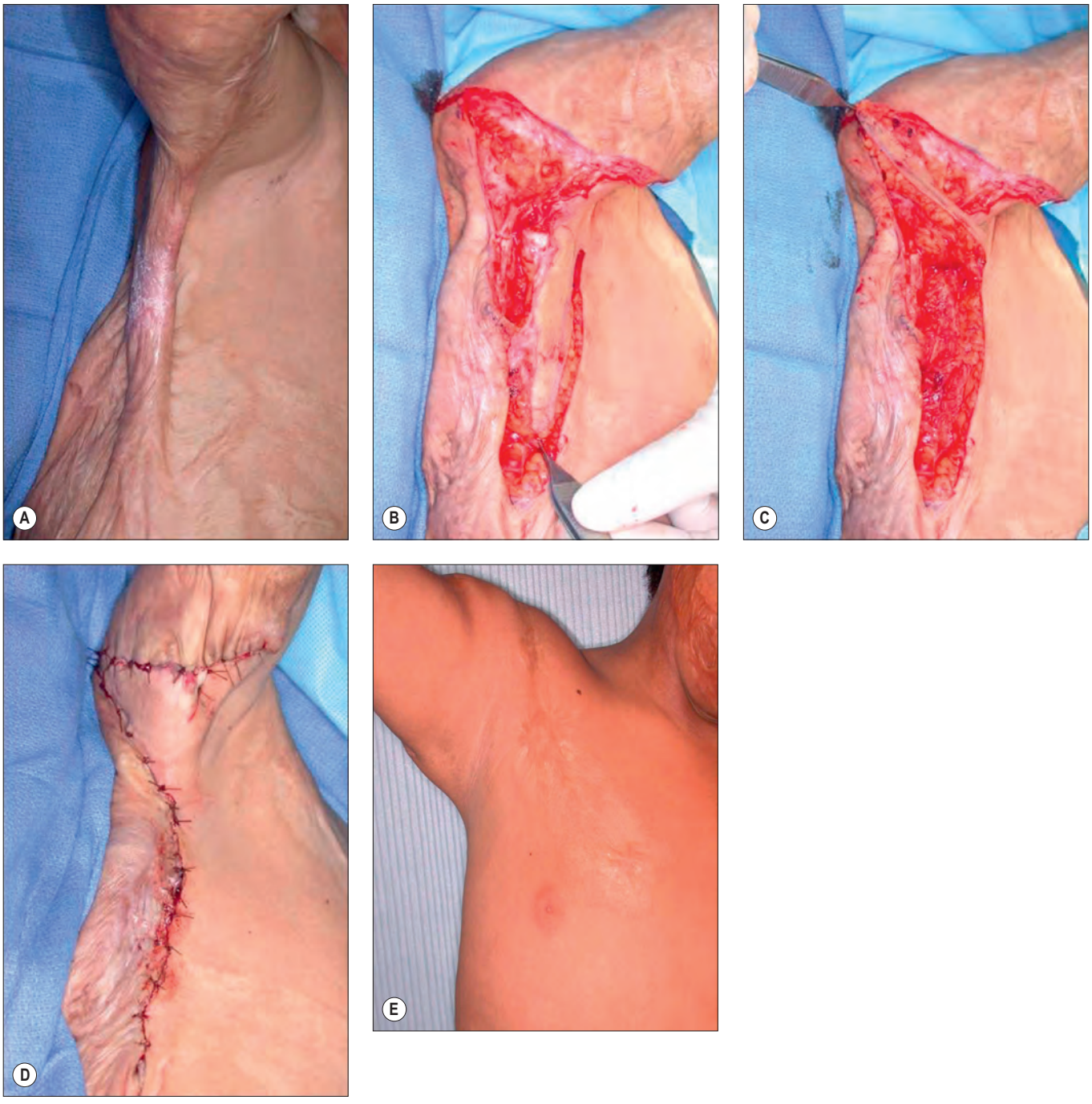


Fig. 53.18 **(A)** Preoperative contracture appearance. **(B–D)** Operative technique of contracture release and three-quarters random fasciocutaneous Z-plasty flap interposition. **(E)** Appearance 2 years after release.

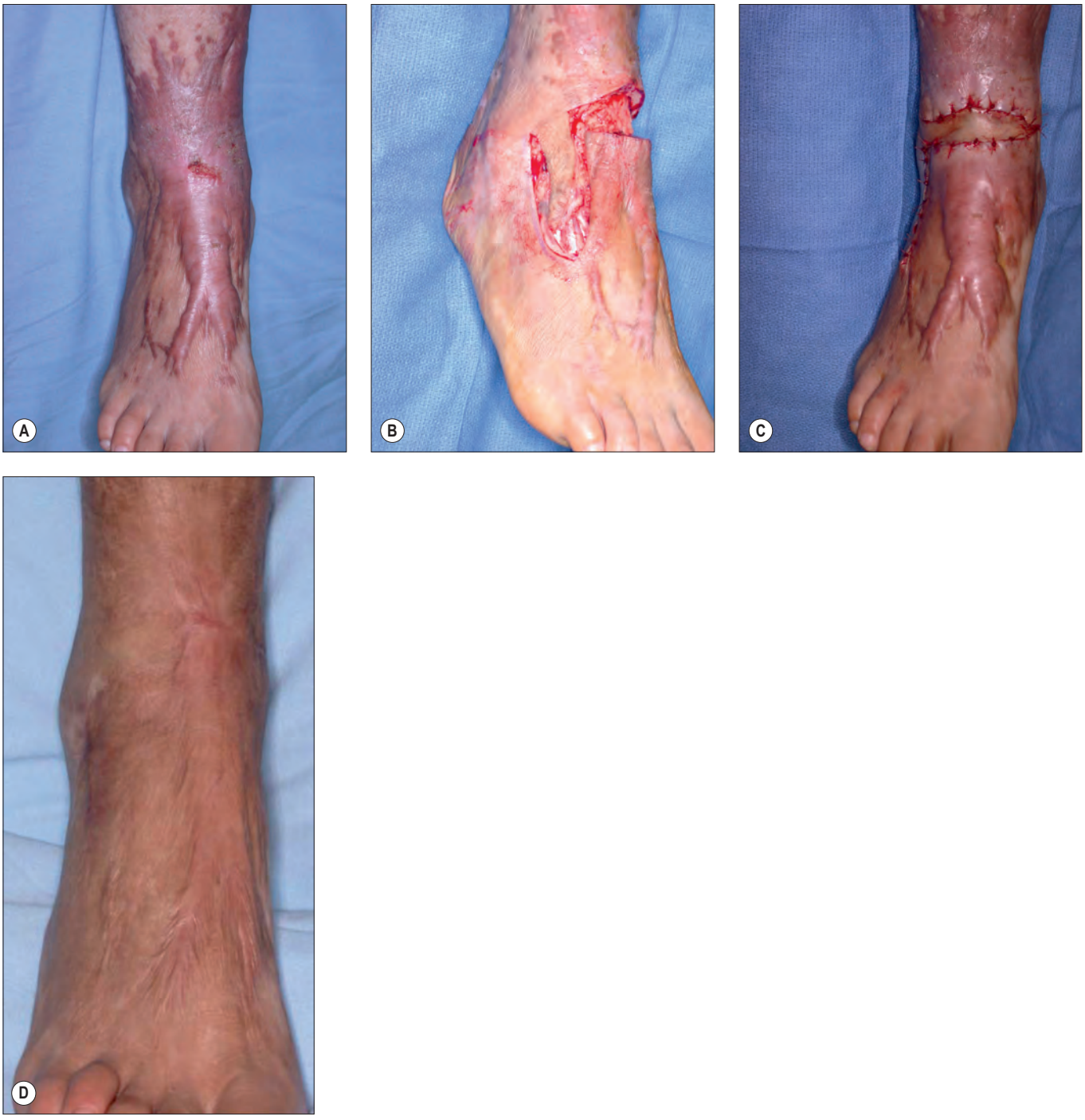


Fig. 53.19 (A) Preoperative contracture appearance. **(B** and **C)** Operative technique of contracture release and three-quarter random fasciocutaneous Z-plasty flap interposition. **(D)** Appearance 3 years after release.

Further Reading

Huang TT, Blackwell SJ, Lewis SR. Ten years of experience in managing patients with burn contractures of axilla, elbow, wrist, and knee joints. *Plast Reconstr Surg*. 1978;61:70-76.

Kuo YJ. Experience of ALT flap. *Ann Plast Surg*. 2002;48:161-166.

Larson DL, Abston S, Evans EB, et al. Contractures and scar formation in the burn patient. *Clin Plast Surg*. 1974;1:653-666.

Larson DL, Evans EB, Abston S, et al. Techniques for decreasing scar formation and scar contractures in the burn patient. *J Trauma*. 1971;11:807-823.

Linaris HA, Larson DL, Willis-Galstaum BA. Historical notes on the use of pressure in the treatment of hypertrophic scars or keloids. *Burns*. 1993;19:17-21.

References

1. Agarwal S, Loder S, Brownley C, et al. Inhibition of Hif1alpha prevents both trauma-induced and genetic heterotopic ossification. *Proc Natl Acad Sci USA*. 2016;113(3):E338-E347.
2. Levi B, Jayakumar P, Giladi A, et al. Risk factors for the development of heterotopic ossification in seriously burned adults: a National Institute on Disability, Independent Living and Rehabilitation Research burn model system database analysis. *J Trauma Acute Care Surg*. 2015;79(5):870-876.
3. Schneider JC, Simko LC, Goldstein R, et al. Predicting heterotopic ossification early after burn injuries: a risk scoring system. *Ann Surg*. 2016 Jun 24;[Epub ahead of print].
4. Cronin TD. Successful corrections of extensive scar contractures of the neck using split thickness skin grafts. Trans First International Congress on Plastic Surgery. 1957;123.
5. Willis B. A follow-up. The use of orthoplast isoprene splints in the treatment of the acutely burned child. *Am J Occup Ther*. 1970;24(3):187-191.
6. Larson DHT, Linaris H, et al. Prevention and treatment of scar contracture. In: Artz CPMJ, Pruitt BA, eds. *Burns A Team Approach*. Philadelphia: WB Saunders; 1979.
7. Larson DL, Abston S, Evans EB, Dobrkovsky M, Linares HA. Techniques for decreasing scar formation and contractures in the burned patient. *J Trauma*. 1971;11(10):807-823.
8. Larson DL, Abston S, Willis B, et al. Contracture and scar formation in the burn patient. *Clin Plast Surg*. 1974;1(4):653-656.
9. Huang TT, Blackwell SJ, Lewis SR. Ten years of experience in managing patients with burn contractures of axilla, elbow, wrist, and knee joints. *Plast Reconstr Surg*. 1978;61(1):70-76.
10. Baur PS, Larson DL, Stacey TR. The observation of myofibroblasts in hypertrophic scars. *Surg Gynecol Obstet*. 1975;141(1):22-26.
11. Linares HA, Kischer CW, Dobrkovsky M, Larson DL. On the origin of the hypertrophic scar. *J Trauma*. 1973;13(1):70-75.
12. Linares HA, Larson DL, Willis-Galstaun BA. Historical notes on the use of pressure in the treatment of hypertrophic scars or keloids. *Burns*. 1993;19(1):17-21.
13. Neugebauer CT, Serghiou M, Herndon DN, Suman OE. Effects of a 12-week rehabilitation program with music & exercise groups on range of motion in young children with severe burns. *J Burn Care Res*. 2008;29(6):939-948.
14. Ponten B. The fasciocutaneous flap: its use in soft tissue defects of the lower leg. *Br J Plast Surg*. 1981;34(2):215-220.
15. Chen B, Song H, Gao Q, Xu M. Pedicled fasciocutaneous flaps for correcting scar contracture in pediatric patients-a retrospective study of 22 cases. *J Pediatr Surg*. 2016;51(7):1207-1215.
16. Kuo YR, Seng-Feng J, Kuo FM, Liu YT, Lai PW. Versatility of the free anterolateral thigh flap for reconstruction of soft-tissue defects: review of 140 cases. *Ann Plast Surg*. 2002;48(2):161-166.
17. Mardini S, Tsai FC, Yang JY. Double free flaps harvested from one or two donor sites for one or two-staged burn reconstruction: models of sequential-link and independent-link microanastomoses. *Burns*. 2004;30(7):729-738.
18. Junker JP, Kratz C, Tollback A, Kratz G. Mechanical tension stimulates the transdifferentiation of fibroblasts into myofibroblasts in human burn scars. *Burns*. 2008;34(7):942-946.
19. Hinz B, Mastrangelo D, Iselin CE, Chaponnier C, Gabbiani G. Mechanical tension controls granulation tissue contractile activity and myofibroblast differentiation. *Am J Pathol*. 2001;159(3):1009-1020.

54 Acute and Reconstructive Care of the Burned Hand

DEREK M. CULNAN, KAREL D. CAPEK, TED HUANG, and WILLIAM LINEAWEAVER

Introduction

The hand is a primary means of communication, aesthetics, emotion, and sexuality. It exists at the core of our humanity. Particularly in the modern age of digital communication, the inability to interface with the digital world via hands is socially and intellectually isolating. Hands are injured in 80% of severe burns and are a primary American Burn Association referral criterion. Loss of hand function from burn injury frequently limits the patient's ability to work and requires evaluation for long-term disability, as discussed in Chapter 63. Functional recovery of the burned hand relies on quick and effective intervention by an experienced burn center.

Initial Assessment and First Aid

Successful restoration of hand function after burn injury begins with first aid, continues through acute care and occupational therapy (OT), and is augmented with reconstructive surgery. A careful history should be taken including the nature of the injury, but also of the patient's hand dominance, occupation, and special hand uses, such as playing a musical instrument.

Initial treatment is directed to prevent both further injury and conversion of the burn penumbra. First, the burning process must be stopped by removing the patient from the heat source and irrigating away any inciting chemicals. Historically, icing the burn had been advocated;[1] however, in modern burn care, maintaining the wound warm is now standard, and ice should be avoided. Blisters should be débrided both to allow assessment of the underlying burned dermis as well as to remove the cytotoxic mediators elaborated in the blister fluid, which can deepen the burn injury.[2]

The burn should be staged for depth at physical examination, and the patient should have an initial assessment of sensation, motor function, skeletal stability, and circulation (Fig. 54.1). The thin dorsal skin can easily suffer a third- or fourth-degree injury, whereas the thick glabrous palmar skin can often heal from even an apparently deep injury. Initial assessment is aimed at gross and limb-threatening injuries. Distracting injuries, pain, and fear can prevent an effective assessment of less obvious injuries, so patients should be followed up and reassessed.

Careful and repeated assessments must be made for compromised perfusion due to compartment syndromes and circumferential eschar constriction. These processes are limb threatening, and a high index of suspicion and prompt response must be maintained. Edema resulting from burn injury and burn resuscitation can cause a delayed appearance of compartment syndrome and eschar compression. Wound edema control is best accomplished with elevation. As discussed in Chapter 8, lymph pressures are typically in the 1–2 cm H_2O range, and this gradient can often be overcome with elevation by suspending the hand 50–100 cm above the phlebostatic axis, thereby creating a sufficient pressure gradient driving lymphatic drainage. Wounds should be dressed in a manner such that the burned hands can be monitored for neurovascular embarrassment and progression of the burned wounds (see Box 54.1).

Acute Care of the Burned Hand

The goals of acute management of hand burns include maintaining perfusion with resuscitation, neurovascular protection through the release of eschar compression and compartment syndromes, removal of necrotic burned tissue, early grafting, and early ROM. Resuscitation and hemodynamic support are critical because the heart is the organ that perfuses the hands. Should eschar compression or compartment syndrome develop, prompt decompression is critical for limb salvage. Clinical examination is usually sufficient to diagnose eschar compressions and compartment syndromes, including paresthesias, pain, passive resistance to extension, and loss of capillary refill in the nail beds.

Escharotomies are the mainstay of decompression in burn care. Incisions are made over the medial and lateral midaxial lines through the skin down to the fascia. The line of release extends both caudad and cephalad beyond the margin of tissue swelling to ensure complete release. Incisions on fingers are made along the midlateral line just dorsal to the digital neurovascular bundle between Grayson's and Cleland's ligaments.[3] Releasing incisions may be extended into the web spaces and to the dorsal surface of the hand to ensure the integrity of vascular supplies to the intrinsic musculatures of the hand. Many centers promote routine performance of escharotomies on both sides of fingers, and we advocate this approach. In a randomized control trial (RCT), a threefold increase in finger salvage was found with extended digital escharotomies.[4] Escharotomies should be carried out liberally because all full-thickness burns will eventually require excision and grafting, including resection of the escharotomy incisions, as seen in Fig. 54.2D, E.

Deep hand and arm burns may be insufficiently decompressed with escharotomies alone; release of fascial compartments will be required. Incisional releases may be carried out involving the forearm muscle compartment and

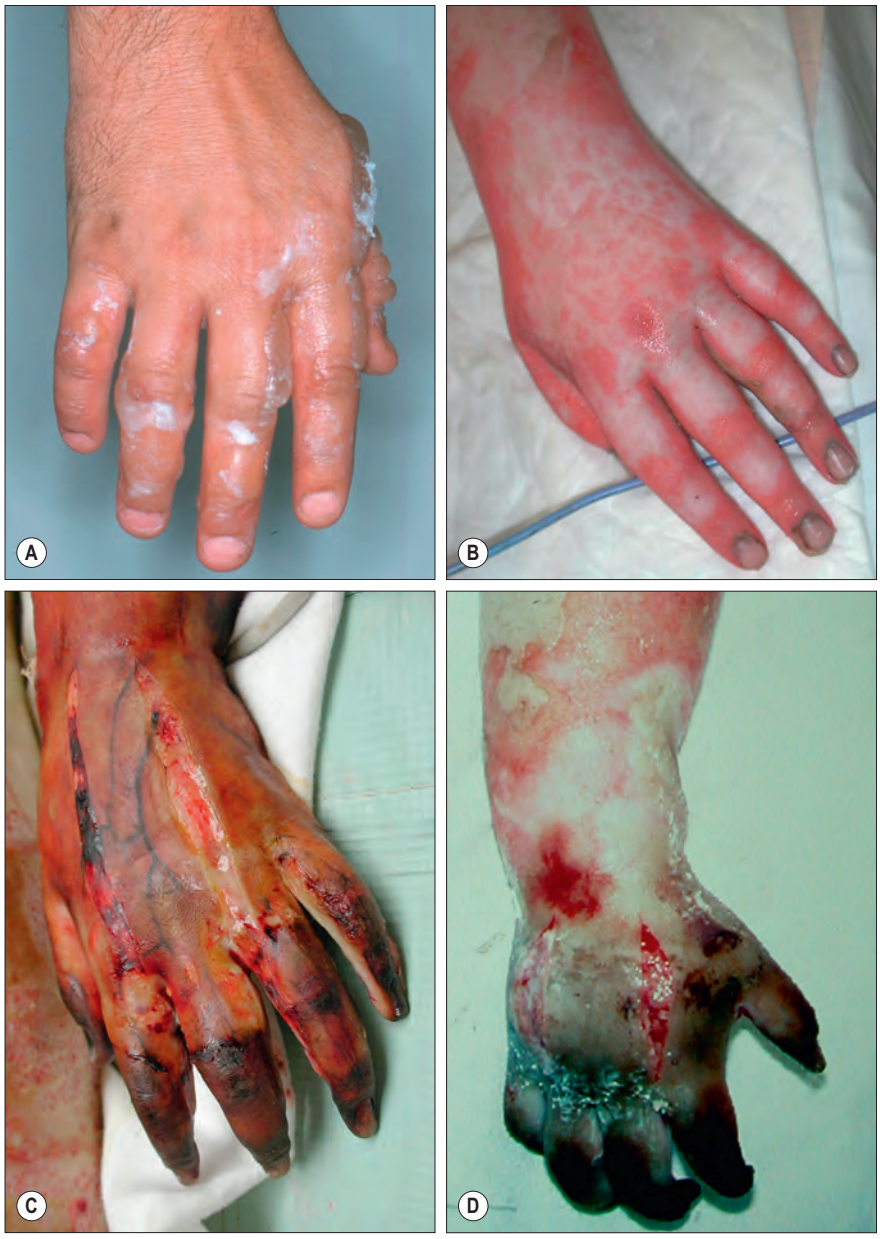


Fig. 54.1 Examples of burned hands. **(A)** A hand that has sustained a first- and second-degree, superficial partial-thickness burn with intact blisters. **(B)** Second-degree burn that is deep partial-thickness, typified by pallor mixed with erythematous changes (e.g., mottling). **(C)** Findings of skin anesthesia and vessel thrombosis suggest full-thickness, third-degree skin burn. **(D)** Carbonization suggests a complete destruction of the structures consistent with a deep, fourth-degree burn.

Box 54.1 Management Priorities of the Burned Hands

1. Evaluate burn and débride blisters
2. Decompression of compartment syndromes and eschar constrictions
3. Early therapy and splinting
4. Early excision and grafting
5. Early and aggressive range of motion (ROM) with occupational therapy
6. Secondary reconstruction of deformities

the carpal tunnel, as well as Guyon's canal (Fig. 54.2). The intrinsic muscles of the hand are particularly susceptible to elevated compartment pressures. These muscles infarct and contract, leading to an intrinsic-minus (claw) hand, discussed later. As such, care should be taken to release the interosseous compartments dorsally, the thenar and hypothenar compartments, and the palmar spaces as shown in Fig. 54.2C. The carpal tunnel and Guyon's canal should routinely be released as part of treatment of compartment syndromes of the hand.

The next goal of therapy is management of the skin injury. Partial-thickness burns to the dorsum of the hand are effectively treated with local care, skin substitutes, and immediate motion. If minimal superficial eschar is present, débridement can be achieved either operatively or with an enzymatic agent such as collagenase. Standard skin substitutes include homograft, xenograft, and ammonic membrane, which provide a durable covering, a wound matrix, growth factors to stimulate wound healing, and minimize chronic wound granulation tissue formation. In recent decades engineered skin substitutes (Integra, TransCyte, Hyalomatrix) provide a similar skin substitution covering and matrix in an acellular manner further discussed in

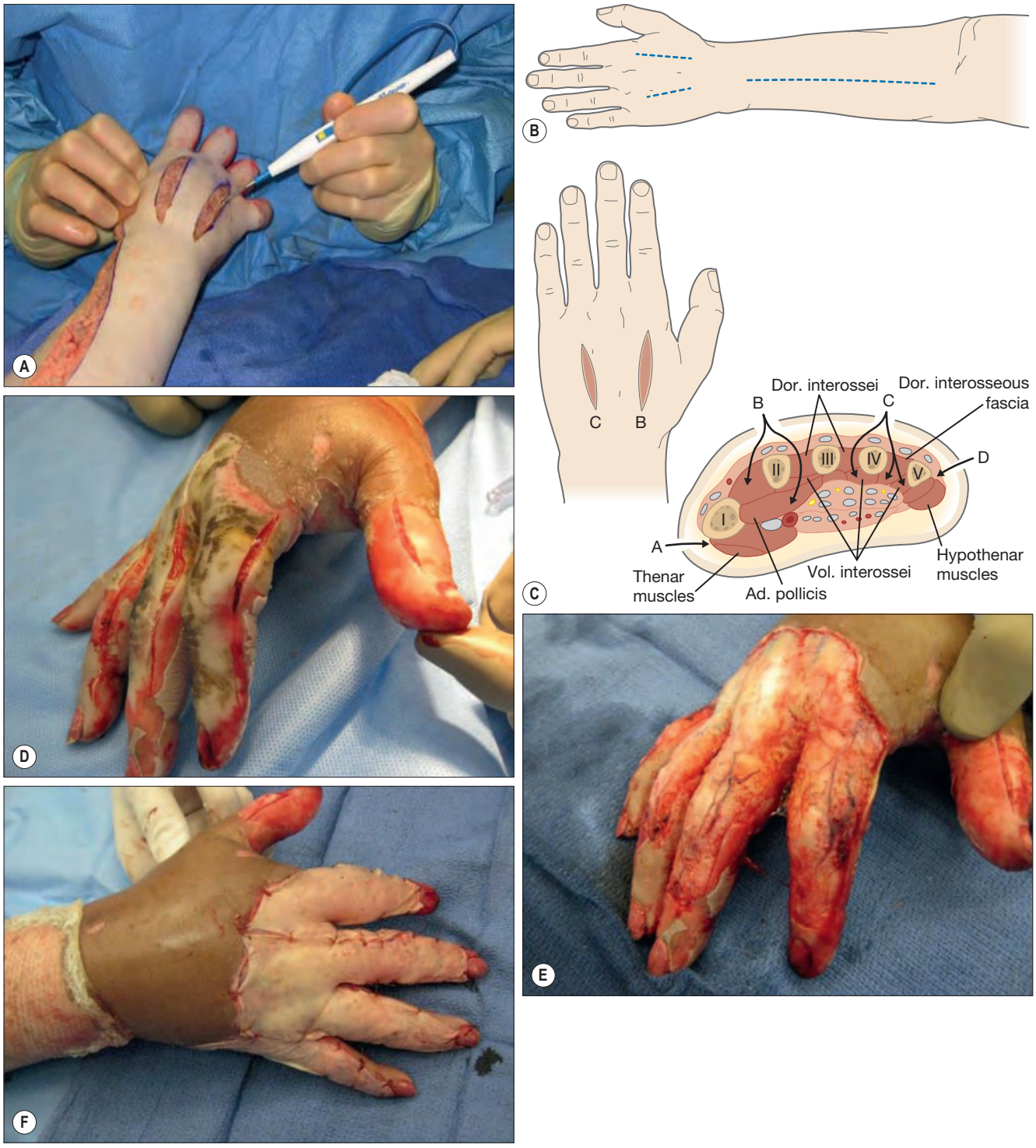


Fig. 54.2 Upper extremity escharotomies and fasciotomies. **(A)** A patient having completion of dorsal escharotomy incisions. **(B)** Drawing of dorsal fasciotomy locations. **(C)** Drawing of dorsal hand fasciotomy locations and a cross-section demonstrating the access to decompress all the compartments of the hand. Note the dorsal incisions decompressing the four dorsal interosseous compartments (incisions B and C), as well as accessing the adductor pollicis compartment via the second dorsal interosseous. The thenar muscles are decompressed via incision "A" volarly and radially, and the hypothenars are decompressed via incision "D" volarly and ulnarly. **(D)** Example of digital escharotomy incisions. **(E)** Subsequent escharotomy demonstrating that escharotomy incisions should be made liberally because all eschar will be subsequently resected. **(F)** Placement of homograft on escharotomized fingers, secured with sutures. (A, D, E, and F are courtesy of Dr. Lineaweaver; B and C are used with permission from Rowland S. Fasciotomy: the treatment of compartment syndrome. In: Green DP, ed. *Operative hand surgery*. vol. 1, 2 edn. New York: Churchill Livingstone; 1988: 678-679.)

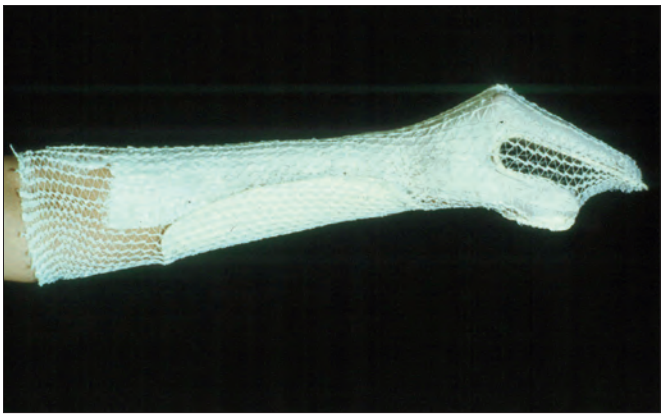


Fig. 54.3 Example of thermoplastic hand splinting. A hand splinted in intrinsic-plus position, also known as the "safe position." The distal interphalangeal–proximal interphalangeal (DIP-PIP) joints are maintained at full extension, metacarpophalangeal (MCP) joints at 70 degrees flexion, and the wrist at 30 degrees extension.

Chapter 15.[5] Other synthetic dressing materials such as nylon mesh with collagen matrix (Biobrane), polylactic acid (Suprathel), and silver ion-containing nonadherent long-term coverings (Mepilex or Acticoat) are used functionally as skin substitutes.[6] Collectively these materials function as skin substitutes, remaining in place, protecting the wound, providing a wound matrix, and allowing reepithelialization. However aggressive care and use of skin substitutes is advised to minimize scarring and fibrosis and maximize long-term hand function. Thermoplastic custom hand splints applied immediately play an important role in maintaining hand position while at rest (Fig. 54.3). Immediate ROM, however, is the most important intervention to maintain hand function. In cases where the wound is not superficial, delayed, or "conservative: burn wound treatment inevitably leads to delays, which can result in a poor outcome for the patient. Early removal of all eschar is at the core of modern burn care. In the setting of large burn wounds, definitive grafting of the hands may need to be delayed due to limitations of available grafts; hand wounds then need to be temporized with cadaveric skin. However grafting of the hands should be a high-priority limb-saving treatment, even in extensive burn injuries.

Deep burns to the dorsum of the hand are common because the skin is thin and the dorsum is exposed to injury in the protective reflex. Additionally, there is very little subcutaneous tissue so the extensor mechanism is susceptible to fourth-degree injury, particularly at the proximal interphalangeal (PIP) joint. The use of a split-thickness sheet skin graft is the preferred covering for the dorsum of the hand, providing the best scars and color match, although 1:1 meshing has similar outcomes.[3] The means of securing the graft, splinting, and the timing of therapy are areas of continuing controversy. Many groups now secure grafts with fibrin sealant or sutures and begin gentle active ROM in the first postoperative day.[7,8] Other groups continue to immobilize fingers in the intrinsic-plus position with K-wires for up to 6 weeks while reporting no permanent loss of ROM or articular surface damage.[9,10] Still other groups advocate immobilization of the hand during engraftment with splints for short periods of time. Finally some continue to argue for grafting the dorsum in the fist position because this increases the total skin length by 20% and mitigates some of the risk of extension contracture because split-thickness skin grafts (STSG) are known to contract up to 30–50% of the total graft area.[11,12] While there are data to support all of these grafting and splinting protocols, the primary goal is to begin hand therapy as soon as possible. In our experience, fibrin glues help achieve this goal effectively with initiation of motion on the first postoperative day (Fig. 54.4).

In cases where the paratenon of the extensor mechanism is compromised, skin grafts may not take well. In these cases the options are to allow granulation tissue to form on the tendons and cover with a skin graft, cover the tendons with an artificial dermal template and delayed skin grafting, or to use immediate flap coverage. Permitting the extensor mechanism to granulate with delayed skin grafting can compromise long-term hand function as the tendon becomes entrapped in scar. Such delayed treatments, however, become the treatment of choice in the setting where large burns and their threat to life are more pressing treatment priorities. Artificial dermal regeneration template materials can be effective in primary burn treatment, but these adjuncts are susceptible to infection in large or colonized burn wounds. In a well-selected patient these adjuncts have minimal complications, high engraftment, good cosmetic and functional outcomes similar to native skin,[5] and they demonstrate improved Vancouver scar scale, fingertip-to-palm score, and prehensile score.[13]

Early flap coverage of dorsal hand burns is an effective technique to cover and protect the extensor mechanism. Flap choice is often limited by the overall physiological state of the patient. The groin flap remains an option for expedience and reliability, although the bulky nature, prolonged inset, limited ROM, and obstruction to OT make it a flap to be used only when other regional or microvascular flaps are contraindicated. The merits of various flap techniques are discussed later in this chapter but are equally relevant to primary coverage. Both the posterior interosseous artery flap and the reversal radial artery flap can cover the majority of the hand. These flaps are reliable, technically straightforward, thin, and do not limit OT, making them practical options for coverage of the burned hand (Fig. 54.5).

Management of burns to the palm is most often expectant. The thick glabrous skin of the palm has deep reticular structures and appendages allowing skin regeneration with minimal sequelae in most burns. In the event that grafting is required, there is continuing controversy over the best graft source: STSG, full-thickness skin graft (FTSG), or medium-thickness glabrous skin graft (MTGSG). Herndon et al. reported that STSG functions as well as FTSG for palm burns.[14] Conversely Pham et al. have demonstrated that FTSG performed better for palm burns in children.[15] MTGSG is the best tissue match, with good graft take and low donor site morbidity.[16] In a 12-year experience with MTGSG, good sensation, color, and donor healing were reported.[17] Plantar glabrous skin also transfers Meissner's corpuscles and sweat glands, structures that may be important to the fine sensation and grip needed on the palms. We tend to use STSG but the appropriate patient can find good utility in all of these techniques.

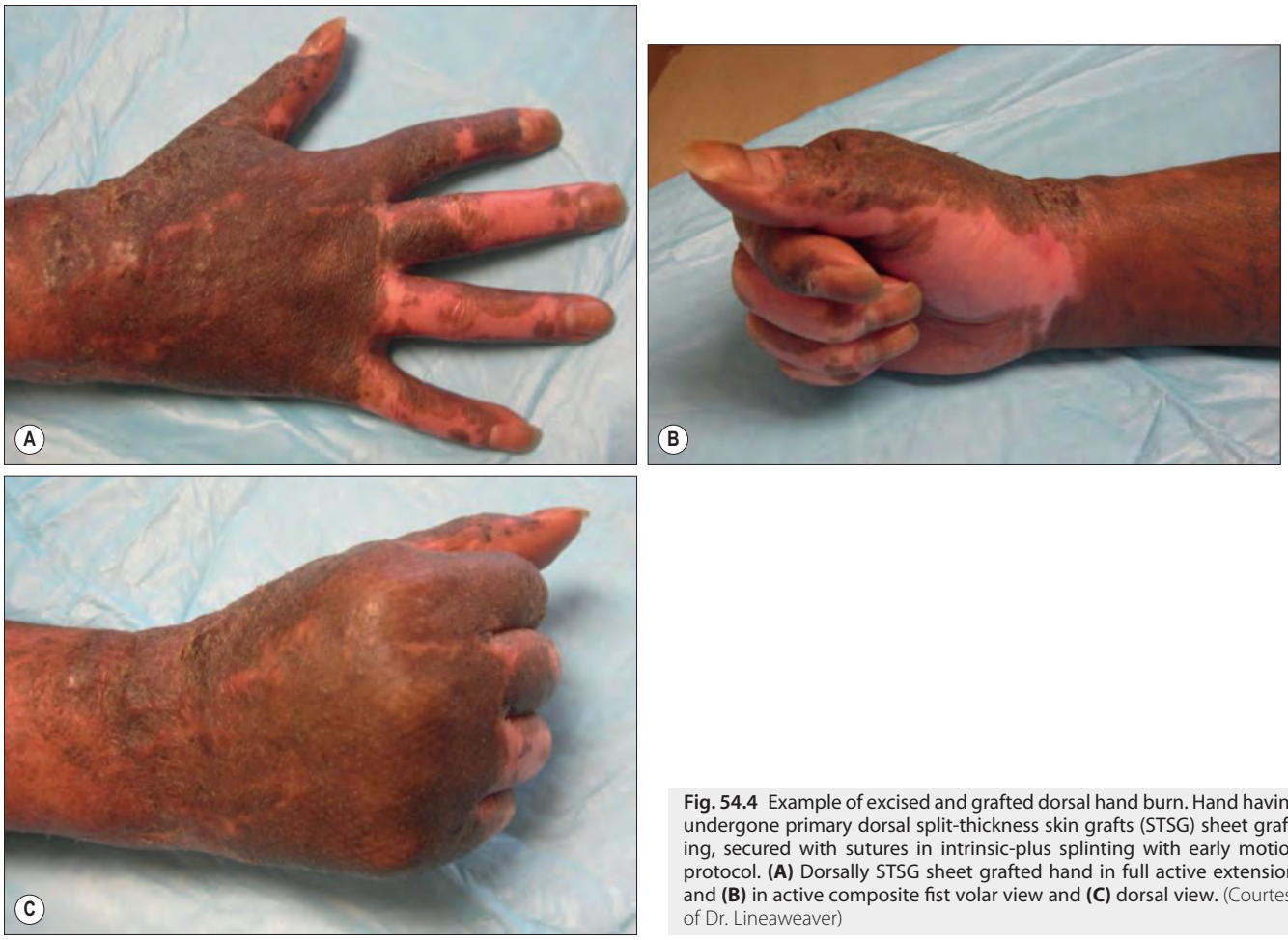


Fig. 54.4 Example of excised and grafted dorsal hand burn. Hand having undergone primary dorsal split-thickness skin grafts (STSG) sheet grafting, secured with sutures in intrinsic-plus splinting with early motion protocol. **(A)** Dorsally STSG sheet grafted hand in full active extension, and **(B)** in active composite fist volar view and **(C)** dorsal view. (Courtesy of Dr. Lineaweaver)

Occupational Therapy of the Burned Hand

Active motion is the means by which the hand maintains plasticity. The burned hand is predisposed to fibrosis because skin grafts and scars contract and deform the hand, while pain, edema, dressings, and splints limit hand mobility. As such, daily OT and a close working relationship between the surgeon and the therapist are critical to functional outcomes, reducing the need for secondary reconstruction to as low as 3.7% at 9 years according to Kreamer and Deitch.[18] A sufficient number of therapists should be available to treat each patient 1–2 times per day. A ratio of one therapist to seven patients is a good rule of thumb to allow for sufficient care. However the practicalities of early and aggressive OT are often limited by the particular practice scenario such as available personnel and other life-saving interventions, such as critical care or large burn wounds. Caring for hand burns requires extensive OT intervention and expertise in terms of physiotherapy and wound care usually only available at specialized centers.

The overall goals of OT are to maintain maximal hand movement, protect grafts, provide effective and well-fitting splints to maintain ligament length, and guide the patient's recovery toward maximum hand function. Intrinsic-plus splinting maximizes ligament and skin stretch in the position of function. The implication that the hand is safe in this position ignores the fact that the best position for the hand is in motion. No splinting should be considered as a resting substitute for active ROM.

OT can perform full ROM of all hand joints in the operating room prior to grafting to establish maximal mobility without pain and allowing the OT to be far more aggressive and expedient. This intervention can occur in parallel with other aspects of an operation thereby not increasing operative time. When fibrin glue or sutures are used to secure a sheet graft, therapists can take down the dressing on postoperative day 1, evaluate the graft, and evacuate any hematoma or seromas. If the graft is adherent to the wound bed, composite fist therapy should be initiated. Grafts are then dressed with functional compressive dressing and intrinsic-plus thermoplastic splints worn at night. Full range of hand motion can be achieved in 5 days with this protocol. Finally compression gloves should be manufactured to limit edema, hypertrophic scarring, and shearing of grafts.

Mobilization of the elbow is critical, and this joint should be kept extended to maintain maximal ligament length. Extension, however, is not a position of function, and, as such, elbow contractures in extension are debilitating because the patient is unable to reach hand to mouth. Therefore elbow ROM exercises are critical. The shoulder is

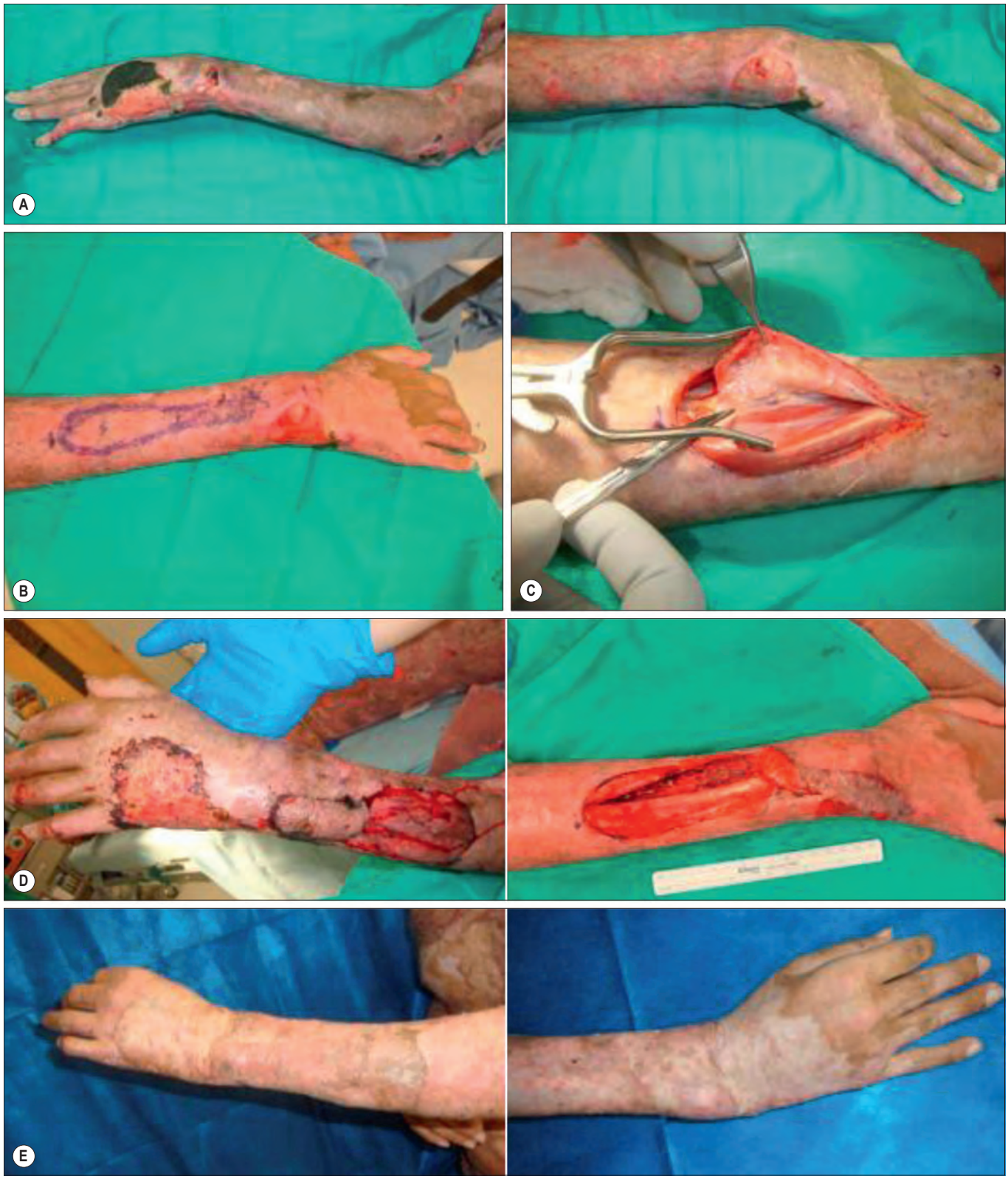


Fig. 54.5 Examples of regional pedicle flaps for hand coverage. **(A)** Dorsal hand and wrist defect, **(B)** markings for posterior interosseous nerve flap, **(C)** elevated in a fasciocutaneous manner, **(D)** rotated and inset to close a dorsal hand defect. **(E)** Follow-up image of healed posterior interosseous nerve flap.

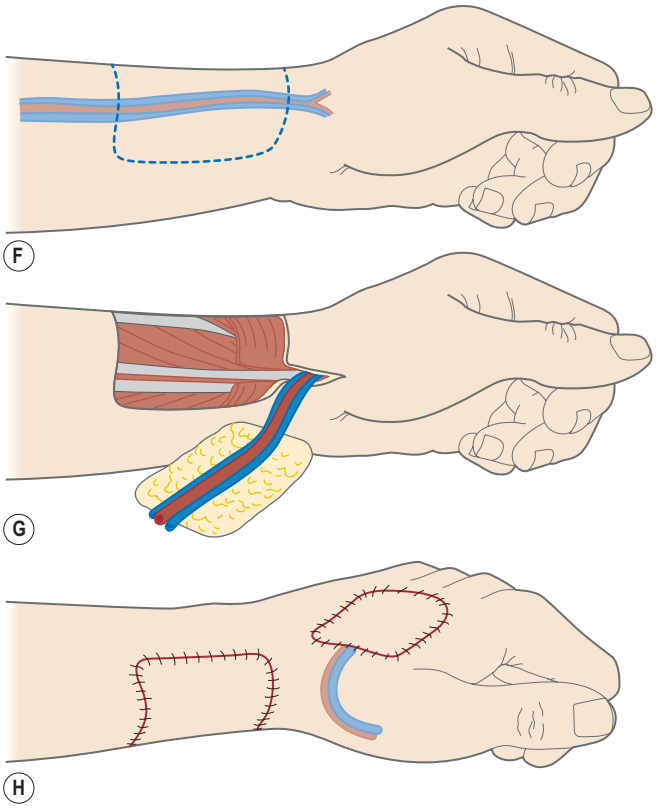


Fig. 54.5, cont'd (F) Line drawing of a distally based radial forearm flap, **(G)** raised and **(H)** inset to cover a dorsal hand injury. (A–E are used with permission from Baylan JM, Chambers JA, McMullin N, et al. Reverse posterior interosseous flap for defects of the dorsal ulnar wrist using previously burned and recently grafted skin. *Burns.* 2016;42(2):e24–30. F–H are used with permission from Lineaweaver WC, Buncke HJ. Flap reconstruction of the hand. In: Jupiter JB, ed. *Flynn's hand surgery*. 4 edn. Philadelphia: Williams & Wilkins; 1991: 607–625.)

similarly best splinted in abduction to prevent axillary contractures. However abduction is not a position of function, and ROM therapy is again critical.

Management of Established Burned Hand Deformities

Long-term hand deformities can develop and cause progressive deformities and disabilities despite aggressive acute care. As discussed earlier, the best option to avoid reconstruction is assiduous acute care. Early excision and grafting of hand burns within 4–6 days of injury gives a fivefold reduction in the need for secondary correction of scars or of being debilitated.[19] When deformities occur refractory to OT, early reconstruction is advocated.[3] It is critical that both the surgeon and the patient have realistic expectations of the reconstruction and acknowledge that full premorbid restoration of hand function can rarely, if ever, be accomplished.

The most common pathophysiology of burn deformity is insufficient skin coverage from scar contracture. This primary skin contracture limits or deforms hand movement and leads to a fibrosis of the tendinous and ligamentous structures of the hand with progressive loss of function. Early establishment of durable, flexible, and sufficient soft tissue coverage is critical to preventive and secondary treatment of these deformities. Chronic wounds also occur commonly and require operative excision and closure. The loss of structures such as digits or extensor tendons is also common, and a reconstructive balance needs to be struck between the desire for definitive reconstruction and the patient's tolerance for additional surgery.

RECONSTRUCTIVE METHODS

It is important when reconstructing the hand to use the "reconstructive elevator" to determine the best solution for the patient and not move in a stepwise fashion through inadequate treatments. First, the contracture is incised or resected, the joints maximally stretched, and the entire extent of the tissue deficit made manifest (Fig. 54.6).

a. *Primary closure of the wound*: This technique is used to close a wound resulting from the excision of hypertrophic scar tissues. Primary closure should only be considered when adjacent skin permits tension-free, nondeforming repair.
b. *Grafting of a wound*: In situations where a skin contracture has occurred, if the contracture can be released leaving an adequate bed for additional skin grafts, then either STSG or FTSG can be considered a sufficient skin envelope.
c. *Skin flaps*: Often an adequate bed cannot be established for a skin graft because critical structures need to be covered or the recurrence of skin graft contracture is a major concern. In these cases a random pattern skin flap can be designed to close the wound. Classic flap designs, including z-plasty, modified three-quarters z-plasty transposition flap technique, rhomboids, rotations, and advancements, are all reasonable choices in the circumstances when adjacent tissue can be used for a flap (Fig. 54.7). The operating surgeon should not feel constrained to one type of tissue rearrangement and should choose the best surgery based on the defect and available adjacent tissue.
d. *Muscle flaps, musculocutaneous (MC) flaps, and fasciocutaneous (FC) flaps*: The vascular supplies to skin flap skin are enhanced by incorporating the muscle, fascia, or paratenon. The flap is mobilized to fill a defect resulting from scar release as a local, regional, or distant microsurgical flap (Fig. 57.16). In many cases early microsurgical reconstruction allows the best and most efficacious coverage of the wound and should be part of the armamentarium of surgeons treating these injuries. Muscle flaps bring a viable muscle to cover a wound, and the flaps themselves are covered with STSG (e.g., rectus flap). Musculocutaneous flaps bring a vascularized muscle with its overlying skin to cover a wound (e.g., latissimus dorsi flap). Fasciocutaneous flaps bring vascularized fascia with overlying skin to cover a defect (e.g., radial artery flap). Fascial flaps bring viable fascia and are subsequently covered with STSG (e.g., temporoparietal fascia flap). The best reconstruction technique depends on the patient's available donor tissue areas and overall health and tolerance for reconstruction and should not be constrained by the surgeon's

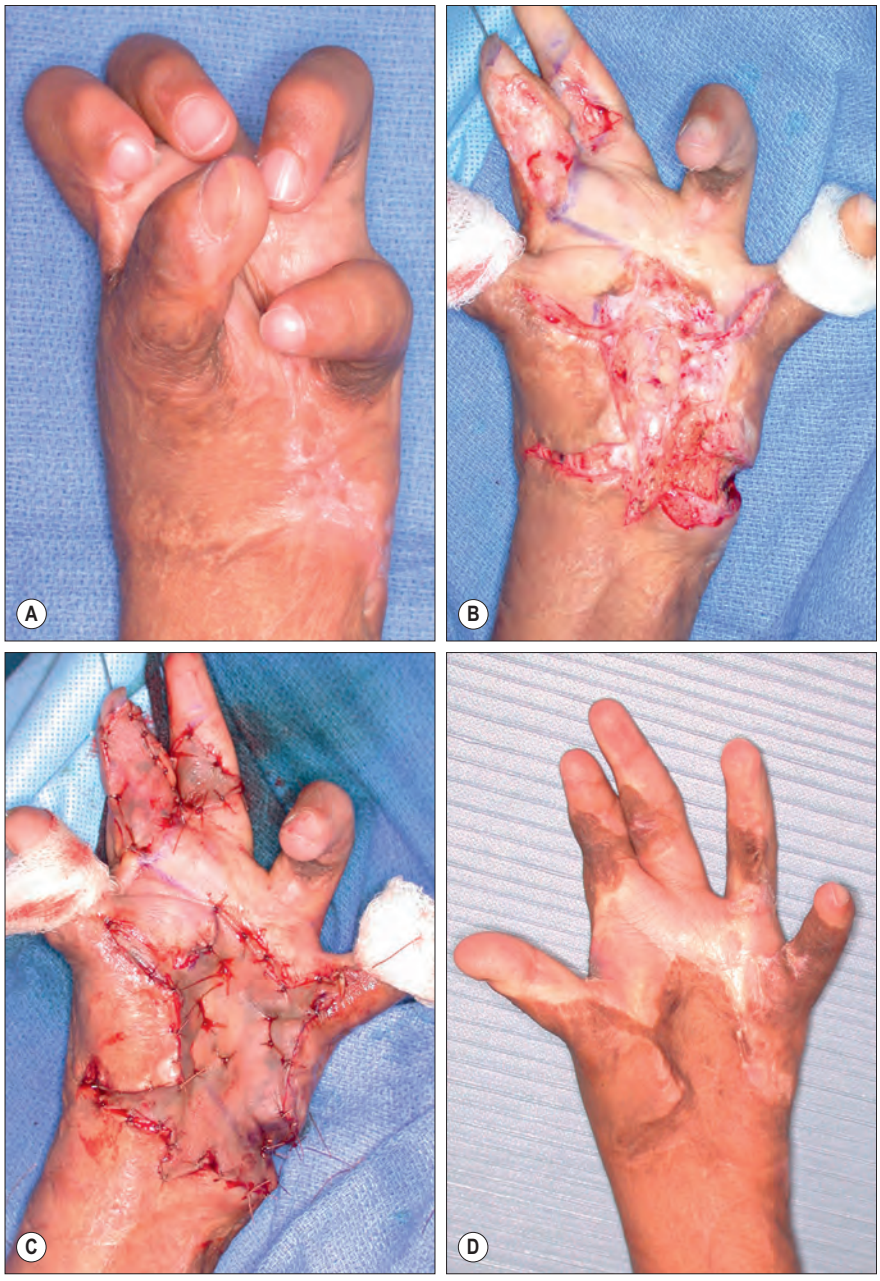


Fig. 54.6 Release of palmar flexion contracture with split-thickness skin grafts (STSG). **(A)** Palmar contracture in a 7-year-old child. **(B)** The tissue deficit created after releasing the contracture and extending the fingers manifests the true skin deficiency. **(C)** STSG inset into the defect. The digits held in extension with intramedullary K-wires. **(D)** The release of the digits achieved by palmar release.

technical ability or knowledge. Regardless of the tissue donor chosen, care must be taken to limit bulk and allow the patient to move the intricate joints of the hand freely.

Reconstruction of Phalangeal Deformities

FLEXION CONTRACTURE DEFORMITIES

Flexion contractures usually occur from deep or full-thickness burns to the volar skin causing inadequate skin length. Joint and tendon sheath contractures can be contributing elements developing secondarily from the deformity and immobilization of the primary skin contracture. The contracted skin is released and a skin defect created by extending the contracted hand, as in Fig. 54.6. The resulting skin defect can then be closed by utilizing a transpositional skin flap technique (e.g., three-quarters z-plasty), pedicled flap, or skin graft, as in Fig. 54.6. Skin grafting is a viable option for closure of defects where no critical structures are exposed. As discussed in the acute burn section, there are controversies over the use of a dermal matrix, FTSG, STSG, or MTGSG should a volar graft be needed. If release of the contracture is inadequate, a capsular release of the affected joint may be needed.

In the setting of exposed critical structures (neurovascular bundles, tendons or bones), upon release of a volar contracture the best reconstruction depends on the available

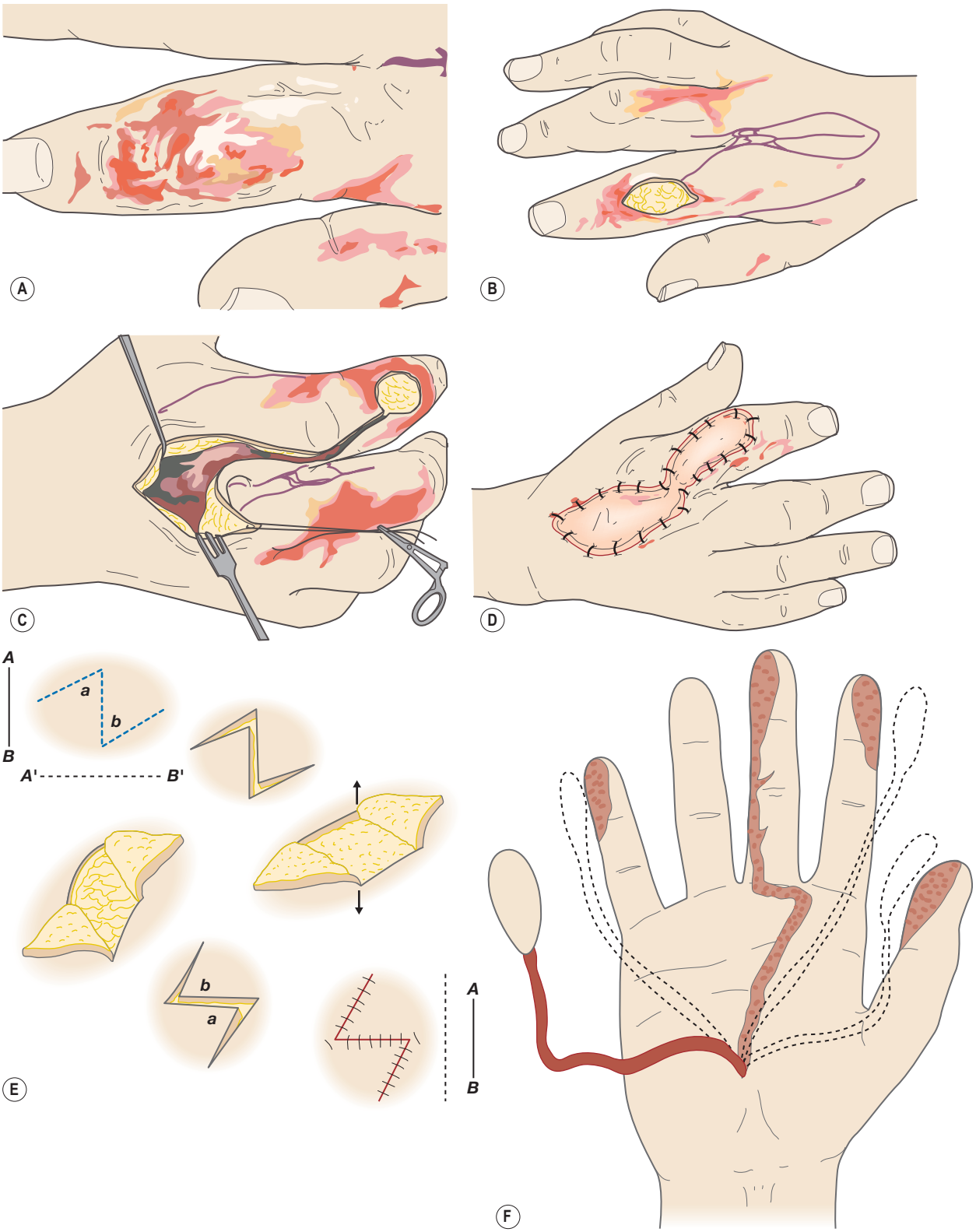


Fig. 54.7 Examples of local flaps for wound coverage in the hand. **(A–D)** Elevation and inset of dorsal interosseous artery flap. These exist in each web space and can be used to cover the finger out to the distal interphalangeal (DIP) joint with sensate tissue. **(E)** Line drawing of a z-plasty transposition flap. An incision is made along the contracture scar then flaps raised perpendicular at angles of 60 degrees. The flaps are then transposed, increasing the length of the scar. Typically flaps with tip angles of 60 degrees will increase in length of a contracture by 60% (75% by calculation). **(F)** Line drawings, elevation, and inset of neurovascular-island flap which can effectively cover the fingers, including the pad, with sensate glabrous tissue.

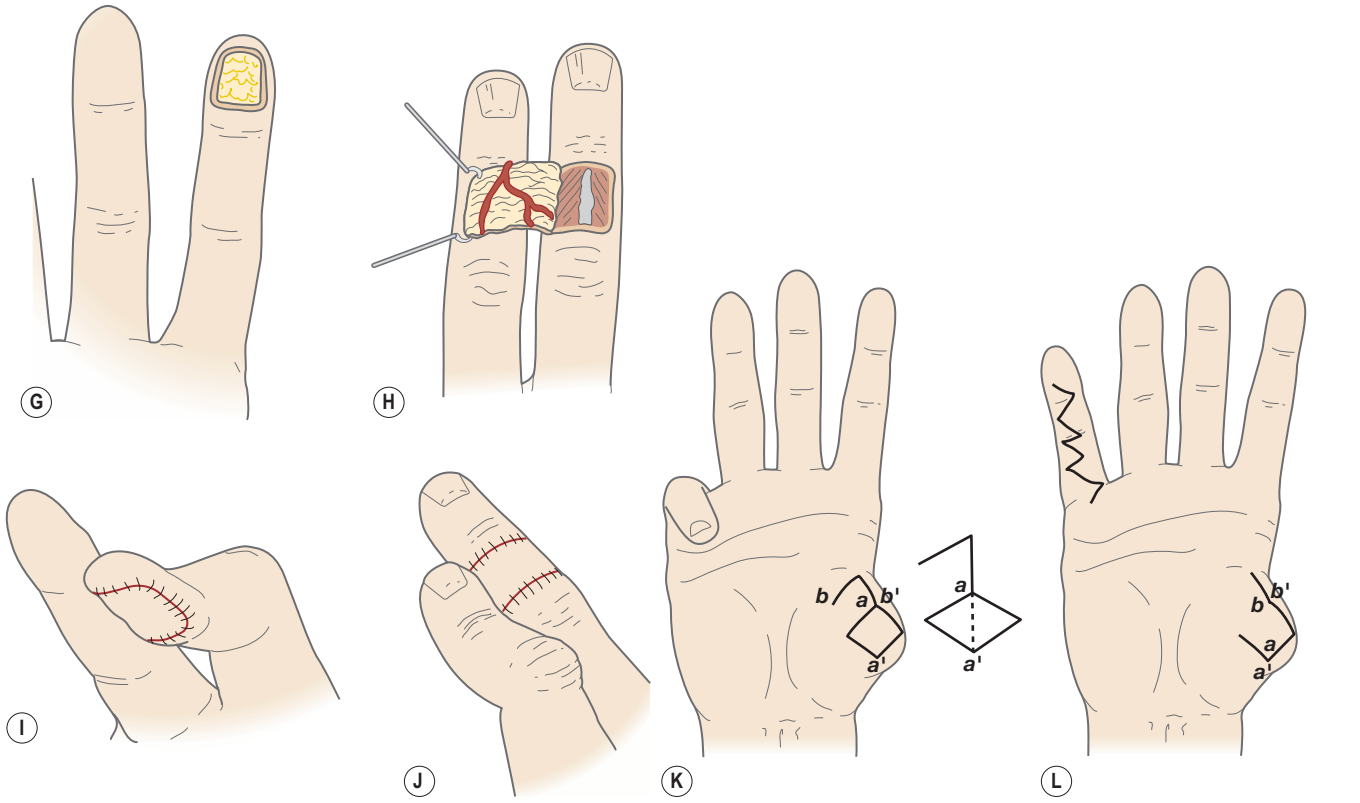


Fig. 54.7, cont'd (G–J) Line drawings, elevation, and inset of cross-finger flap which can effectively cover any part of the finger. **(K)** Line drawing of a hand with a flexion contracture of the small finger and an unstable thumb amputation wound marked with a Limberg (rhomboid) flap closure that will deepen the first web space and close the defect. The internal angles of the Limberg flap are 60 and 120 degrees, the width equals a to a' and the donor defect of b to b' must close primarily. **(L)** Line drawing showing the Limberg flap rotated into position as well as the flexion contracture of the small finger released by transposition of multiple z-plasty flaps. (A–D are used with permission from Agir H, Sen C, Alagoz S, Onyedi M, Isil E. Distally based posterior interosseous flap: primary role in soft-tissue reconstruction of the hand. *Ann Plast Surg*. 2007;59(3):291–296. E–K are used with permission from Lineaweaver WC, Buncke HJ. Flap reconstruction of the hand. In: Jupiter JB, ed. *Flynn's hand surgery*. 4 edn. Philadelphia: Williams & Wilkins; 1991: 607–625.)

donor tissue. The use of an axial lateral digital flap, a neurovascular island flap (Littler flap), a dorsal metacarpal artery flap, or a cross-finger flap may be necessary for a finger that has lost sensory supply to restore not only the soft tissue deficit but also the sensory supply (Fig. 54.7). When local flaps are inadequate, a dermal matrix may allow a staged reconstruction. The reconstructed finger is maintained at full extension by splinting. Alternatively a Kirschner wire placed intramedullary or underneath the flexor tendon sheath to maintain finger position for a period of 10–14 days can be effective.

EXTENSION CONTRACTURE DEFORMITIES

Burns to the dorsum of the hands are common, and these burns are often significant due to the thin skin and finely tuned extensor mechanism. Deformities here occur from insufficient skin envelope, exposed or compromised tendons and joints, tendon adhesion, and tendon disruptions (e.g., Boutonnières deformities). Surgical intervention is often needed to correct an established deformity refractory to OT interventions.

When there is insufficient skin on the dorsum of the hand, contractures can be released, constricting scar tissue resected, and the defect regrafted with STSG. STSG reconstruction can compromise tendon glide if the paratenon is compromised, although early motion protocols help maintain motion. For small defects, a three-quarters z-plasty transposition flap can be beneficial over the metacarpophalangeal (MCP) joint (Fig. 54.8). Often, for large deficits over the dorsum, a distant flap is needed, such as a distally based posterior interosseous flap, which can provide large-area durable coverage with good tendon glide.[20] This flap can be used when the donor area is burned and even in the acute burn setting when the donor area is recently skin grafted[21] (Fig. 54.5). Similarly propeller flaps can be constructed with reliability in the upper extremity.[22] Temporoparietal fascia free flaps can also provide excellent tendon glide, and microvascular flap coverage should be available to hand burn patients. Classically, large defects of the dorsum of the hand are covered with groin flaps, which are described later in the electrical burn section (Fig. 54.9). It is far preferable to use a flap that allows one-stage coverage and early motion, so groin flaps should only be employed in the rare circumstance where local, regional, and free flaps are contraindicated.

Extension contractures to the fingers are also common. They are released by incising the scar over the deformed finger joint(s) (i.e., the deformed distal interphalangeal [DIP], PIP, and MCP joints). If needed, the joint capsule is released. The resultant defect can be closed with the three-quarters z-plasty technique (Fig. 54.8). STSG can be used

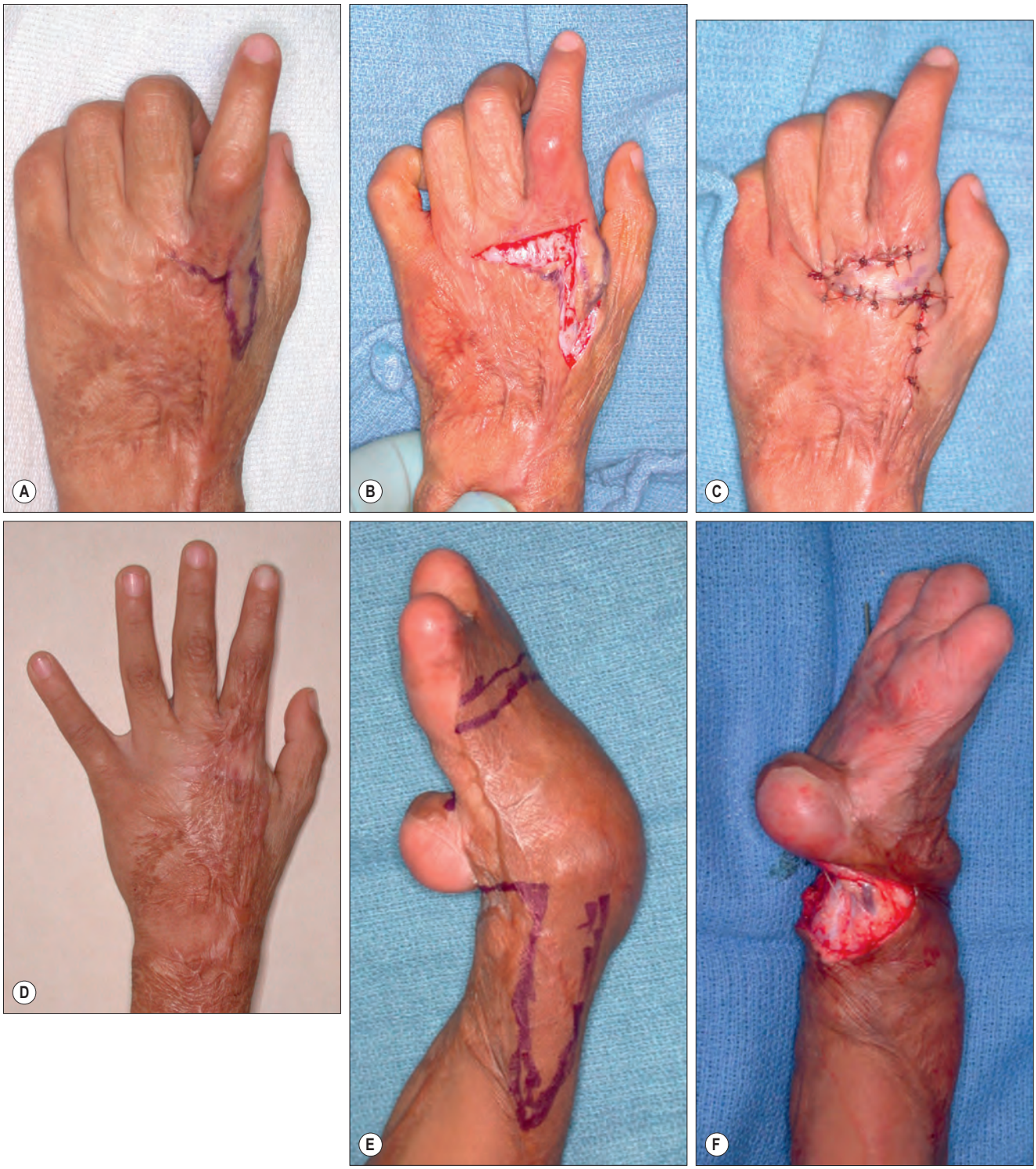


Fig. 54.8 Examples of contractures treated with local transpositional three-quarters z-plasty. **(A)** Metacarpophalangeal (MCP) joint extension contracture with three-quarters z-plasty transposition flap marked. **(B)** MCP contracture released with transverse incision and transposition flap raised. **(C)** Three-quarters z-plasty flap rotated into position and flap donor area closed directly, **(D)** with follow-up at 3 years. **(E)** Release of flexion contracture of wrist with three-quarters z-plasty transposition flap marked. **(F)** Skin defect is manifest when the flexion contracture is released with a transverse incision.

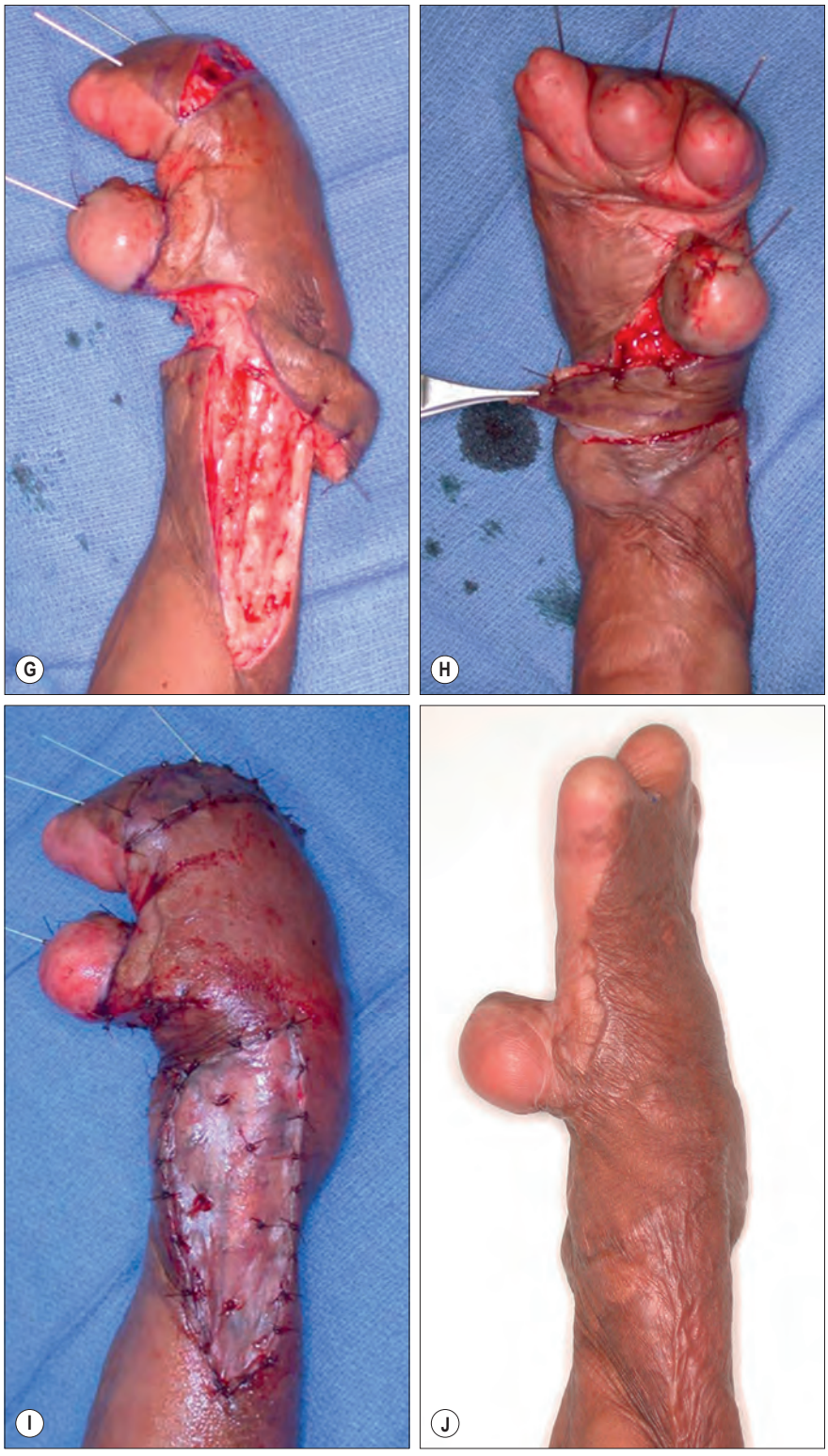


Fig. 54.8, cont'd (G) Transposition flap raised in a fasciocutaneous manner and **(H)** rotated into the skin defect on the volar wrist. **(I)** Flap donor area closed with split-thickness skin graft, and **(J)** contracture release persists at 4-year follow-up.

for defects over the MCP joint. Dorsal metacarpal artery flaps allow coverage of the extensor hood out to the DIP joint. These flaps are elastic, durable, and sensate coverage for digits.[23] FTSG and cross-finger flaps also provide effective coverage options (Fig. 54.7).

The thin covering of the dorsum of the finger results in many central slip injuries and resultant Boutonniere deformities. PIP fusion or amputation is common because tenoplasty often fails in this setting of poor soft tissue coverage. Finally fat grafting can be used to repair contour deformities from severe contracture and burns to the hand.[24] Fat grafts may also improve tendon glide by elevating prior skin grafts off the extensors (Fig. 54.10). In a recently published series fat grafting was shown to significantly improve scar,

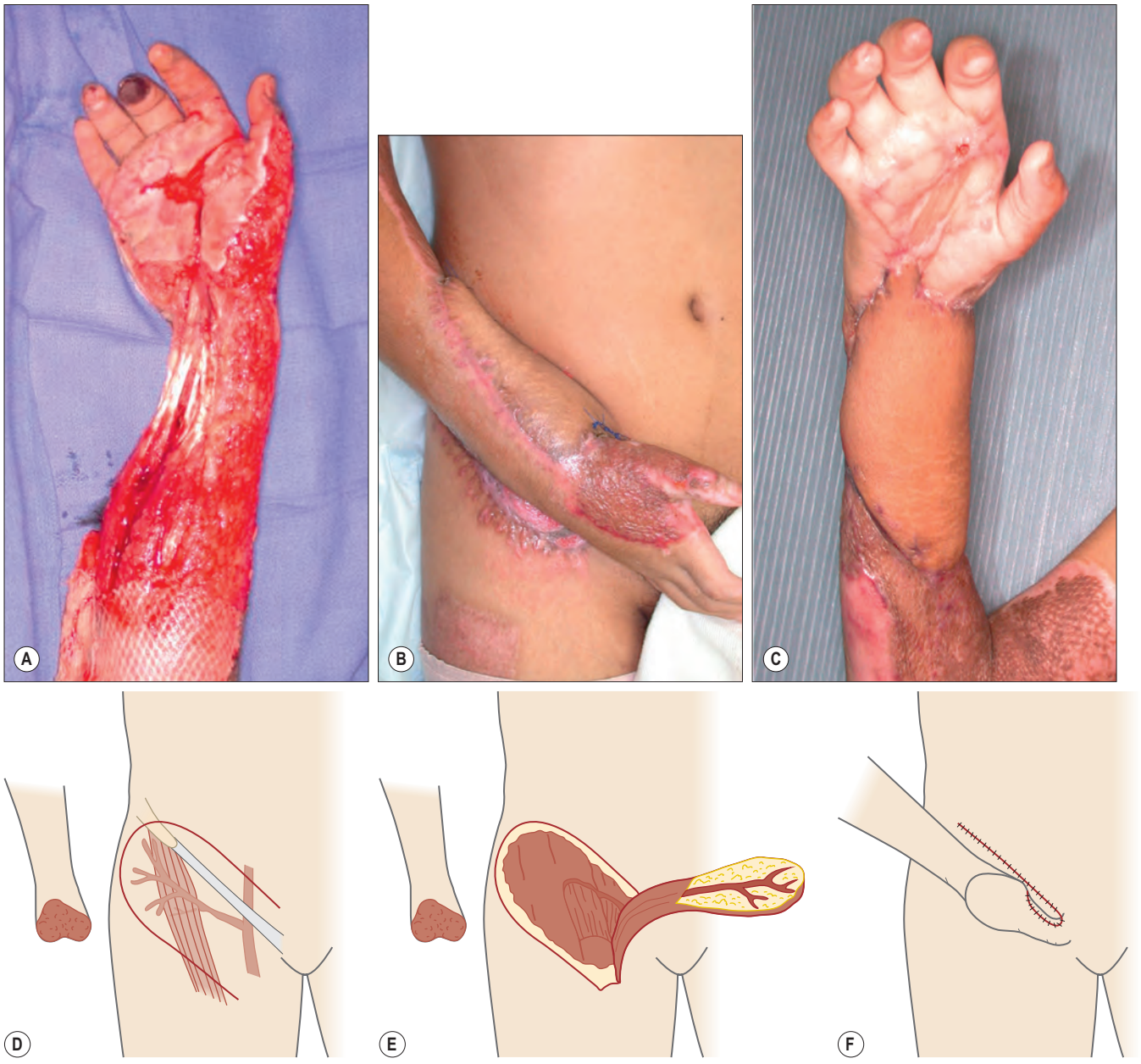


Fig. 54.9 Abdominal flap. **(A)** Extensive volar burn covered with inferior superficial epigastric artery-based abdominal flap **(B)**. **(C)** Abdominal flap following division. **(D–F)** Line drawings demonstrating the anatomy and inset of a superficial epigastric artery-based abdominal flap. (D–F used with permission from Lineaweaver WC, Buncke HJ. Flap Reconstruction of the hand. In: Jupiter JB, ed. *Flynn's hand surgery*. 4 edn. Philadelphia: Williams & Wilkins; 1991: 607–625.)

contour, and Michigan Hand Outcome Assessment compared to the unaffected hand.[25]

WEB SPACE CONTRACTURE

Narrowing of the web space is a common sequela of hand burns. Placement of unburned tissues in the dorsal aspect of the web space is the key to reconstruction. Reconstruction can be achieved through the use of a triangular skin flap mobilized from either the radial or ulnar side of the fingers and then rotated into a contracted web space, especially to the second, third, and fourth, to achieve the release. Z-plasty, advancement flaps, and V-Y advancements are also viable means of reconstruction. No additional physiotherapy is necessary. Unrestricted use of the hand daily will restore the web space and the movements of the fingers (Fig. 54.11).

First Web Space Contracture

First web space contracture is functionally significant because of limitations of thumb extension, abduction, and opposition. While conventional techniques, such as z-plasty and skin grafting, may be used to reconstruct the deformity, the technique combining two z-plasties with one central

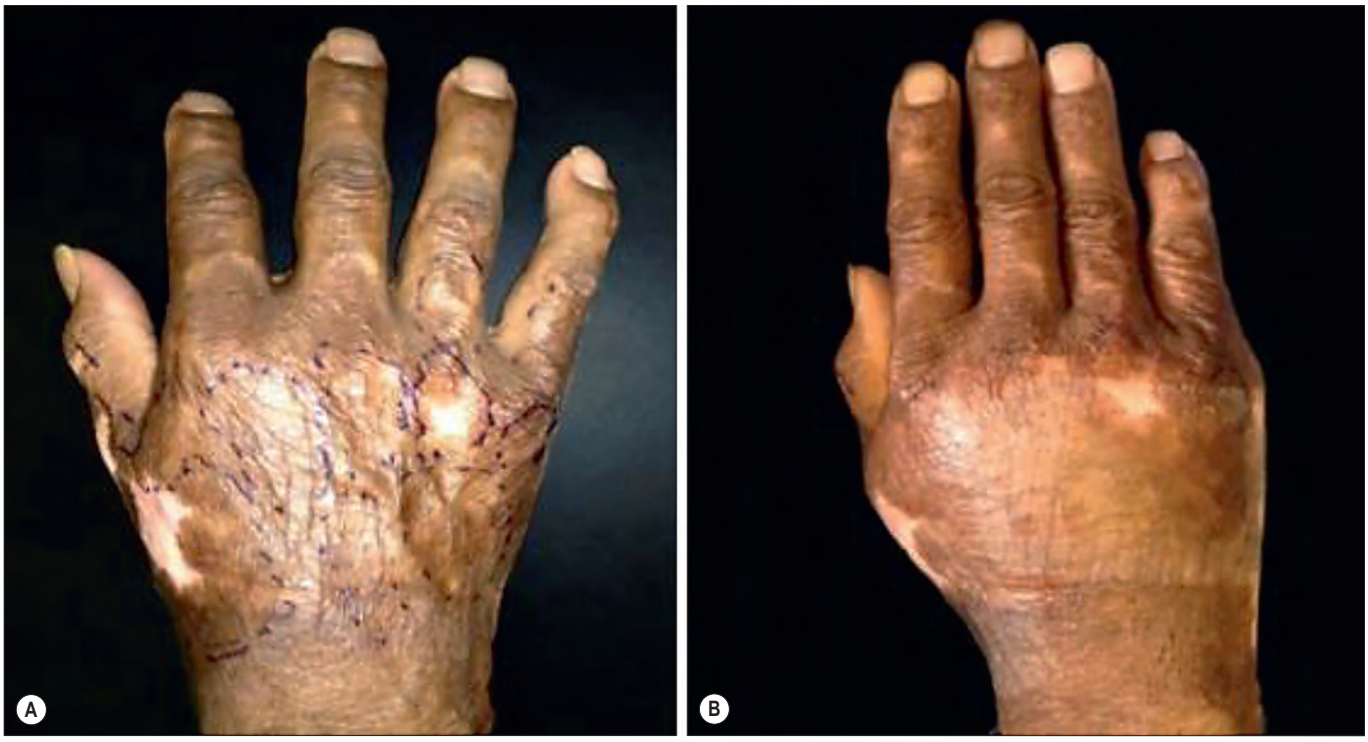


Fig. 54.10 Fat grafting dorsal hand under split-thickness skin graft (STSG). Hand with dorsum extension contracture and contour defect treated with fat grafting. **(A)** Dorsally STSG hand with extension contracture. Note the sharp demarcation of the STSG's skin color and contour from the native skin at the level of the metacarpophalangeal (MCP) joint and wrist. **(B)** Six-month follow-up after a single fat grafting with a modest but significant increase in range of motion, scar quality, and hand outcome score in this preliminary study. Note the clear line demarcating the previously placed STSG at the level of the MCP and wrist, which now has improved contour and color. The authors postulate multiple graftings might have cumulative effects by releasing tethered skin and remodeling the subcutaneous layer in the hand. (From Byrne M, O'Donnell M, Fitzgerald L, Shelley OP. Early experience with fat grafting as an adjunct for secondary burn reconstruction in the hand: technique, hand function assessment and aesthetic outcomes. *Burns*. 2016;42(2):356–365.).

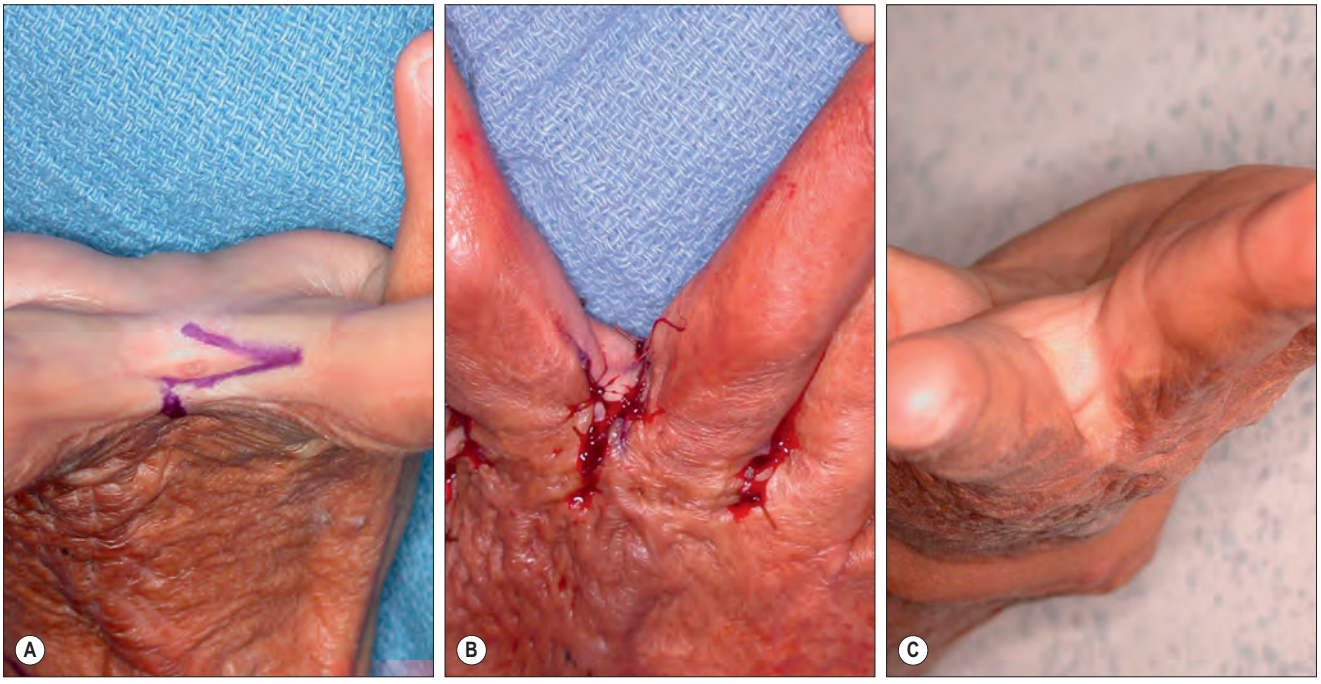


Fig. 54.11 Release of web space contracture. **(A)** Contracture of the right second web space with markings for three-quarters z-plasty transposition flap release. **(B)** The flap was rotated dorsally and the wound was closed primarily. **(C)** The appearance of the operative site 3 years following the release.

V-Y plasty, commonly known as the trident flap technique, the "jumping-man" technique, seagull-wing flap technique, or five-flap technique, is a simple and effective approach to providing the release. An approximately 30–40% increase in the first web space is obtainable using this release technique (Fig. 54.12).

RECONSTRUCTION OF A DEFORMED THUMB

It is estimated that 45–50% of hand function is forfeited with the loss of a thumb.[26] Reconstruction of the thumb should be offered to patients, and many techniques are available, from a toe-to-thumb transplantation to the creation of a

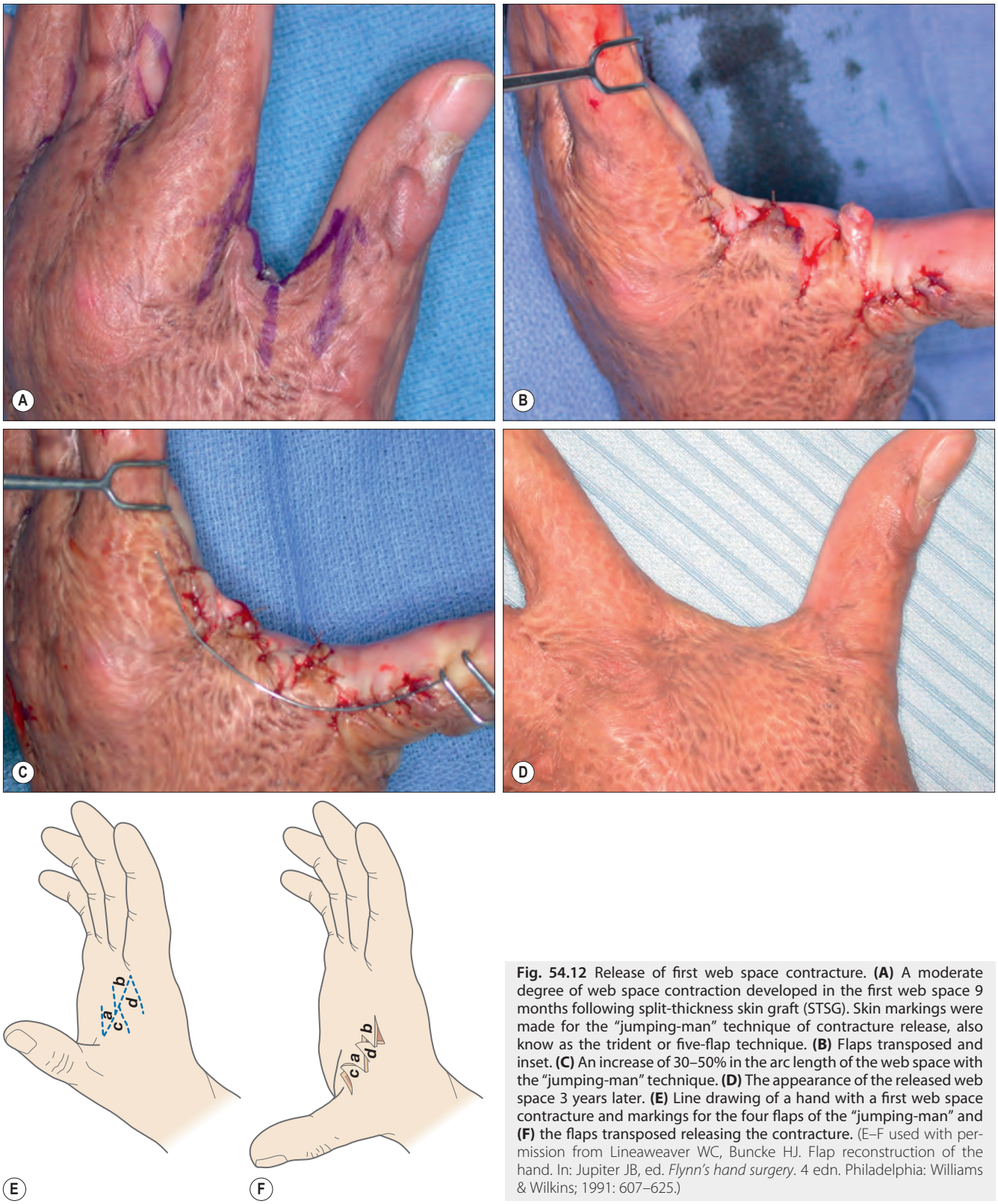


Fig. 54.12 Release of first web space contracture. **(A)** A moderate degree of web space contraction developed in the first web space 9 months following split-thickness skin graft (STSG). Skin markings were made for the "jumping-man" technique of contracture release, also know as the trident or five-flap technique. **(B)** Flaps transposed and inset. **(C)** An increase of 30–50% in the arc length of the web space with the "jumping-man" technique. **(D)** The appearance of the released web space 3 years later. **(E)** Line drawing of a hand with a first web space contracture and markings for the four flaps of the "jumping-man" and **(F)** the flaps transposed releasing the contracture. (E–F used with permission from Lineaweaver WC, Buncke HJ. Flap reconstruction of the hand. In: Jupiter JB, ed. *Flynn's hand surgery*. 4 edn. Philadelphia: Williams & Wilkins; 1991: 607–625.)

digital post. In many patients deepening the first web space provides an adequate post for grip and pinch.

The technique of stacking a remnant of the index finger to the thumb ray to elongate the thumb remnant and deepen the first web space has been used in Galveston for the past 30 years. Functionally this is a form of pollicization of the index finger. The remnant of the index finger is transected at the metacarpal or proximal phalanx level. The index finger is mobilized as a flap with its neurovascular bundle intact. The proximal bone margin of the index finger is fixed to the distal end of the thumb remnant. Resection of the index metacarpal deepens the first web space. The procedure carries low morbidities and could be performed in an outpatient surgical facility (Fig. 54.13).

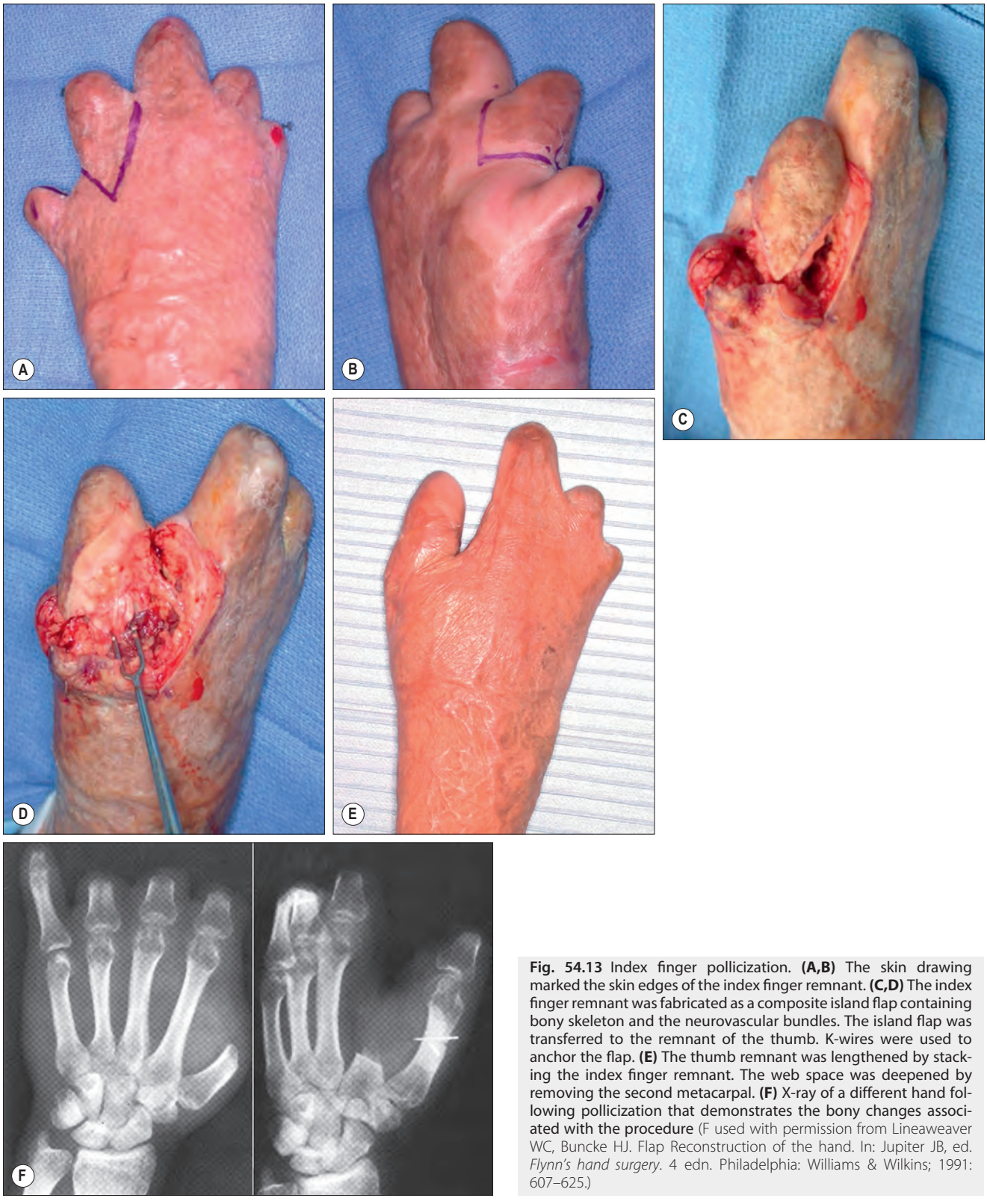


Fig. 54.13 Index finger pollicization. **(A,B)** The skin drawing marked the skin edges of the index finger remnant. **(C,D)** The index finger remnant was fabricated as a composite island flap containing bony skeleton and the neurovascular bundles. The island flap was transferred to the remnant of the thumb. K-wires were used to anchor the flap. **(E)** The thumb remnant was lengthened by stacking the index finger remnant. The web space was deepened by removing the second metacarpal. **(F)** X-ray of a different hand following pollicization that demonstrates the bony changes associated with the procedure (F used with permission from Lineaweaver WC, Buncke HJ. Flap Reconstruction of the hand. In: Jupiter JB, ed. *Flynn's hand surgery*. 4 edn. Philadelphia: Williams & Wilkins; 1991: 607–625.)

Microvascular toe-to-thumb transfer has been demonstrated to lead to good functional outcomes.[27] The technique is beyond the scope of this chapter,[28] but it can provide very high satisfaction and result in a functional and sensate thumb.[29] Furthermore, multiple toes can be transferred to reconstruct function in the fingerless "metacarpal only" hand (Fig. 54.14).[30]

RECONSTRUCTION OF A CLAW HAND

The burned hand can develop a claw deformity from multiple etiologies. The classic claw hand, the intrinsic-minus hand familiar to all hand surgeons, can develop from ulnar nerve injuries either in the primary burn injury, compression at Guyon's canal, or compression at the cubital tunnel.

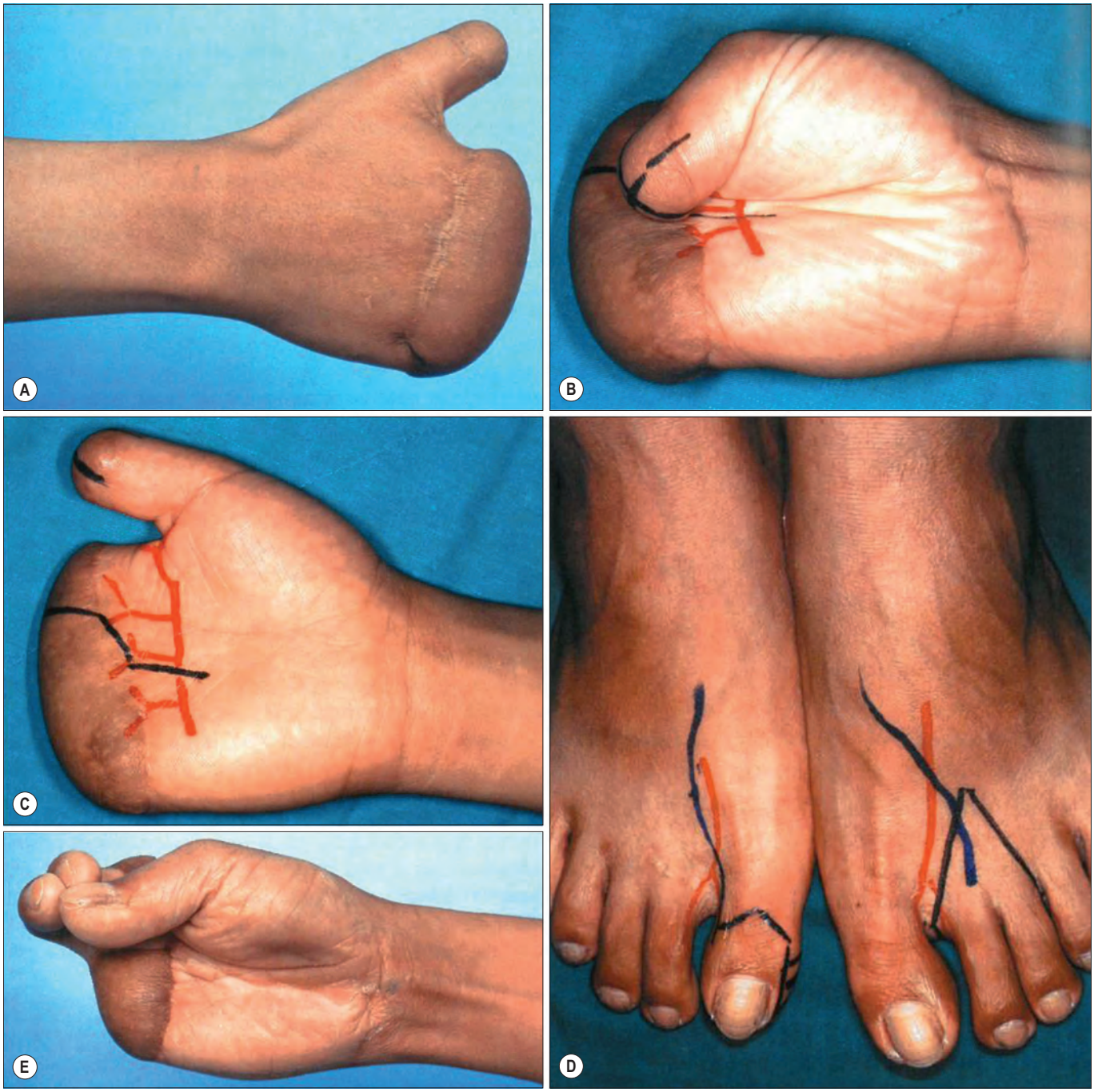


Fig. 54.14 Toe-to-hand transfer. **(A)** Metacarpal hand after closure with pedicled groin flap. **(B)** Thenar muscle function maintained. **(C)** Design of skin incision with recipient vessels marked. **(D)** Donor toes marked with right great toe and left combined second and third toes. **(E)** Tripod pinch present at 3-year follow-up. (From Vivek Jain F-CW. The metacarpal hand. In: Norman Weinzweig JW, ed. *The mutilated hand*. Lansing: University of Michigan/Elsevier Mosby; 2005: 280.)

In these cases ulnar nerve decompression can improve hand function.

A claw hand deformity can occur from necrosis of intrinsic hand musculature thereby creating an intrinsic-minus repose. In these cases ulnar nerve tendon transfers used to treat the intrinsic-minus hand from ulnar nerve injuries are not typically successful in the burned hand due to the overall soft tissue damage to the hand. Joint fusions in a position of function can improve overall hand function.

A claw-like deformity can also occur in burned hands with intact ulnar innervation and intrinsic musculature (Fig. 54.15). Scar contracture can create intrinsic-minus repose with MCP hyperextension and PIP contracture. This claw-like hand is treated by total scar excision and coverage with skin grafts or flaps. Early and aggressive OT is essential to regain intrinsic function.[31]

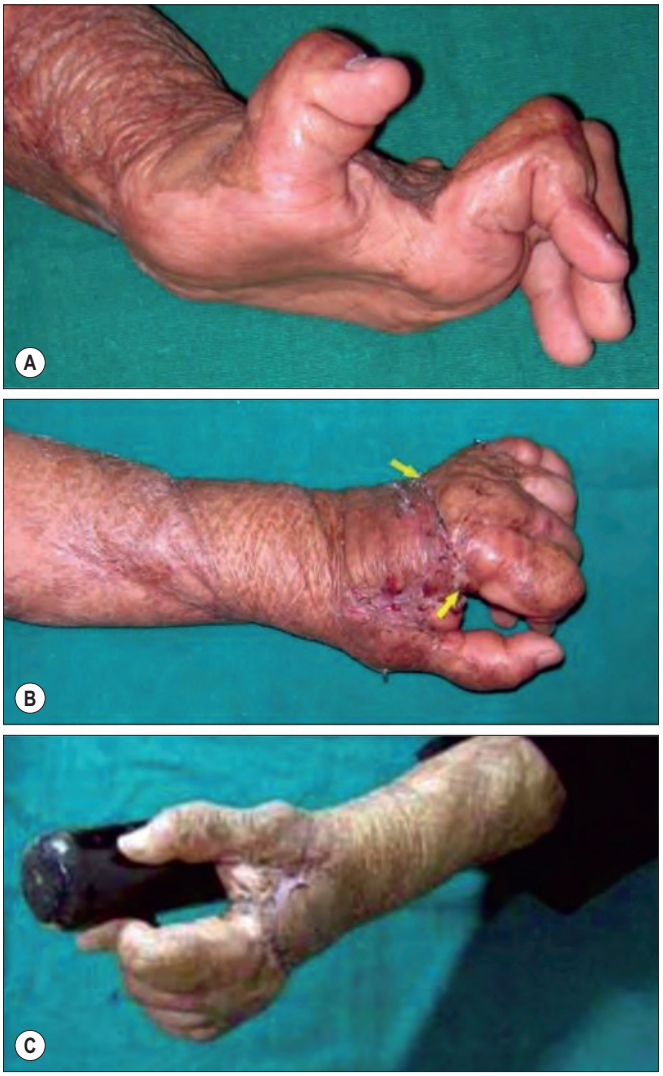


Fig. 54.15 Claw-like hand. *(A)* Classic presentation of the "claw-like hand" with metacarpophalangeal (MCP) joint hyperextension, interphalangeal (IP), proximal and interphalangeal (PIP) flexion, and thumb adduction. This intrinsic-minus repose appears identical to a claw hand from an ulnar nerve palsy but in this case is from a severe dorsal contracture. **(B)** Treatment consists of a transverse releasing incision proximal to the MCP (*arrows*) allowing MCP capsulotomy and flexion, then closure with a split-thickness skin graft (STSG). **(C)** Follow-up demonstrates composite grip and intrinsic function of the hand. (From Sabapathy SR, Bajantri B, Bharathi RR. Management of post burn hand deformities. *Ind J Plast Surg*. 2010;43(Suppl):S72–79.)

Electrical Injuries Involving the Upper Limb

Electrical injuries are discussed in detail in Chapter 38 on electrical burns, but they are important to consider here because the upper extremity is a common contact point for electrical injury. Injuries often include the entire extremity (i.e., the shoulder to the hand). The damaged structures noted are mostly the muscles in the arm, neurovascular bundles, and the skin over contact points in the forearm and in the hand. The bones typically generate heat due to their high resistance and burn the tissue from the inside out. Thus a fourth-degree injury is common, and aggressive treatment is needed.

Various classification schemes have been described for electrical burns of the upper extremity but are clinically cumbersome and do not guide treatment. Treatment and diagnostic priorities are the same as all burn injuries: reestablishment of blood flow, débridement of necrotic tissue, decompression, early graft coverage, and early ROM. The incidence of extremity amputation in cases with deep, circumferential electrical burns can be in the range of 25–80%, attributable to vascular injuries. Assessment of vascular injuries and vascular compression in patients with electrical burns is, therefore, extremely important at the time of initial evaluation. The structural and functional integrity of the arteries is assessed with clinical exam, Doppler flow, magnetic resonance imaging (MRI), and angiography. Surgical exploration remains the definitive strategy for diagnosis and treatment. Patients sustaining electrical burns of the upper limb are frequently found to suffer other life-threatening injuries. Surgical débridement of burn wounds and wound exploration are planned as part of their overall stabilization.

Decompressive Escharotomy and Fasciotomy

Decompression to reestablish blood flow is particularly critical in electrical injuries. Tissue destruction particularly involving deep structures inevitably leads to interstitial extravasation of tissue fluid and tissue swelling. The release of muscle compartments is necessary in instances where the muscle compartments are swollen. Without releasing procedures, ischemia can cause muscle necrosis and nerve injury (Fig. 54.2). Deep muscles in contact with the bones, such as the pronator quadratus and rotator cuff muscles, are particularly at risk of necrosis and should be evaluated during decompressive surgery. Necrotic muscles should be removed as soon as possible to prevent systemic toxicity such as renal failure.

Early Débridement

In patients with obvious, deep burns to the arm and with life-threatening injuries, early proximal amputation should be considered. A proximal amputation can quickly remove extensive necrotic muscle, particularly when the rotator cuff muscles are infarcted. Prompt amputation of an

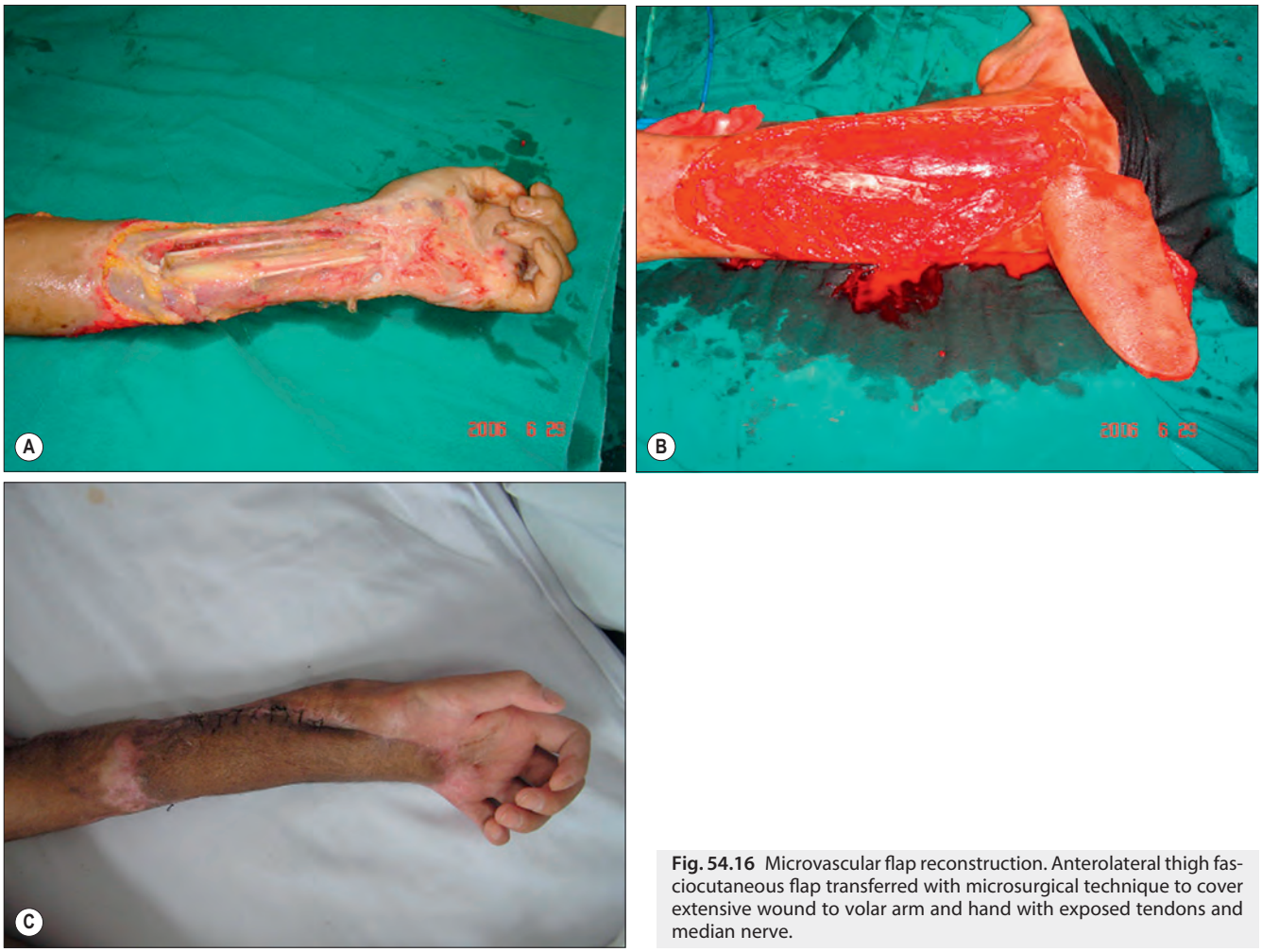


Fig. 54.16 Microvascular flap reconstruction. Anterolateral thigh fasciocutaneous flap transferred with microsurgical technique to cover extensive wound to volar arm and hand with exposed tendons and median nerve.

unsalvageable upper extremity can be a life-saving procedure that avoids hemorrhage and sepsis as well as the metabolic complications of multisystem organ failure from myonecrosis. This can be life-saving due to the risk of renal failure from rhabdomyolysis and the susceptibility of necrotic muscle to mold infection.

Complete débridement is advisable in the 1–2 days following injury. The procedures should include removal of all devitalized tissues, ascertaining the viability of intrinsic muscles and pronator and supinator muscles. Every effort should be made to preserve all forearm nerve structures unless nerve viability is clearly lost. Vascular continuity, in instances where the patency of both radial and ulnar arteries is compromised, may be restored by means of vein grafts, although often arterial thrombosis is a marker of severe necrosis and nonreconstructable disease.

Wound Management

The magnitude of tissue damage in high-voltage electrical burns is often so extensive that it involves muscles and blood vessels. Limb removal, in such instances, is the sole treatment option left to minimize lethal consequences of the injuries. The conventional regimen of a split-thickness skin graft for wound coverage is often not feasible because wound beds are devoid of vascular supplies and/or tissue loss is extensive (Fig. 54.16). Instead, local or distant flaps are used for wound coverage and protection of nerves, vessels, joints, and tendons. The pedicled abdominal flap has utility in this setting because the arm is within the zone of injury and local or regional flaps may have been compromised (Fig. 54.9).[32,33] However, even in the setting of electrical injuries, distant pedicled flaps should only be used in the rare instances where local, regional, and microvascular flaps are contraindicated or unavailable. An angiogram can clarify which regional flaps and microvascular recipient vessels are available.

FUNCTIONAL RECONSTRUCTION OF LIMB DEFORMITIES

Loss of limb function is not uncommon following electrical injuries. Insufficient vascular supply, extensive nerve and musculotendinous damage, and loss of muscle functions involving the shoulder girdle and the forearm, as well as loss of intrinsic musculatures of the hand are factors responsible for the difficulties encountered. Maintaining joint mobility and replacement of lost soft tissue in the forearm and hand are two key features necessary for functional reconstruction. Patients are encouraged to follow an OT regimen to maintain joint mobility, particularly of the finger joints.

Successful nerve grafting for sensory restoration and/or tendon transfer procedures for digital movements require prior skin flap procedures mobilized from an adjacent area or a free flap transferred via microsurgical means to restore the soft tissue coverage of the injured site. Restoration of the tendon activities is contemplated once these procedures are completed. At a minimum, the rehabilitative regimen in general takes 2–3 years to complete. Centers unable to offer the full range of reconstruction should refer patients to those more versed in limb salvage and hand surgery.

Conclusion

Effective hand reconstructive procedures rely not only on the surgeon's surgical judgment and skill but also on effective OT and the patient's compliance with rehabilitative treatment. As such it should only be attempted at centers with specialized surgical and therapeutic expertise. An experienced burn reconstructive hand surgeon can help move a patient toward even greater maximal medical improvement. A well-planned regimen is essential to restore these individuals to their former lives. This must be carried out in a multidisciplinary manner with an experienced surgeon and therapist.

Complete references available online at www.expertconsult.inkling.com

Further Reading

Agir H, Sen C, Alagoz S, Onyedi M, Isil E. Distally based posterior interosseous flap: primary role in soft-tissue reconstruction of the hand. *Ann Plast Surg*. 2007;59(3):291-296.

Byrne M, O'Donnell M, Fitzgerald L, Shelley OP. Early experience with fat grafting as an adjunct for secondary burn reconstruction in the hand: technique, hand function assessment and aesthetic outcomes. *Burns*. 2016;42(2):356-365.

Greenbalgh DG. Management of acute burn injuries of the upper extremity in the pediatric populations. *Hand Clin*. 2000;16(2):175-186.

Luce EA. The acute and subacute management of the burned hand. *Clin Plast Surg*. 2000;27(1):49-63.

McKee DM. Acute management of burn injuries to the hand and upper extremity. *J Hand Surg*. 2010;35(9):1542-1544.

Moore ML, Dewey WS, Richard RL. Rehabilitation of the burned hand. *Hand Clin*. 2009;25(4):529-541.

Sabapathy SR, Bajantri B, Bharathi RR. Management of post burn hand deformities. *Indian J Plast Surg*. 2010;43(suppl):S72-S79.

Tredget EE. Management of the acutely burned upper extremity. *Hand Clin*. 2000;16(2):187-203.

Vivek Jain F-CW. The metacarpal hand. In: Norman Weinzweig JW, ed. *The Mutilated Hand*. Lansing: University of Michigan/Elsevier Mosby; 2005:280.

References

1. Raine TJ, Heggers JP, Robson MC, et al. Cooling the burn wound to maintain microcirculation. *J Trauma*. 1981;21(5):394-397.
2. Nissen NN, Gamelli RL, Polverini PJ, et al. Differential angiogenic and proliferative activity of surgical and burn wound fluids. *J Trauma*. 2003;54(6):1205-1210, discussion 1211.
3. Smith MA, Munster AM, Spence RJ. Burns of the hand and upper limb – a review. *Burns*. 1998;24(6):493-505.
4. Salisbury RE. Reconstruction of the burned hand. *Clin Plast Surg*. 2000;27(1):65-69.
5. Danin A, Georgesco G, Touze AL, et al. Assessment of burned hands reconstructed with Integra((R)) by ultrasonography and elastometry. *Burns*. 2012;38(7):998-1004.
6. Kok K, Georgeu GA, Wilson VY. The Acticoat glove-an effective dressing for the completely burnt hand: how we do it. *Burns*. 2006;32(4):487-489.
7. Branski LK, Mittermayr R, Herndon DN, et al. Fibrin sealant improves graft adherence in a porcine full-thickness burn wound model. *Burns*. 2011;37(8):1360-1366.
8. Butts CC, Sahawneh J, Duffy A, et al. Cost-benefit analysis of outcomes from the use of fibrin sealant for fixation of skin grafts in small-size burns compared to staples as historical controls: a retrospective review. *Ann Plast Surg*. 2015;74(2):173-175.
9. Harrison DH, Parkhouse N. Experience with upper extremity burns. The Mount Vernon experience. *Hand Clin*. 1990;6(2):191-209.
10. Sungur N, Ulusoy MG, Boyacgil S, et al. Kirschner-wire fixation for postburn flexion contracture deformity and consequences on articular surface. *Ann Plast Surg*. 2006;56(2):128-132.
11. Burm JS, Chung CH, Oh SJ. Fist position for skin grafting on the dorsal hand: I. Analysis of length of the dorsal hand surgery in hand positions. *Plast Reconstr Surg*. 1999;104(5):1350-1355.
12. Burm JS, Oh SJ. Fist position for skin grafting on the dorsal hand: II. Clinical use in deep burns and burn scar contractures. *Plast Reconstr Surg*. 2000;105(2):581-588.
13. Dantzer E, Queruel P, Salinier L, et al. Dermal regeneration template for deep hand burns: clinical utility for both early grafting and reconstructive surgery. *Br J Plast Surg*. 2003;56(8):764-774.
14. Pensler JM, Steward R, Lewis SR, et al. Reconstruction of the burned palm: full-thickness versus split-thickness skin grafts–long-term follow-up. *Plast Reconstr Surg*. 1988;81(1):46-49.
15. Pham TN, Hanley C, Palmieri T, et al. Results of early excision and full-thickness grafting of deep palm burns in children. *J Burn Care Rehabil*. 2001;22(1):54-57.
16. Bunyan AR, Mathur BS. Medium thickness plantar skin graft for the management of digital and palmar flexion contractures. *Burns*. 2000;26(6):575-580.
17. Wu LC, Gottlieb LJ. Glabrous dermal grafting: a 12-year experience with the functional and aesthetic restoration of palmar and plantar skin defects. *Plast Reconstr Surg*. 2005;116(6):1679-1685.
18. Kraemer MD, Jones T, Deitch EA. Burn contractures: incidence, predisposing factors, and results of surgical therapy. *J Burn Care Rehabil*. 1988;9(3):261-265.
19. Tambuscio A, Governa M, Caputo G, et al. Deep burn of the hands: early surgical treatment avoids the need for late revisions? *Burns*. 2006;32(8):1000-1004.
20. Agir H, Sen C, Alagoz S, et al. Distally based posterior interosseous flap: primary role in soft-tissue reconstruction of the hand. *Ann Plast Surg*. 2007;59(3):291-296.
21. Baylan JM, Chambers JA, McMullin N, et al. Reverse posterior interosseous flap for defects of the dorsal ulnar wrist using previously burned and recently grafted skin. *Burns*. 2016;42(2):e24-e30.
22. Vitse J, Bekara F, Bertheuil N, et al. Perforator-based propeller flaps reliability in upper extremity soft tissue reconstruction: a systematic review. *J Hand Surg Eur Vol*. 2016;42(2):157-164.
23. Eski M, Nisanci M, Sengezer M. Correction of thumb deformities after burn: versatility of first dorsal metacarpal artery flap. *Burns*. 2007;33(1):65-71.
24. Lisa A, Maione L, Vinci V, et al. Early experience with fat grafting as an adjunct for secondary burn reconstruction in the hand: Technique, hand function assessment and aesthetic outcomes. *Burns*. 2016;42(7):1617-1618.
25. Byrne M, O'Donnell M, Fitzgerald L, et al. Early experience with fat grafting as an adjunct for secondary burn reconstruction in the hand: technique, hand function assessment and aesthetic outcomes. *Burns*. 2016;42(2):356-365.
26. Kurtzman LC, Stern PJ, Yakuboff KP. Reconstruction of the burned thumb. *Hand Clin*. 1992;8(1):107-119.
27. Raveendran SS, Syed M, Shibu M. Toe-to-hand transfer in a severely burned upper limb: a surgical dilemma. *J Plast Reconstr Aesthet Surg*. 2009;62(11):e463-e465.
28. Valauri FA, Buncke HJ. Thumb reconstruction – great toe transfer. *Clin Plast Surg*. 1989;16(3):475-489.
29. Williamson JS, Manktelow RT, Kelly L, et al. Toe-to-finger transfer for post-traumatic reconstruction of the fingerless hand. *Can J Surg*. 2001;44(4):275-283.
30. Vivek Jain F-CW. The metacarpal hand. In: Norman Weinzweig JW, ed. *The Mutilated Hand*. Lansing: University of Michigan Press/Elsevier Mosby; 2005:280.
31. Fufa DT, Chuang SS, Yang JY. Postburn contractures of the hand. *J Hand Surg Am*. 2014;39(9):1869-1876.
32. Al-Qattan MM, Al-Qattan AM. Defining the indications of pedicled groin and abdominal flaps in hand reconstruction in the current microsurgery era. *J Hand Surg*. 2016;41(9):917-927.
33. Chow JA, Bilos ZJ, Hui P, et al. The groin flap in reparative surgery of the hand. *Plast Reconstr Surg*. 1986;77(3):421-426.

55 Management of Burn Injuries of the Perineum

MOHAMED E. ISMAIL ALY and TED HUANG

Introduction

Burns of the perineal area are relatively uncommon despite the common involvement of the lower trunk and the lower extremities in burn injuries. The incidence of perineal burns was reported at around 12/1000 admissions more than 25 years ago.[1] While the occurrence of perineal burns has remained at around 1.0–1.5% at our institution, 35 children underwent genito-perineal reconstruction out of 1133 presenting with perineal burns between 2002 and 2009.

The continuous improvement in the survival rate following extensive burns of total body surface area (TBSA) more than 40% could account for the increase in the number of patients requiring secondary reconstruction.

Management During the Acute Phase of Injury

A conservative approach is usually the first line of management of perineal burns during the acute phase of admission.[1,2] The perineal area is cleansed daily with appropriate antiseptic and the wound is covered with antibiotic topical dressing. To avoid urine contamination of the burn area and the development of urethral strictures, the urethral tract is stented using an indwelling Foley catheter. The catheter is also used to decompress the urinary bladder and monitor urine output during the acute admission. The perineal area is neither splinted nor braced, the thighs are maintained at 15 degrees of abduction using a wedge splint to minimize hip contractures.

Other complications of perineal burns presenting during the acute injury phase include penile shaft necrosis, testicular necrosis, urethral stricture, and rectal prolapse. Although the Shriners Children Burns Hospital and the University of Texas Medical Branch Hospitals in Galveston, Texas, have adopted conservative management of perineal burns, the approach to wound care is, in practice, quite variable. The management plan is often modified depending on the anatomical structures involved in individual patients.

The burn is left to demarcate over time with the wound left to heal by secondary intention. Non healing wounds are reconstructed using partial-thickness or full-thickness skin grafts. On rare occasions, a local skin flap may be utilized from the adjacent normal skin to reconstruct full-thickness skin defects of the penile and scrotal areas.

BURNS OF THE PENIS

Burn injuries limited to the penis, although possible, are quite rare (Fig. 55.1). Concomitant involvement of the penis with burn injuries of the lower trunk and the perineal area, on the other hand, is quite common. Initial patient management, in addition to resuscitative measures, consists of wound care and urethral stenting. As mentioned earlier, an indwelling Foley catheter of appropriate size is inserted to stent the urethral tract and monitor urine output.

The catheter is removed once the swelling around the penile shaft has subsided and the wound status is delineated. No attempt is made to débride the burn wound early; the wound is left to demarcate and heal by secondary intention.

SKIN LOSS OVER THE PENILE SHAFT AND SCROTUM

Spontaneous healing is expected in most instances of burn injuries to the penis and scrotum since full-thickness injury of the penile and scrotal skin is relatively uncommon. Skin grafting, with a partial-thickness or full-thickness graft, could be used to cover the wound when healing is delayed (Fig. 55.2).

In rare instances, a skin flap is required to reconstruct structures such as the urethral tract and/or scrotal sac because of full-thickness skin loss. An inguino-pudendal skin flap mobilized from the inguinal crease area may be used if the use of a skin graft is judged not to be feasible.[3] The use of musculocutaneous flaps, such as a gracilis flap, is not recommended. The subsequent high tissue temperature developing in the skin paddle of the flap can potentially interfere with spermatogenesis.

BURNS OF LABIA MAJORA

Isolated burns of the labial area are rare, and such burns are often associated with injuries of surrounding areas such as the abdomen and inguinal folds. As in the management of burns of male genitalia, the injured areas are left to heal by secondary intention (Fig. 55.3).

Distortion of the labial structures mostly due to scar contraction in the pubic and inguinal areas is addressed by reconstruction at a later stage.

PERINEAL WOUND COVERAGE

An isolated burn injury of the perineal area is, as mentioned earlier, extremely rare; nevertheless the perineum

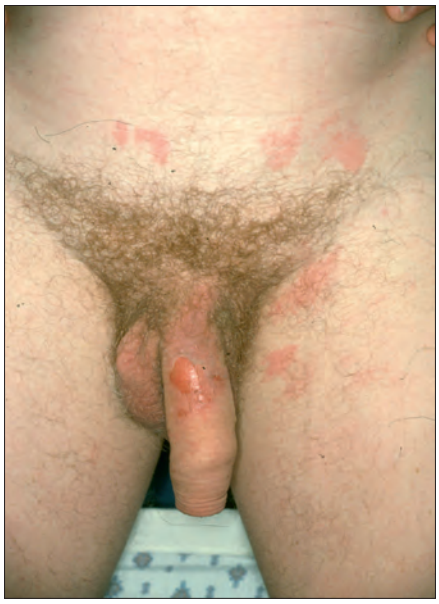


Fig. 55.1 An isolated burn injury of the penis is relatively uncommon. This was a 27-year-old man who sustained scald burns of the penis from accidentally spilling hot coffee onto his lap.

will be involved in extensive lower trunk/buttock burn injuries. The extent of scar contraction following wound healing will vary per the depth of burns. While the wound may heal spontaneously with residual minimal scarring, perineal contractures are a common sequela regardless of the methods used for wound care (Fig. 55.4).

The natural inclination of patients to adduct the thighs and hips while lying supine in bed during the recovery phase of acute burn injuries seems to aggravate scar contraction.

ANAL BURNS

Burns involving the anus are rare, although the area could be involved in extensive perineal burns. In the case of full-thickness skin loss around the anal opening, the use of a skin flap may be necessary to reduce the risk of stricture development. A skin flap mobilized from the adjacent area is required to reconstruct the perianal area. Wound coverage with a skin graft is technically difficult and will lead to the development of an anal stricture following graft contracture.

RECTAL PROLAPSE

Rectal prolapse can occur occasionally in young children with extensive burn injuries with or without perineal involvement. The pathophysiology of the development of rectal prolapse in infants with extensive burns remains unclear.

Redundant rectal mucosa; the structural relationship of the rectum to other pelvic organs such as the sacrum and coccyx, urinary bladder and uterus; and lack of muscular support provided by the pelvic musculature are anatomical features unique to infants 1–3 years old. All this could account for the development of rectal prolapse in this age group. A sudden increase in intraabdominal pressure, malnutrition, and constipation could conceivably aggravate the magnitude of the rectal mucosa descending through the anal opening.[4] Clinically, in addition to eversion of rectal mucosa, the presence of edematous swelling involving the buttocks and perianal area is quite common, despite the lack of burn injuries. The onset can be quite sudden without any obvious precipitating event; however, straining or the Valsalva maneuver can produce an eversion of the rectal canal through the anal opening.

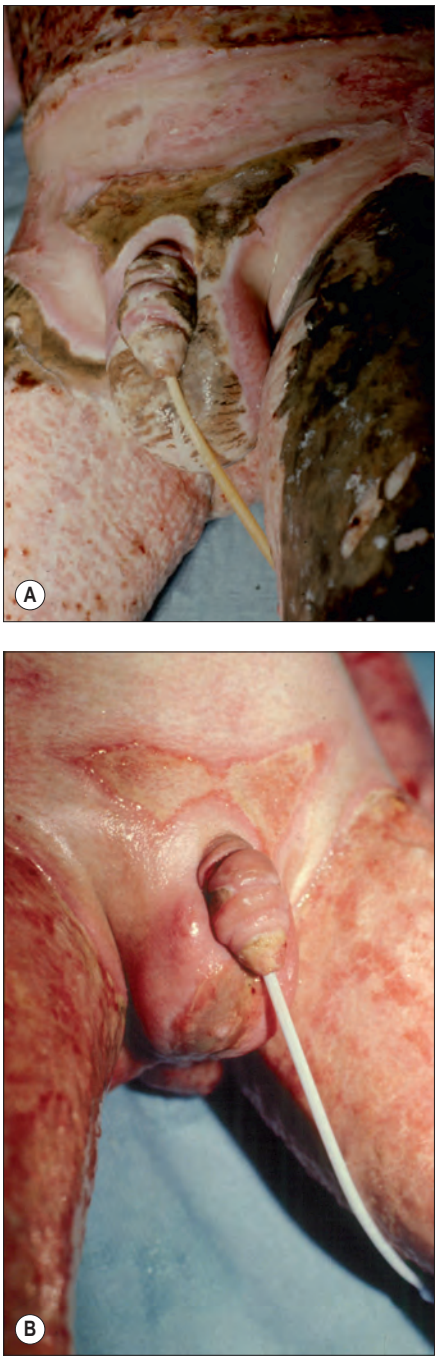
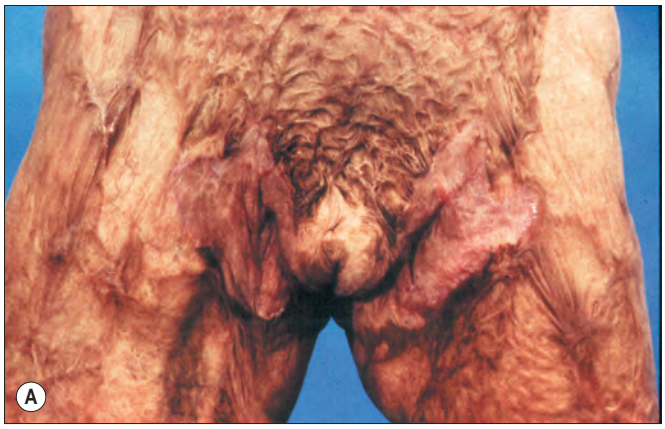


Fig. 55.2 **(A)** Burns of the penis are more commonly associated with injuries of the lower trunk and lower extremities. **(B)** Although skin grafts were used to achieve wound closure around the perineum, the major bulk of the penile wounds healed by secondary intention.



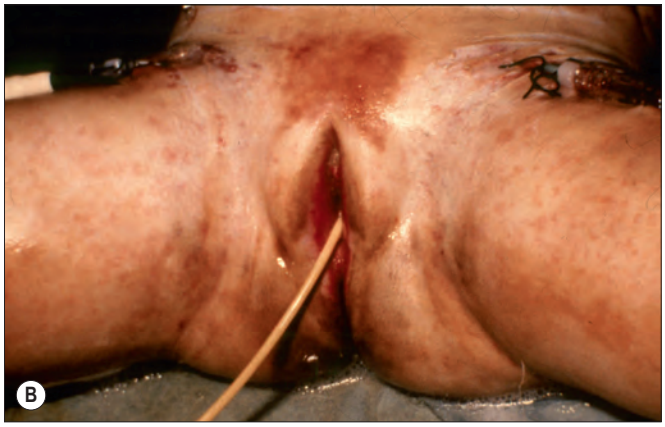


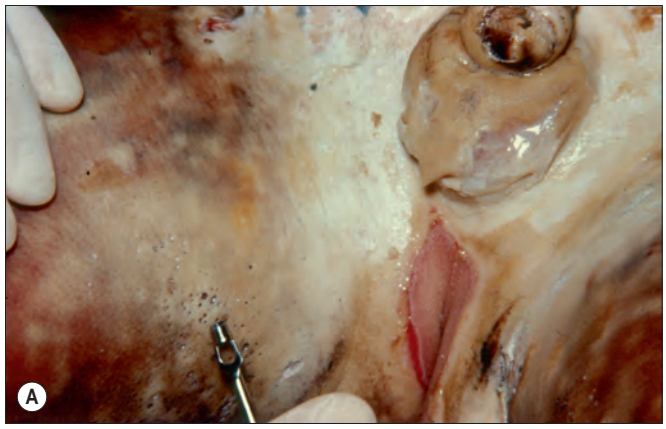
Fig. 55.3 **(A)** Burn injuries that involved the lower trunk and thighs, including the labia. While the lower abdomen and thighs required skin grafting, the labial injury was left to heal by secondary intention. **(B)** The appearance of the genitalia 5 years following the injury.

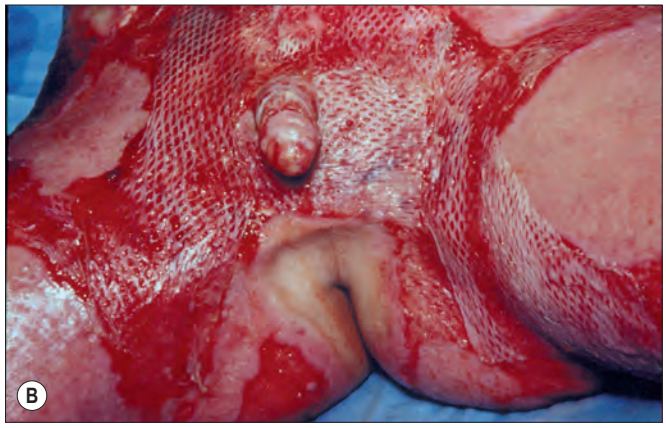
The treatment consists of rectal padding, daily cleansing of the perineal and perianal area, and a stool softener added to the dietary regimen to facilitate bowel movement. Spontaneous resolution of the rectal mucosa prolapse is likely as the nutritional status of the patient improves and tissue swelling subsides (Fig. 55.5). Surgical intervention, although in most instances unnecessary, is indicated if the prolapse is not readily reducible due to the development of anal sphincter dysfunction and/or intussusception.[4,5]

Reconstruction of Established Deformities of the Perineum and Perineal Structures

Cicatricial contractures around the perineum are the most common sequela of perineal burns.[1,6] The magnitude of the contracture is exaggerated as a result of burn scar contraction in the inguinal crease and inferior-medial gluteal folds. Other complications, although relatively uncommon, included complete loss of the penis, anal stenosis, and intractable rectal prolapse.

There are numerous reconstructive techniques available such as z-plasty scar release, interpositional skin flap technique, incisional release of scars and closure with local skin flaps, or skin grafts to reconstruct the deformities. In practice, the technique used to reconstruct perineal and genital deformities varies depending on the magnitude of scarring around the perineum and the extent of functional impediment encountered.





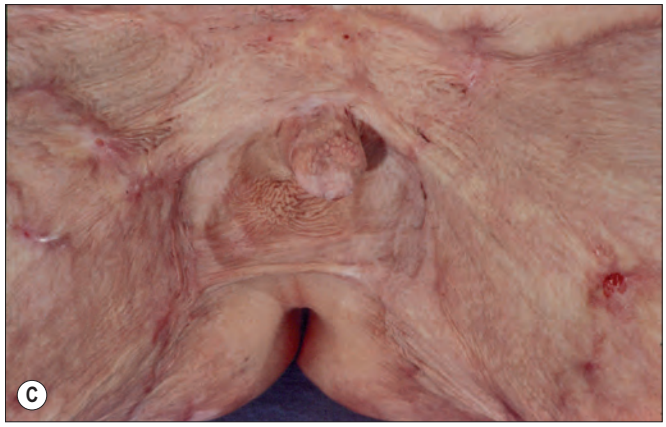
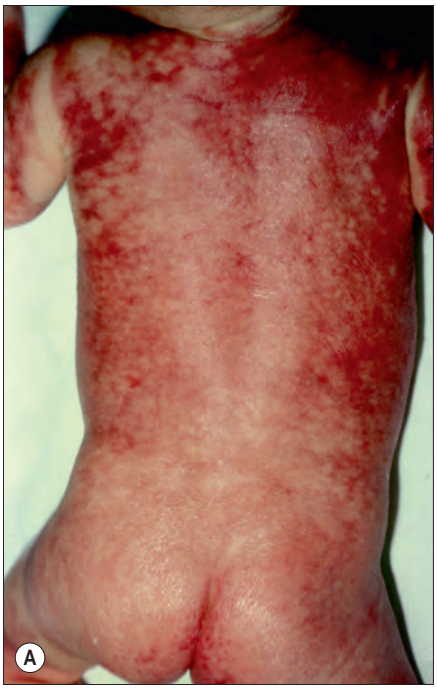
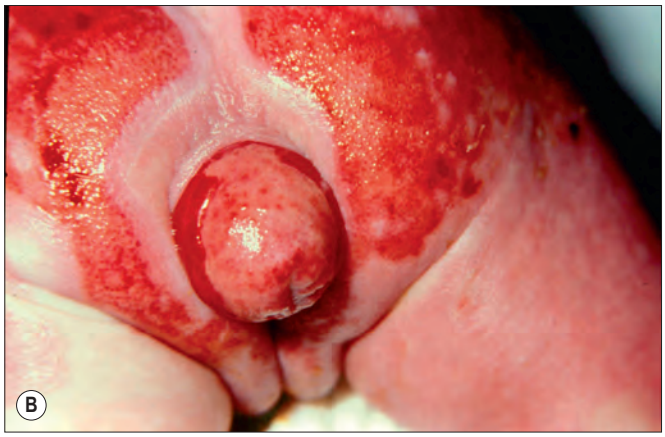


Fig. 55.4 **(A)** The patient was an 8-year-old child who sustained third-degree burn injuries of the trunk and lower extremities also involving the penis and the scrotum. **(B)** The wound including the scrotum was débrided, and skin was grafted using a meshed partial-thickness skin graft. **(C)** Scar hypertrophy and burn scar contractures developed at a later stage; tight scars across the perineum interfered with thigh movement.

RECONSTRUCTION OF PENILE DEFORMITY

The task of assessing the exact extent of penile deformities can be difficult. Distortion of the penile anatomy





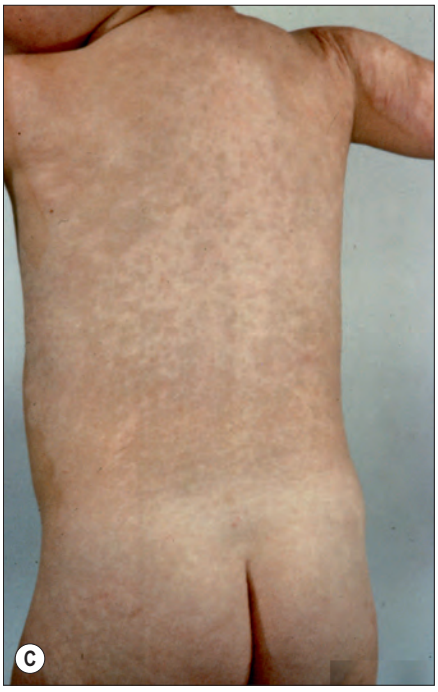


Fig. 55.5 **(A)** This patient was a 2-year-old girl who had sustained 65–70% total body surface burns. **(B)** Prolapse of the rectum appeared 12 days following the injury and was managed conservatively. **(C)** The prolapse receded spontaneously 2 months later as she recovered from the burn injury.

attributable to scar contracture could be due to skin loss or a combination of skin and Buck's fascia involvement. In addition, scarring in the pubic area and/or the inguinal fold can further exaggerate the extent of penile deformity, as mentioned earlier.

Engorging the penile shaft is required to assess the extent of penile deformity because the gross appearance of a flaccid penis can be misleading. Artificial penile erection is created under anesthesia by placing a tourniquet at the base of the penis using a piece of quarter-inch Penrose drain and normal saline solution is injected into the corpus cavernosum sufficiently to induce congestion. The cause of shaft deformity whether attributable to skin loss and/or fascial loss will be delineated once the artificial erection is achieved.

The skin defect produced following incisional release of the scar is covered with a full-thickness skin graft if Buck's fascia is not involved in the burn injury. In rare instances, if Buck's fascia is involved, surgical release of the fascial deformity is required. A dermal graft harvested from the lower abdomen can be used to reconstruct the fascial defect. A skin flap mobilized from the area along the groin crease as an island pedicled skin flap could provide an alternative cover to reconstruct the skin defect.

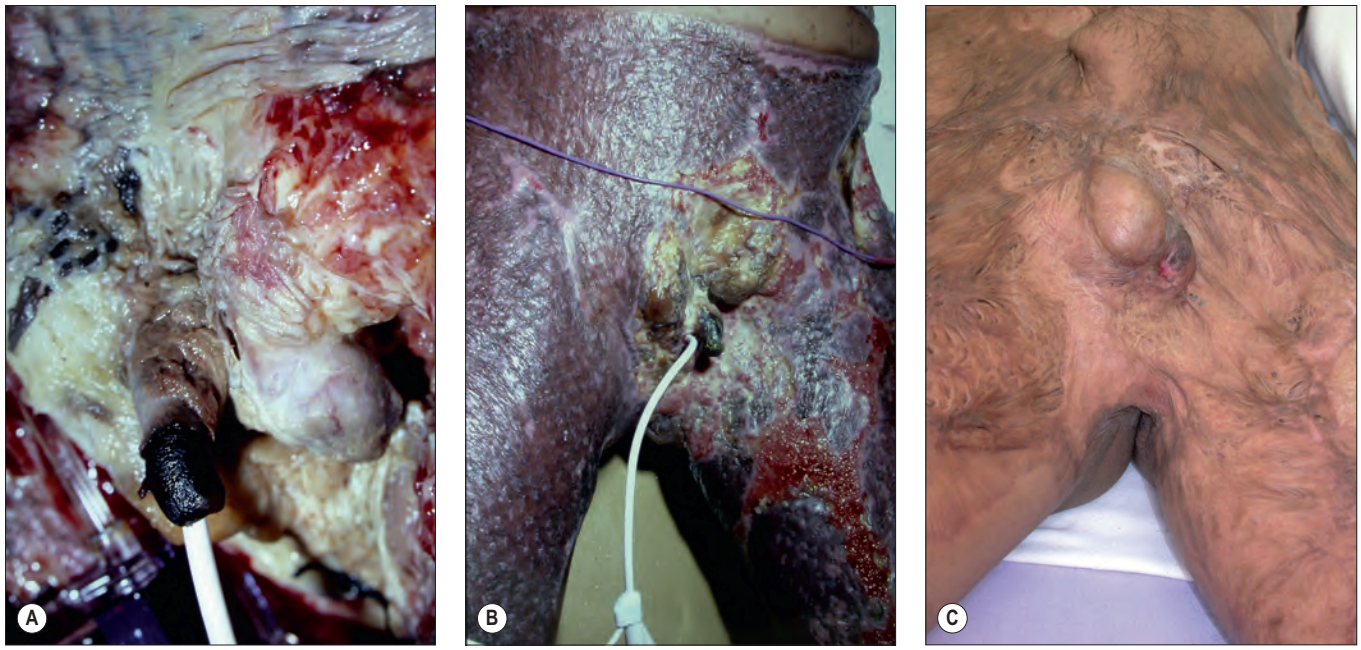


Fig. 55.6 **(A)** A full-thickness burn of the penis, although uncommon, can occur, and the outcome is devastating, as seen in this 10-year-old boy. No attempt was made to remove the penile tissue, even though it appeared grossly necrotic. Instead, the wound was left to demarcate, and an indwelling Foley catheter was used to stent the urethra. **(B)** The patient lost the phallus entirely. **(C)** The patient can urinate through a short remnant of the penis. Reconstruction of the penile shaft was planned for a later stage.

Complete loss of the penis, although devastating, is extremely rare (Fig. 55.6). If present, penile reconstruction is delayed until puberty. The delay is often necessary due to limited soft tissues that can be harvested for genital reconstruction soon after the burn injury.

There are several methods currently available to reconstruct a neo-phallus: a segment of rectus abdominis musculocutaneous flap, for instance, may be mobilized from the lower abdomen to form a neo-phallus. Although the appearance of a reconstructed phallus may be cosmetically acceptable, the structure usually lacks sensation; it serves as a urinary conduit at best.

The microsurgical tissue transfer of a combination of an innervated radial forearm osteocutaneous flap and big toe pulp has been described for penile reconstruction.[7] While the urethral tract was reconstructed utilizing a full-thickness skin graft or a tube-within-a-tube technique at the time of penile reconstruction using a radial forearm osteocutaneous flap, the pulp of the big toe was used to reconstruct a glans penis. The big toe pulp provided a structural contour resembling the glans, and cooptation of the digital nerve to the penile nerve restored sensory nerve functions (Fig. 55.7).

RECONSTRUCTION OF SCROTAL DEFORMITIES

Full-thickness burn injuries of the scrotum often result in scar encasement of testicular structures; reconstruction requires surgical release of the scarred areas. A thin skin flap such as the inguino-pudendal flap or a flap mobilized from the adjacent area is required to cover the resultant defect. A musculocutaneous flap such as a gracilis flap is not suitable for scrotal reconstruction because of the thickness of the flap and possible reduction in spermatogenesis due to high tissue temperature within the flap. Even though contracture deformity is likely to occur in the long term, a skin graft can be used to cover the defect following scar release.

RECONSTRUCTION OF LABIAL DEFORMITY

An isolated contour deformity of the labia majora is relatively uncommon; nevertheless scar contraction occurring in the suprapubic and pubic area, as well as the inguinal fold, could distort the normal configuration of the labia. Primary surgical release of the contracted scar tissues around the pubic and inguinal fold areas is an essential step to determine the extent of labial deformity and the reconstructive technique for the deformed labia.

To restore a contour deformity caused by skin and subcutaneous tissue loss, a skin flap may have to be mobilized from the adjacent area. To reconstruct a contour deformity due to parenchymal tissue loss, lipo-modeling (i.e., transfer of freshly harvested fat cells) could be useful. To inject free fat cells to augment the labial contour, the cells are aspirated from the lower abdomen using the inner cannula of a no. 14 Intracath needle attached to a 3-mL syringe. The fat is prepared and injected in the desired area as per the "Coleman" technique.[8]

RECONSTRUCTION OF BAND DEFORMITY AROUND THE PERINEUM

Scarring and scar contracture of the perineum is a common sequela of perineal burns, especially if they are left to heal by secondary intention. Although it seldom causes difficulties to the young patient, perineal scars could potentially

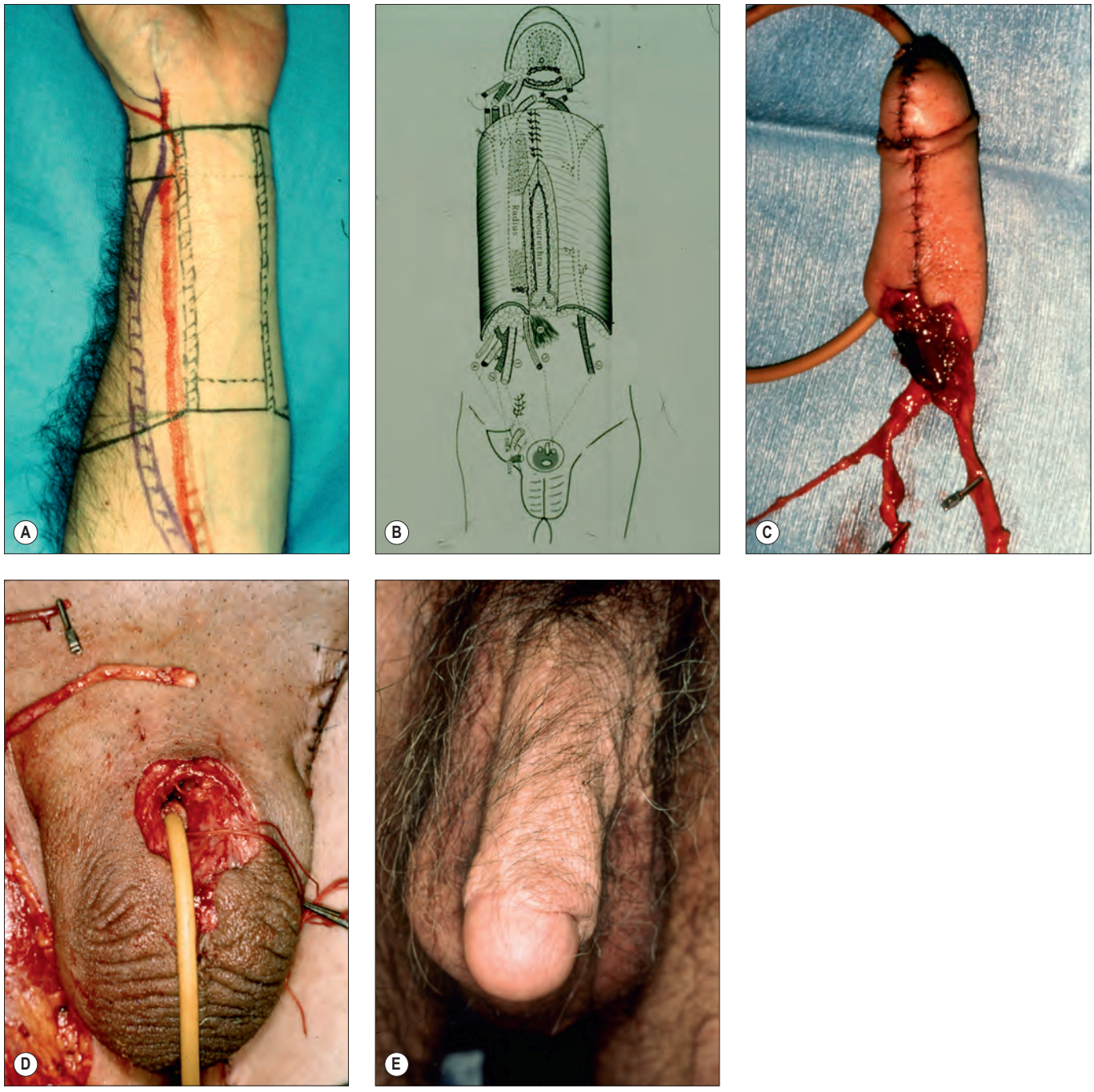


Fig. 55.7 (A) There are various techniques available for penile reconstruction; a radial forearm composite flap, one of the methods currently in use, was chosen to reconstruct a phallus structure for a 51-year-old man who lost his penis following tumor excision. **(B)** As shown in a schematic drawing, a section of the skin with radial artery attached is harvested from the volar surface of the forearm and utilized for penile reconstruction. A tube-inside-a-tube was used to reconstruct the urethral tract. In addition, the pulp from the big toe was also used to reconstruct the glans penis. **(C)** The tissues were assembled with vessels and nerve structures set for anastomosis. **(D)** The appearance of genitalia before reconstruction. **(E)** The appearance of the reconstructed penis. (A,B,E from Sasaki K. Penile reconstruction: combined use of an innervated forearm osteocutaneous flap and big toe pulp. *Plast Reconstr Surg.* 1998;104:1054–1058.)

interfere with function and physical mobility because of tightness or contractures. In addition, the patient may encounter difficulties with bowel movement because of gluteal contractures and cicatricial changes involving the anal opening.

The deformity developing in the perineal area is usually a tight band in the suprapubic area or between the ischial tuberosities. The scars result in inadequate spreading of the buttocks and discomfort while sitting, eventually producing significant functional impairment.

Although a contracted perineal band can be incised to achieve release, the task of reconstructing the resultant defect can be difficult. Recurrence of contractures is a common sequela following the use of a skin graft. Instead,

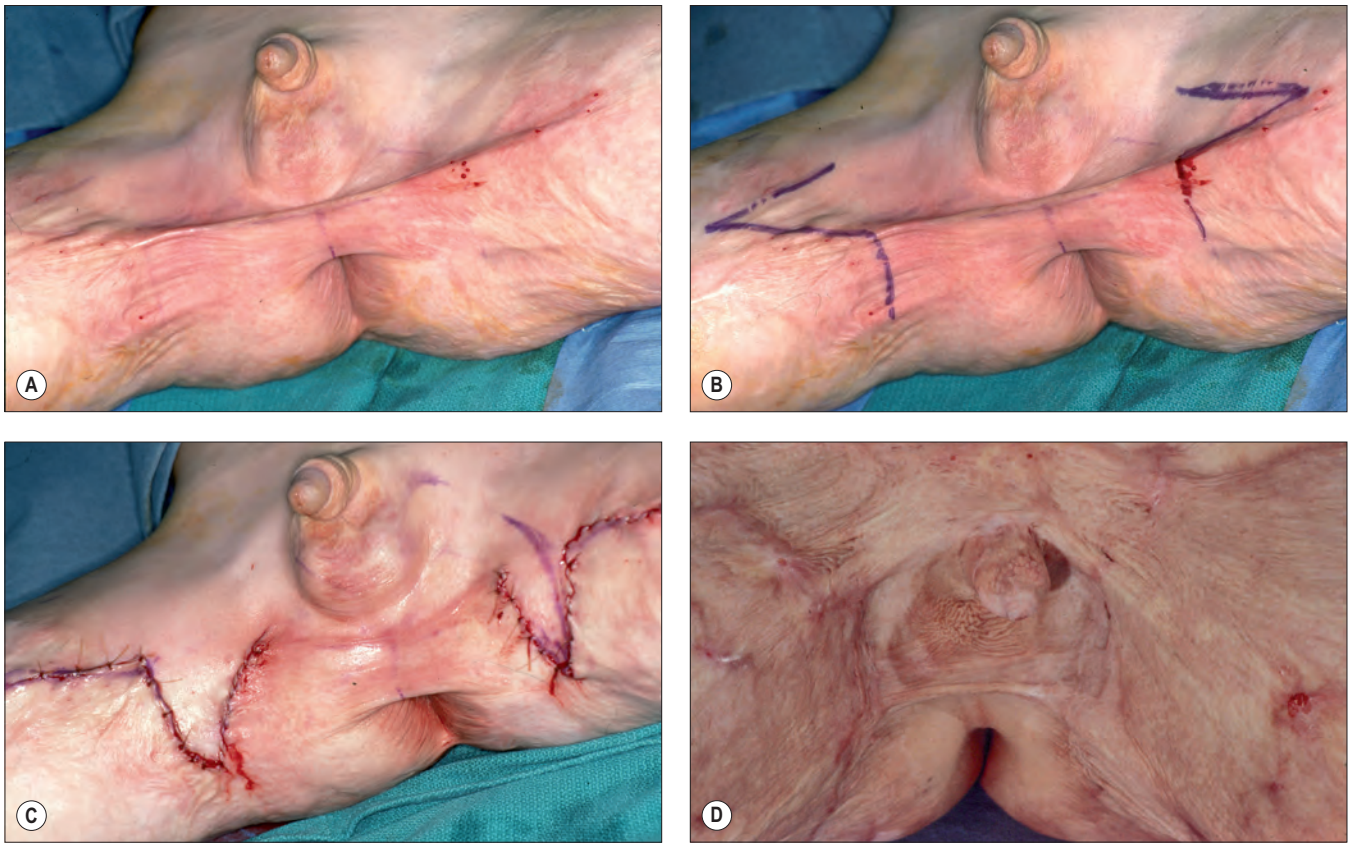


Fig. 55.8 **(A)** A tight scar band in the perineal area following burn injuries involving the perineum and the lower extremities. **(B)** Releasing incisions were placed in the areas distal to the anal opening to avoid injuring the anal sphincter. A triangular flap was designed within the uninjured area at each end of the scar band. A releasing incision was set perpendicularly to the direction of the scar band. **(C)** Each triangular flap was rotated 90 degrees to close the open wound resulting from incisional release. **(D)** Tight bands develop in the perineal area.

multiple z-plasties are the preferred reconstruction technique to release scar bands around the perineum.

The Technique of Multiple Z-Plasties

With the patient placed in lithotomy position, tightness and scar bands can be delineated with abduction of the hip joint (Fig. 55.8A). A line is drawn across the scar band along the horizontal direction of the band. The length of the horizontal line may extend from one side of the scarred area to the other. A triangular flap with its apex at the end of the horizontal line is marked. The angle may vary between 30 and 60 degrees depending on the uninjured tissues available at both ends of the horizontal line. The length of the limb of each triangle will be the same as the incision made perpendicular to the horizontal line to release the tight band (Fig. 55.8B).

Two z-plasties (i.e., two triangular flaps with a 30- to 60-degree angle and a 90-degree angle, respectively) are formed as the flaps are raised along the skin markings made. Release of a contracted scar band is achieved by rotating these two flaps at each end (Fig. 55.8C). The release of a tight band across the perineal area is maintained by interposing a segment of the soft tissues mobilized. Fig. 55.8D shows the appearance of the perineum 4 years following the releasing procedure.

Although the extent of perineal release may be limited because of the scarred tissues surrounding the triangular flaps, the z-plasty technique produces a change in the direction of scar tissue pull, thus diminishing the tightness around the perineal area.

RECONSTRUCTION OF ANAL STRICTURES

While burn injuries rarely involve the entire anorectal canal, it is not unusual for the perianal skin and the external sphincter ani muscle to be involved in extensive perineal burns. Anal strictures due to scar contraction and the cicatricial involvement of the external sphincter ani muscle are common sequelae. Cicatricial changes around the anal opening can and will usually interfere with bowel movement.

The treatment requires surgical release of constricted scar bands around the anal opening. An interpositional skin flap fashioned as an island flap or a modified z-plasty with skin flaps mobilized from the adjacent area is used to make up the tissue defect (Fig. 55.9).

The use of skin grafts to reconstruct the defect is not useful because, usually, graft application is difficult and stricture recurrence is common.

RECONSTRUCTION OF RECTAL PROLAPSE

Although the problem of rectal prolapse is, in most instances, self-limiting and the prolapse will recede spontaneously as

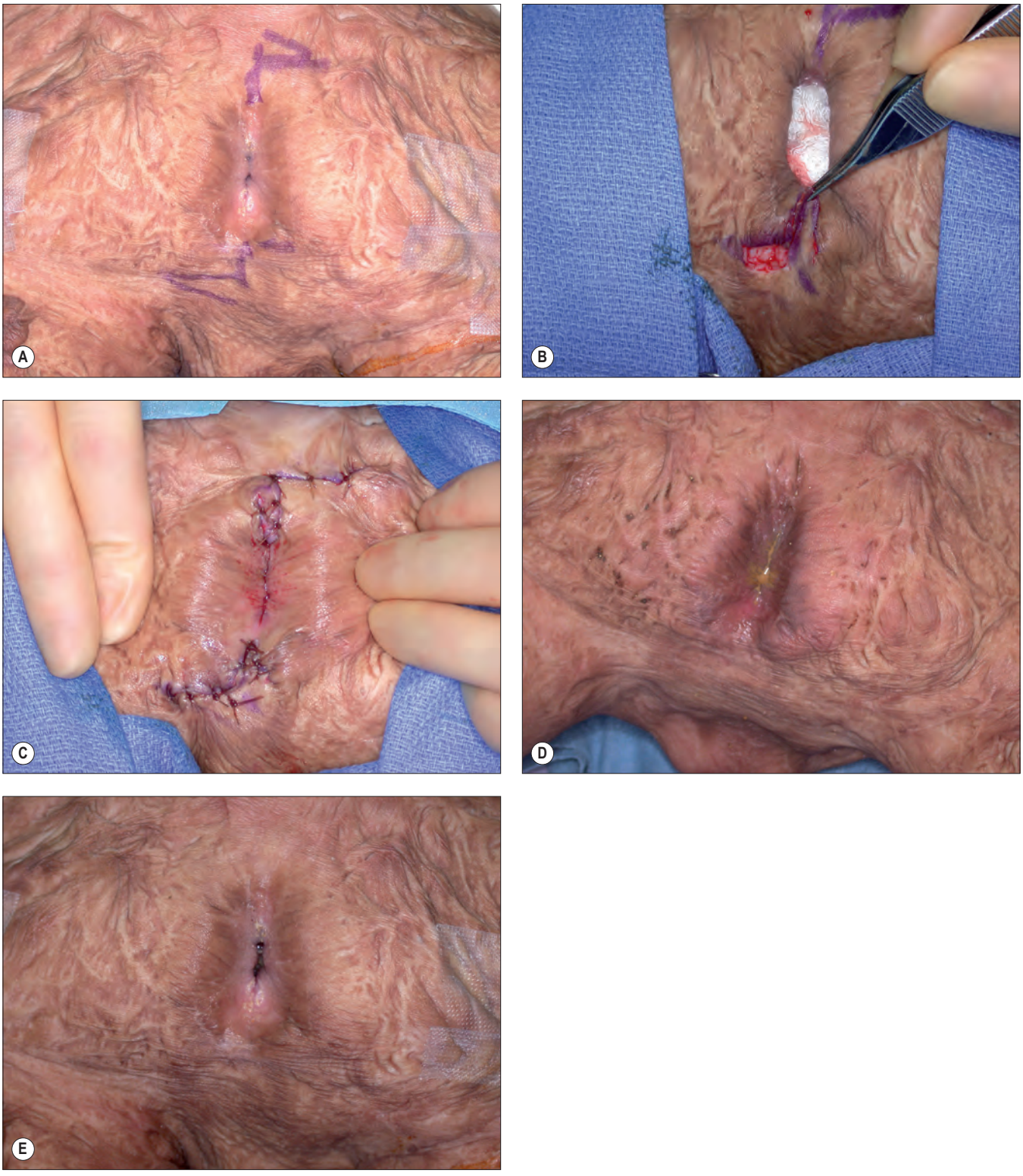


Fig. 55.9 **(A)** A 4-year-old boy developed, in addition to a tight scar band across the perineum, anal incontinence because of cicatricial contractures involving the entire perineal area. **(B)** A modified multiple z-plasties technique was utilized to reconstruct the perineal contracture and anal stenosis. **(C)** Skin flaps were rotated into the areas to reconstruct the deformity following the surgical release. **(D)** The appearance of the anal area before release. **(E)** The appearance of the anal area 9 months following release.

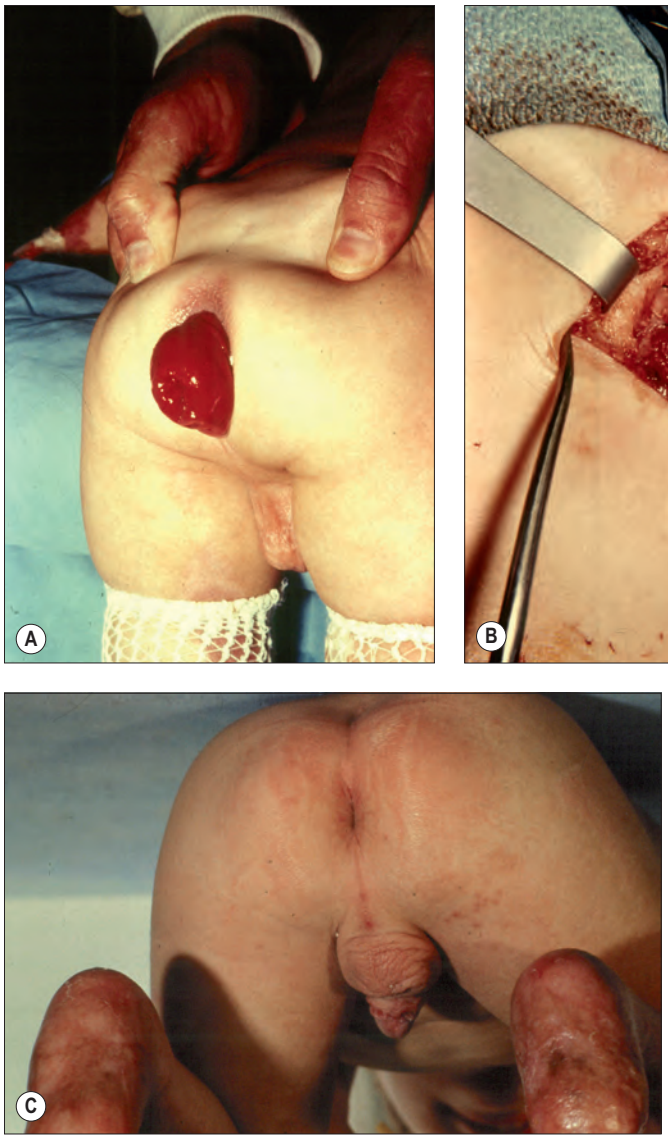


Fig. 55.10 **(A)** A 2-year-old boy who had sustained a third-degree scald burn that involved the lower extremities; he developed rectal prolapse 10 days following the injury. **(B)** He underwent a rectopexy procedure due to the persistent eversion of the rectal mucosa. **(C)** The patient regained anal continence 6 months after the surgery.

the nutritional status of the patient and wound healing improves, surgical intervention is required if the rectal prolapse becomes intractable (Fig. 55.10).[5]

Conclusion

Burn injuries of the perineum are relatively uncommon, and management during the acute phase of injury is conservative. The urethral tract is stented with an indwelling Foley catheter and the wound is cleansed daily. Neither a splint nor a brace is used to immobilize the perineal area, and the wound is usually left to heal by secondary intention. The resultant deformity, with the rare exception of total loss of the penis, is limited.

Instead disfigurement of the scrotal/labial contour and/or scar bands around the genital area are the common presentation in most patients. The reconstructive approach to these deformities centers around scar release of tight bands around the perineal structures. Incisional release and reconstruction utilizing z-plasty techniques or an interpositional skin flap is effective in correcting the deformities.

Complete references available online at
www.expertconsult.inkling.com

Further Reading

Alghanem AA, McCauley RL, Robson RC, et al. Management of pediatric perineal and genital burns: twenty-year review. *J Burn Care Rehabil*. 1990;11:308-311.

Ashcraft KW, Garred JL, Holder TM, et al. Rectal prolapse: 17-year experience with the posterior repair and suspension. *J Pediatr Surg*. 1990;25(9):992-995.

Huang T. Twenty years of experience in managing gender dysphoric patients: I. Surgical management of male transsexuals. *Plast Reconstr Surg*. 1995;96:921-930.

Sasaki K, Nozaki M, Morioka K, et al. Penile reconstruction: combined use of an innervated forearm osteocutaneous flap and big toe pulp. *Plast Reconstr Surg*. 1998;104:1054-1058.

References

1. Alghanem AA, McCauley RL, Robson MC, et al. Management of pediatric perineal and genital burns: twenty-year review. *J Burn Care Rehabil*. 1990;11(4):308-311.
2. Rutan RL. Management of perineal and genital burns. *J ET Nurs*. 1993;20(4):169-176.
3. Huang TT. Twenty years of experience in managing gender dysphoric patients: I. Surgical management of male transsexuals. *Plast Reconstr Surg*. 1995;96(4):921-930; discussion 931-934.
4. Rowe MI, O'Neil JA, Grosfeld JL, eds. *Other Disorders of Anus and Rectum, Anorectal Function, Essentials of Paediatric Surgery*. Chicago, III: Mosby Year Book; 1995:451-462.
5. Ashcraft KW, Garred JL, Holder TM, et al. Rectal prolapse: 17-year experience with the posterior repair and suspension. *J Pediatr Surg*. 1990;25(9):992-994; discussion 994-995.
6. Pisarski GP, Greenhalgh DG, Warden GD. The management of perineal contractures in children with burns. *J Burn Care Rehabil*. 1994;15(3):256-259.
7. Sasaki K, Nozaki M, Morioka K, et al. Penile reconstruction: combined use of an innervated forearm osteocutaneous flap and big toe pulp. *Plast Reconstr Surg*. 1999;104(4):1054-1058.
8. Coleman SR. Structural fat grafting: more than a permanent filler. *Plast Reconstr Surg*. 2006;118(3 suppl):108s-120s.

56 Reconstruction of Burn Deformities of the Lower Extremity

WILLIAM LINEAWEAVER and DEREK M. CULNAN

Assessment of Salvage Potential

Acute care of a burned lower extremity prioritizes circulation and coverage. These goals are achieved through escharotomies and fasciotomies as necessary and excision and coverage of the burn wounds. Reconstruction of lower-extremity burn sequelae, however, requires a more complex and detailed definition of defects, deformities, and functional goals. Assessment of a lower limb for secondary post-burn reconstruction is therefore directed toward a useful outcome.[1]

Sensation is an important element in lower-extremity salvage potential. A desensate foot can be a source of chronic wounds and may be a less functional outcome than a below-knee prosthesis. Treatable sites of sensory nerve compression are increasingly recognized in burned lower extremities, and nerve decompression at the tarsal tunnel (for plantar sensation) and the popliteal fossa (for dorsal sensation) can be initially considered to restore foot sensation.[2]

Muscle function must be sufficient to provide useful active motion at the ankle, knee, and hip. If direct muscle damage is incompatible with function, limb salvage may be abandoned. Some muscle deficits, such as peroneal nerve palsy with foot drop, may be associated with nerve compression, and decompression may be an effective reconstruction to restore muscle function.

Satisfactory lower-extremity salvage potential requires functional skeletal components. Associated fractures must be stably healed. Major joints must have sufficient cartilage surfaces and capsule integrity to contribute to limb function.

When evaluating a lower-extremity soft tissue burn complication, the surgeon should consider whether the problem is a deformity or a defect.[3]

A *deformity* implies a distortion of parts correctible by rearrangements of local tissue. For example, a single vertical scar band across a popliteal fossa, causing a flexion contracture of the knee, may be incised and lengthened by local Z-plasties that transpose adjacent supple tissue into the scar site and permit knee extension. A *defect* is an absence of parts and requires replacement by distant tissue. Dorsal toe contractures, when released, may be secondary to soft tissue deficiency which, when revealed by contracture release, will require skin grafts to cover the defect (Fig. 56.1). Full-thickness soft tissue loss around a knee joint may require a local muscle flap (e.g., a gastrocnemius belly) or a microsurgical flap for adequate treatment of the defect (Fig. 56.2). Clear definition of the problem should result in an appropriate selection of a reconstruction strategy.

Finally the status of the second lower-extremity provides a context for assessment of the burned lower extremity. A patient with one intact lower extremity may be less interested in complex reconstructive salvage of a functionally impaired extremity. Elective amputation with prosthetic may be a less complicated path to ambulation supported by the uninjured extremity. Two injured lower extremities, however, may make reconstruction a higher priority in either or both since loss of both lower extremities is a substantially greater disability than single lower-extremity loss.[4]

Amputations

Assessment of burn injuries to a lower extremity can lead to the conclusion that there is insufficient salvage potential to justify attempts at reconstruction. Lack of sensation, extensive muscle or joint damage, and a functioning second lower extremity may add up to a decision to amputate the impaired portion of a lower extremity.

Dislocated, dorsally contracted toes can be removed with simple amputations at the metatarsophalangeal joints. More extensive damage to the forefoot can be treated with amputations at the tarso-metatarsal level or through the ankle joint (Lisfranc and Symes procedures, respectively). Such amputations require sufficient sensation and circulation to obtain a stable result.[5]

Unreconstructable injury involving the foot and ankle can proceed to below-the-knee amputation. The priorities of that procedure include stable coverage of the tibia and fibula as well as preservation of sufficient skeletal length to support a prosthesis. The amputation closure is best achieved with tissue from the posterior calf. A refinement of amputation closure consists of using the proximal gastrocnemius muscle and its overlying skin to create a durable, myocutaneous pad.[6] This technique can be further modified to use gastrocnemius muscle covered with skin grafts from initial burn care (Fig. 56.3).

Severe damage extending proximal to the knee may lead to above-knee amputation. In this procedure, maximum secure length is useful. Anterior and posterior thigh muscles are mobilized and stabilized to each other to form the basis of closure of the overlying skin. Here also muscle covered with skin grafts can be satisfactory for stable stump closure.

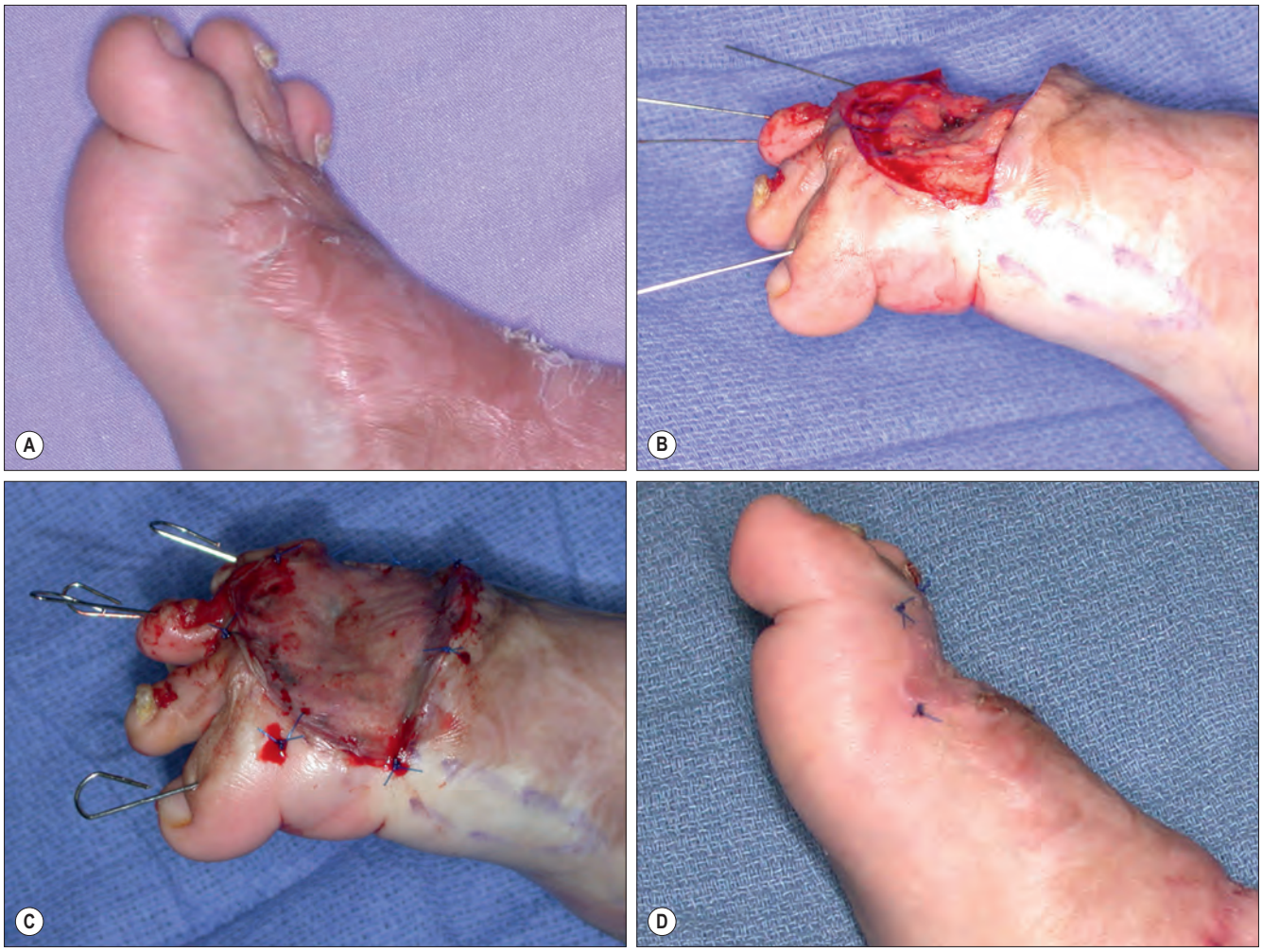


Fig. 56.1 In children with recent onset of toe extension contracture, surgical manipulation of the volar plate of the MTP joint capsule is usually unnecessary. **(A)** Cicatrical dorsal toe contracture creating a hammer toe like deformity. **(B)** A Kirschner's wire of 0.020–0.035 inch size is inserted through the proximal phalanx to keep the digit in full extension while maintaining the MTPJ in 45–60° plantar flexion. **(C)** Split-thickness skin graft is placed to fill the skin defect. **(D)** The wires are removed 10–14 days later, once the take of skin graft or flap is established.

Hip disarticulation can be life-saving in burn wounds of the groin and perineum exposing major vessels. In late reconstruction of contractures of the hip, a hip disarticulation can replace a nonfunctional lower extremity with a stable wound that can support a prosthesis.

Early Reconstruction

Some specific maneuvers can contribute to the prevention of later complications.

For deep burns of the dorsum of the foot involving the toes, K-wire fixation of the toes across the metatarsophalangeal joints can effectively splint the toes to prevent hyperextension contractures while soft tissue coverage is established. Early splinting and physical therapy can be applied to ankle and knee burns to maximize range of motion and minimize contractions.

Flap reconstruction is a rare element in acute burn management, but such procedures can be considered to treat specific sites.[7]

Deep wounds around the ankle can be covered with local flaps to prevent unstable wounds, especially over the malleoli (Fig. 56.4). Full-thickness burns around the knee are within the range of local flaps that can provide stable coverage to protect the joint and avoid flexion contractures (Fig. 56.2).

Deep burns of the groin can lead to consideration of unilateral or contralateral inferiorly based rectus flaps that can securely cover the femoral canal structures and allow early motion at the hip (Fig. 56.5).

Late Reconstruction

By dorsal release of the metatarsophalangeal joints, hyperextension contractures of the toes are relieved. If scar incision reveals a defect, skin grafts can provide stable tissue replacement.[8] If the dorsal skin is sufficiently supple, the problem may be considered a deformity treatable by creating a V-shaped flap over the metatarsophalangeal joints, advancing the flap to allow reduction of the toes to at least

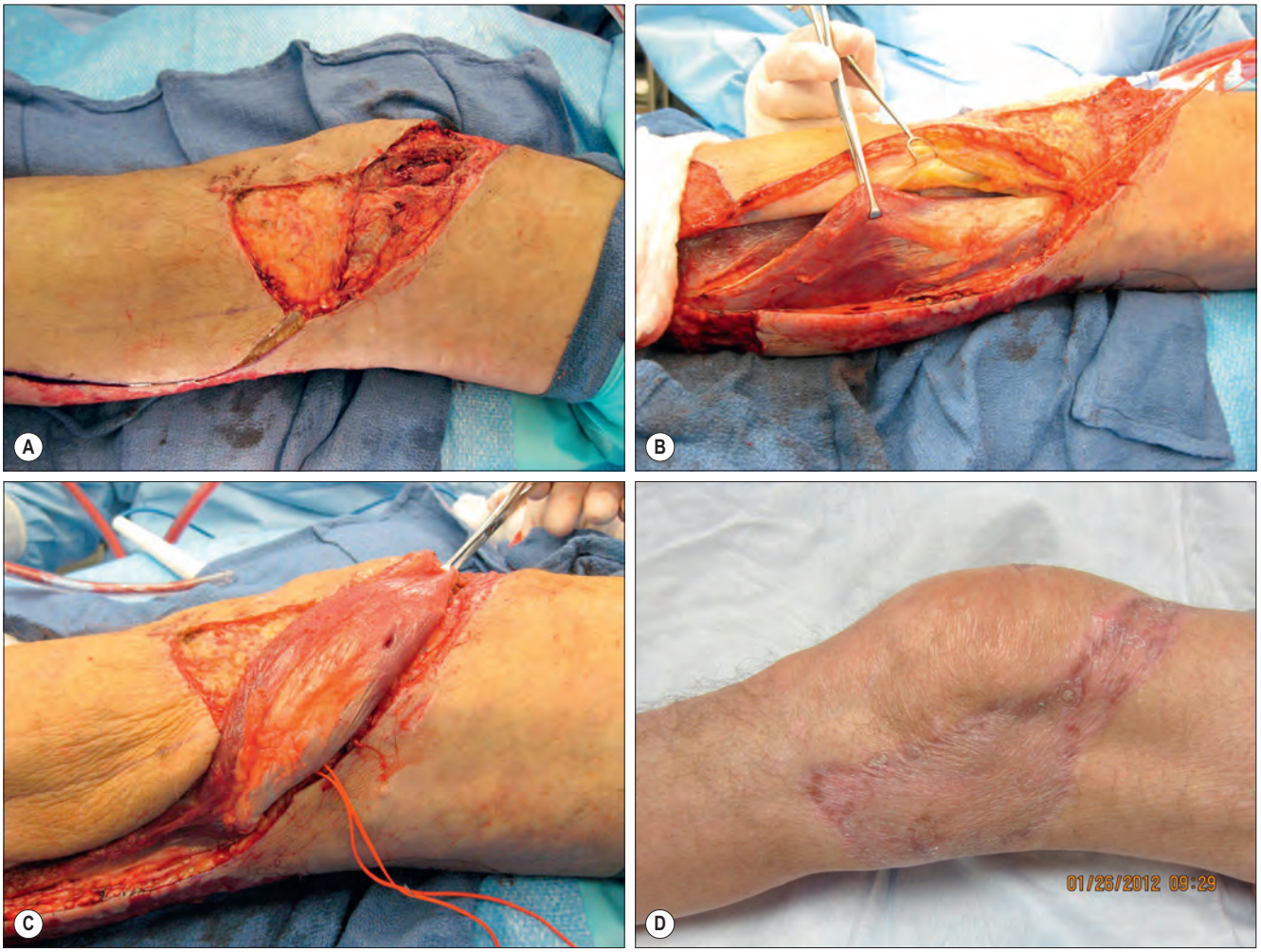


Fig. 56.2 **(A)** A full-thickness injury has exposed the lateral surface of the knee capsule. **(B)** The lateral gastrocnemius muscle is mobilized; the peroneal nerve is protected with vessel loop. **(C)** The muscle is set into the defect. **(D)** The muscle and overlying skin graft at 4 months.

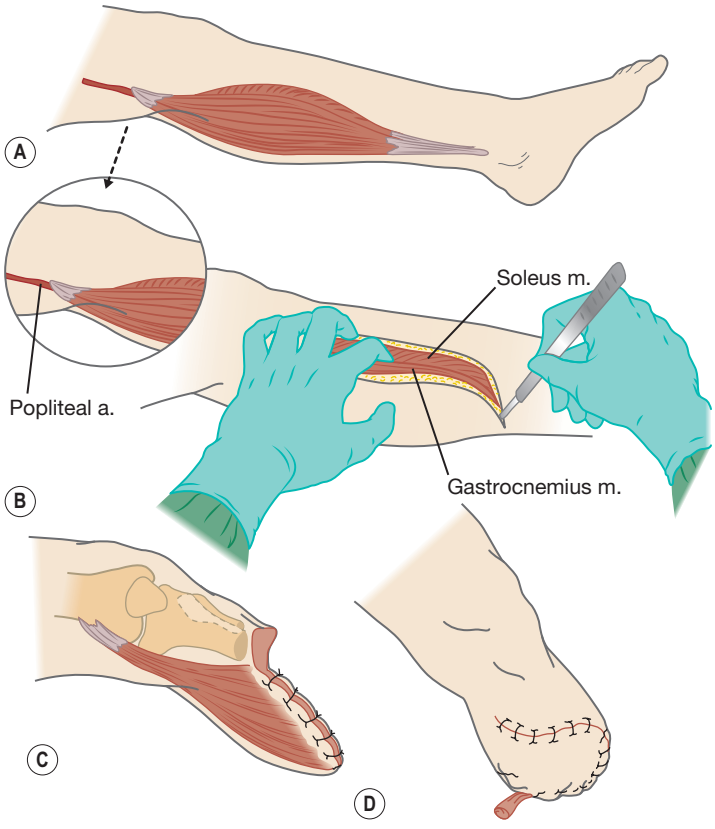


Fig. 56.3 Below knee amputation. **(A)** Gastrocnemius and soleus demonstrated in anatomic position with popliteal artery supply. **(B)** Demonstration of medial incision raising myocutaneous flap for amputation closure. **(C)** Gastrocnemius raised and Tibia/Fibula resected with amputated leg. **(D)** Flap inset with BRA closure.

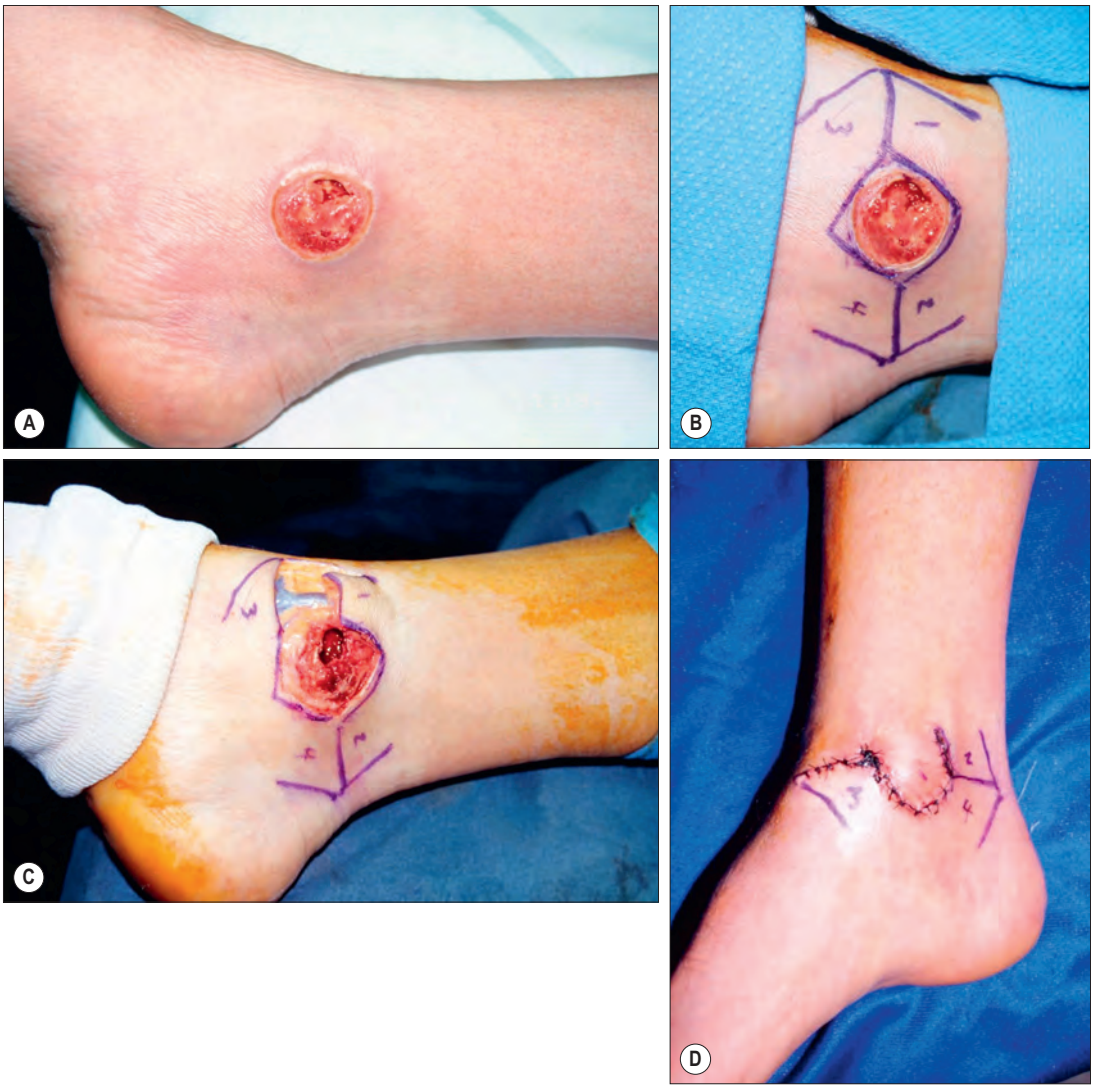


Fig. 56.4 (A) A full-thickness injury exposes the medial malleolus. **(B)** Potential rhomboid flaps are outlined. **(C)** Flap 1 captures supple tissue. **(D)** The margin of the donor site permits primary closure of the donor site after flap transposition.

neutral, and closing the donor site with mobilized marginal skin (or well-healed skin-graft) to complete a V-Y advancement (Fig. 56.6).

Anterior contractures of the ankle result in dorsiflexion, whereas posterior contractures cause plantar flexion. Anterior contractures are treated by incision and/or excision of scarred soft tissue to restore ankle range of motion. Such a release creates a defect with exposure of the tibialis anterior tendon. Coverage here is best achieved by a flap, and consideration can be given to local perforator flaps or microsurgical flaps (Fig. 56.7). Perforator flaps should be carefully chosen to be certain that the critical vessels have not been obliterated by burn injury. Microsurgical flaps should also be considered within the possibilities of tissue not compromised by the burn injury.[9] Cutaneous flaps, including anterolateral thigh flaps, radial forearm flaps, and scapular flaps, may be critically damaged in a burn patient. In such cases, muscle flaps (including rectus, latissimus, and gracilis flaps) can be reliable reconstructive options. These muscles are covered with skin grafts after their vascular and marginal insets.[10] Muscles also can be harvested through overlying skin grafts, therefore increasing their potential availability in burn reconstruction.

Posterior ankle contracture frequently includes shortening of the Achilles tendon. This structure must be mobilized from adjacent and proximal scar. If this tenolysis does not provide enough ankle mobility, the tendon itself must be lengthened with a step cut procedure.[1] Soft tissue coverage of the resulting defect and tendon exposure requires a flap. Local flap options include perforator flaps, including, most simply, a lateral calcaneal flap if it is available[9,11,12] (Fig. 56.8). Microsurgical flaps are otherwise an option, and either cutaneous or muscle flaps can be used.[10]

A contracture of the knee can be as simple as a deformity caused by a vertical scar band that can be incised and restored to length with local Z-plasties. If resection of scar tissue results in a defect, a lateral or medial gastrocnemius muscle flap can resurface an entire popliteal fossa, with restoration of extension. If local muscle cannot be utilized, microsurgical flaps can be effective, and a large unit such

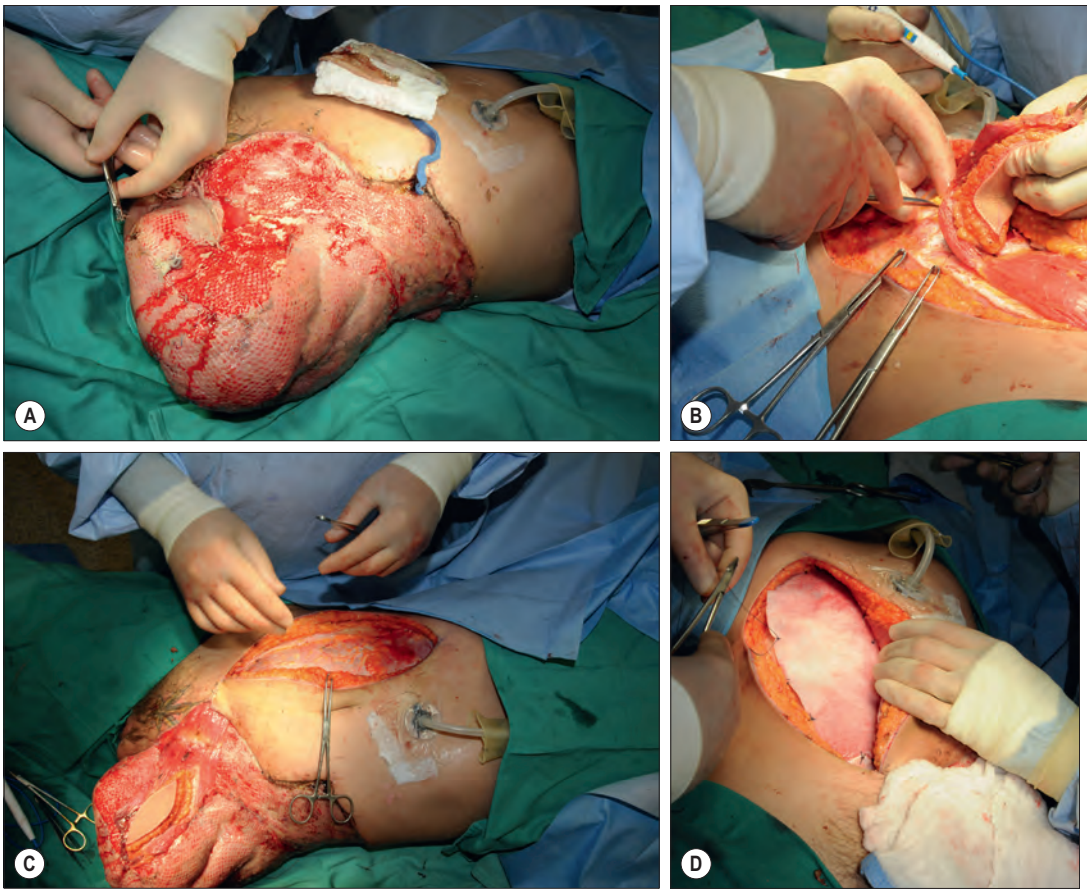


Fig. 56.5 **(A)** The stumps of the femoral vessels are exposed in scar tissue on the surface of the amputation stump. **(B)** The right rectus muscle with a superior skin paddle is elevated to the deep inferior epigastric vessels. **(C)** Transposition of the myocutaneous flap covers the vessels. **(D)** Primary closure is performed over the repaired rectus sheath while split-thickness skin grafts are applied to the rest of the stump.

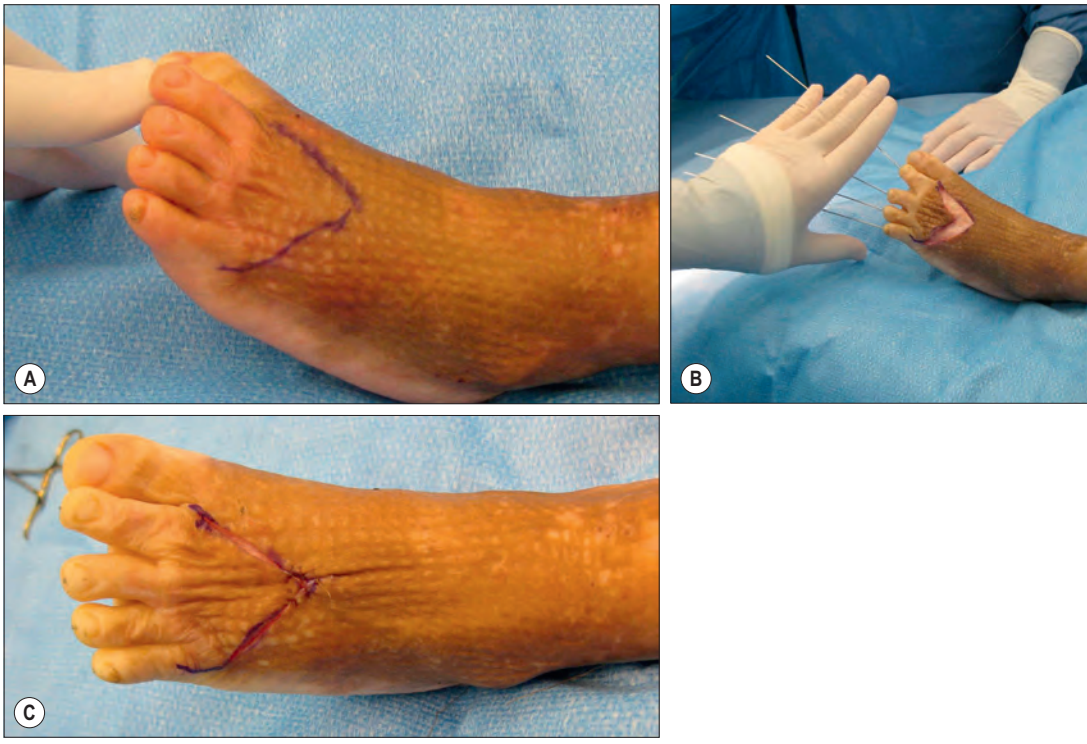


Fig. 56.6 **(A)** Dorsal skin grafts have contributed to contractures that have fixed the toes in extension. **(B)** The "V" component has been elevated and advanced while the toes are pinned in metatarsophalangeal flexion. **(C)** Primary closure of the donor defect completes the "V-Y" flap advancement.

as a rectus or latissimus can be considered. The vessels in Hunter's canal are reliable, deep recipient sites for vascular insets using the long pedicle vessels harvested with latissimus or rectus flaps.[13]

Hip flexion contractures occur most commonly in children. Treatment consists of resection of superficial and deep scar to allow extension while protecting the femoral vessels and nerves. The resulting defect can usually be managed with a skin graft, while extensive wounds with wide neurovascular exposure may require an inferiorly based rectus flap or a sartorius turnover flap.[14]

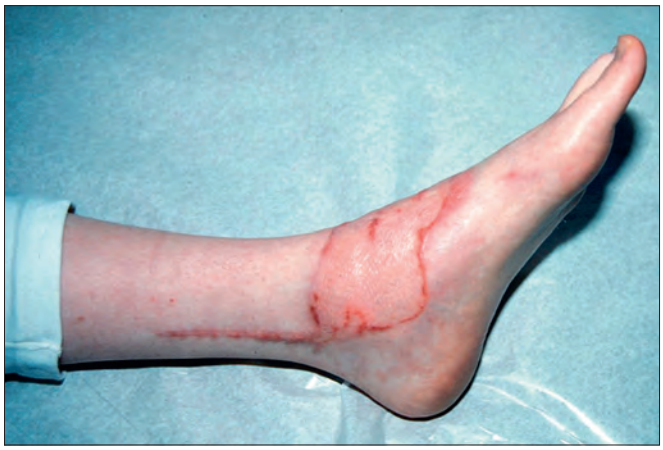


Fig. 56.7 Late result of anterior ankle coverage with a microvascular rectus flap and a split-thickness skin graft.

Grafts and Flaps

Clear understanding of these reconstructive units allows coherent planning. Both grafts and flaps are applied to the treatment of defects. Both also must be selected from areas not compromised by burn injuries. The elemental difference between grafts and flaps consists of the difference between their blood supplies.

Grafts have no intrinsic circulation and must survive on the bed on which they are placed by the processes of serum imbibition, inosculation, and neovascularization. Grafts therefore require beds of vascular tissue and cannot be applied reliably to bone or tendon. Split-thickness skin grafts, usually harvested by a dermatome, revascularize more promptly, and their donor sites, which heal by epidermal regeneration from the dermis, allow large grafts to be utilized. Split-thickness grafts, however, tend to contract with their underlying beds and can be relatively fragile to external trauma. Full-thickness skin grafts include epidermis and dermis. Their donor sites must be closed as wounds, so the available area for these grafts is very limited. They also take longer to revascularize and require optimal beds and extended immobilization. These grafts have the

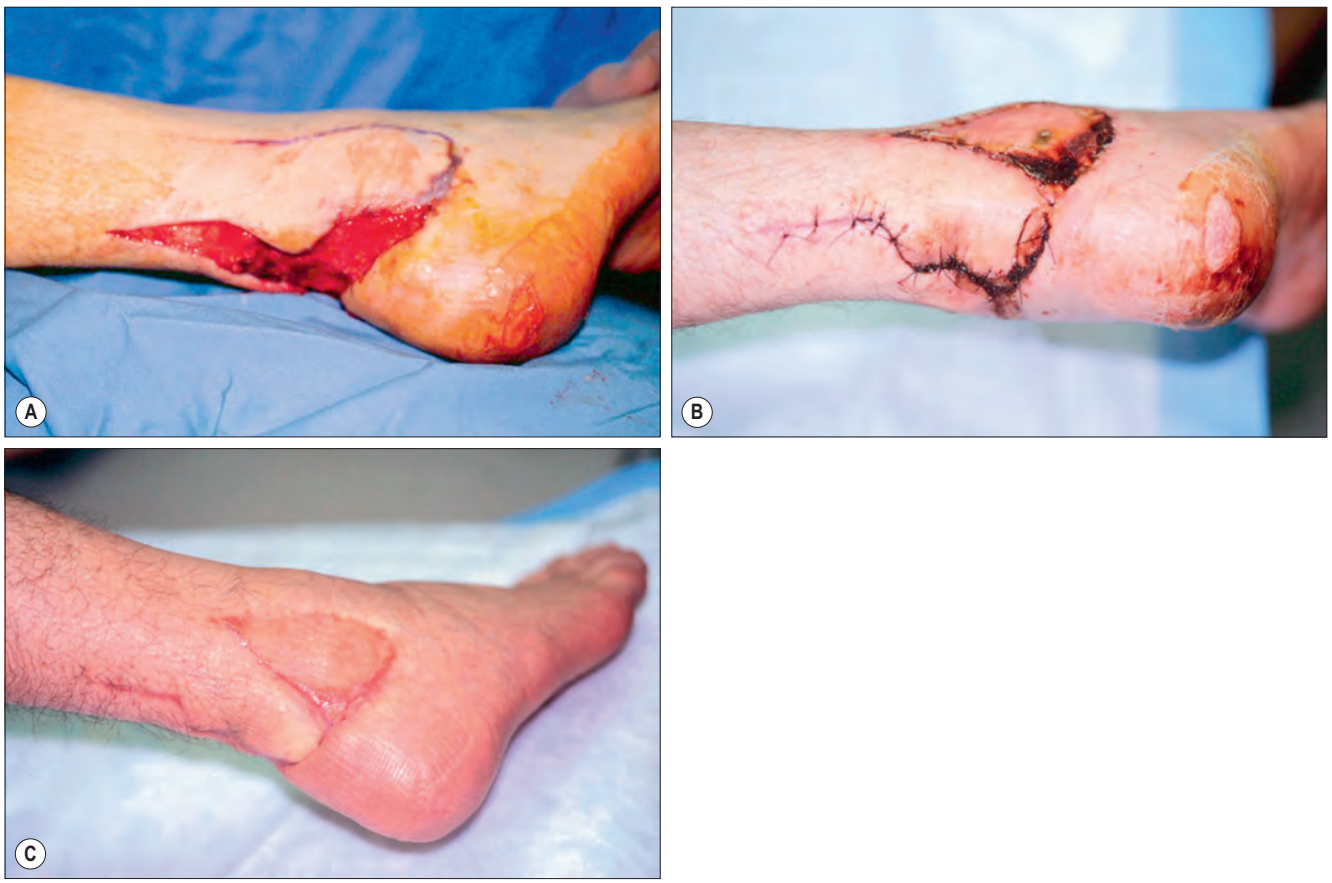


Fig. 56.8 **(A)** Contracted scar is excised and a lateral calcaneal flap is outlined. **(B)** The flap is rotated into the defect. **(C)** Late results include stable coverage and functional range of motion; the donor defect was covered with a full-thickness skin graft.

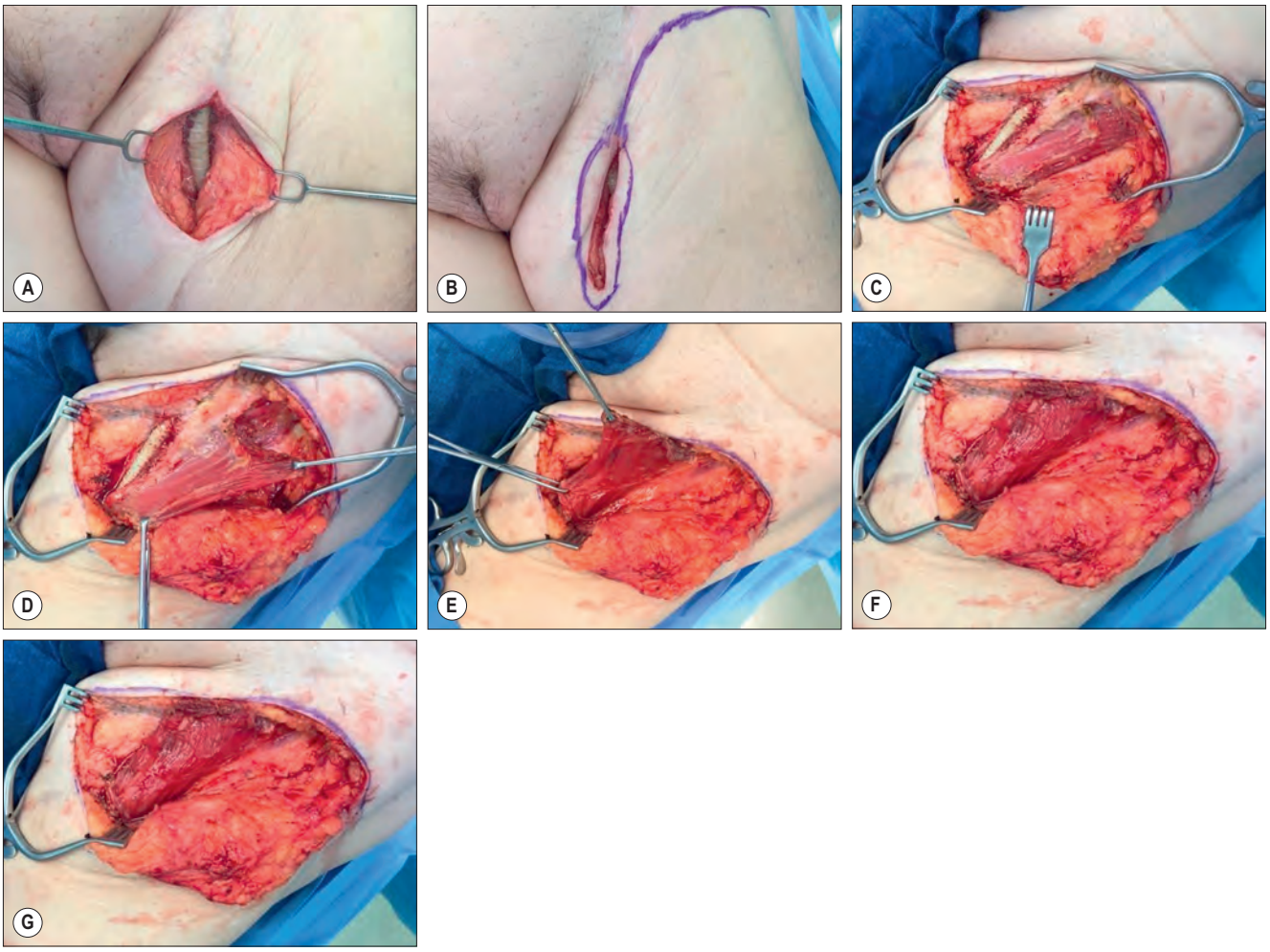


Fig. 56.9 **(A)** Resection of an unstable wound exposes an underlying vascular graft. **(B)** A rotation flap is outlined. **(C)** Elevation of the flap exposes the sartorius muscle. **(D)** The origin of the muscle is transected. **(E)** Using the muscle as a turnover rotation flap preserves the segmented medical vascular pedicles. **(F)** Flap inset covers the vascular graft. **(G)** Inset of the rotation flap completes the reconstruction. (From Dr. Lineaweaver)

advantages of decreased contracture, greater durability, and some potential for sensory reinnervation based on dermal end organs in the graft and nerve regeneration from the underlying defect.[14]

Flaps contain intrinsic blood supplies and therefore can be reliably used to cover bone, tendon, and poorly vascularized defect surfaces. Flaps also generally contain more tissue and can fill deep, irregular defects. Flaps have limited potential for contracture.

Cutaneous flaps include local pattern flaps that have no defined vascular pedicle. These flaps are based on empirical designs that include advancement flaps (e.g., V-Y patterns), rotation flaps, and transposition flaps (e.g., Z-plasties and rhomboid patterns). These flaps require supple tissue, although they interestingly can often succeed using well-healed skin grafts, especially if the grafts were placed over muscle. Pedicled flaps include defined arteries and veins critical to the flap's survival (Fig. 56.9). Perforator propeller flaps are increasingly utilized as versatile options in lower-extremity reconstructions.[15]

Microsurgical flaps can be harvested remote from the defect. Utilizing pedicle vessels, the flap insets will include microsurgical anastomoses to vessels at the site of the defect. Such procedures are reliable in acute and delayed burn surgery. There has long been a reluctance to employ microsurgical flaps in the acute settings due to prior reports demonstrating increased flap loss in the 5- to 21-day period following injury. Those data have been refuted in more recent series and microsurgical procedures can serve as reliable, versatile reconstructive units in critical defects.[16–18]

Conclusion

In approaching a burn complication in a lower extremity, the reconstructive surgeon proceeds from a careful analysis of salvage potential to specific definition of deformity and defect. This sequence leads to identification of an optimum reconstructive technique selected from the wide range of procedures available for modern reconstructive surgery.

Complete references available online at
www.expertconsult.inkling.com

References

1. Maquina P. Reconstruction of lower extremity burns. In: Pu L, Levine J, Wei F, eds. *Reconstructive Surgery of the Lower Extremity*. St. Louis: Quality Medical Publishing; 2013:1175-1190.
2. Wu C, Calvert C, Cairn B, et al. Lower extremity nerve decompression in burn patients. *Ann Plast Surg*. 2013;70:563-567.
3. Lineaweaver W. Problem analysis in reconstructive surgery. In: Wei F, Mardini S, eds. *Flaps and Reconstructive Surgery*. New York: Elsevier; 2009:3-6.
4. Huang C, Jackson JR, Moore N, et al. Amputation: energy cost of ambulation. *Arch Phys Med Rehabil*. 1979;6:18-24.
5. Burgess EM. Major amputations. In: Nora P, ed. *Operative Surgery*. Philadelphia: Lea & Febiger; 1980:1052-1069.
6. Dellon AL, Morgan R. Myodermal flap closure of below the knee amputation. *Surg Gynecol Obstet*. 1981;153:383-386.
7. Lineaweaver W, Craft-Coffman B, Oswald T. Incidence of flap procedures in the management of burn patients. *J Miss State Med Assoc*. 2015;56:60-64.
8. Chang J, Kung T, Levi B, et al. Surgical management of burn flexion and extension contractures of the toes. *J Burn Care Res*. 2014;35:93-101.
9. Uygar F, Duman H, Ulkar E, et al. Are reverse flow cutaneous flaps an appropriate option for the reconstruction of severe post burn lower extremity contractures? *Ann Plast Surg*. 2008;61:319-324.
10. Parrett B, Pribaz J. Lower extremity reconstruction. *Rev Med Clin Condes*. 2010;21:66-75.
11. Parrett B, Talbot S, Pribaz J, et al. A review of local and regional flaps for distal leg reconstruction. *J Reconstr Microsurg*. 2009;25:445-456.
12. Grishkevich V. Proximally based sural adipose- cutaneous/scar flap in elimination of ulcerous scar soft-tissue defect over the Achilles tendon and posterior heel region. *J Burn Care Res*. 2014;35:e143-e150.
13. Cartotto R, Cicuto B, Kiwanuka H, et al. Common post burn deformities and their management. *Surg Clin North Am*. 2014;96:817-837.
14. Barbour JR, Schweppe M, O SJ. Lower extremity burn reconstruction in the child. *J Craniofac Surg*. 2008;19:970-988.
15. Teven CM, Mhlaba J, O'Connor A, et al. The utility and versatility of perforator-based propeller flaps in burn care. *J Burn Care Res*. 2017;38(1):20-27.
16. Ibrahim AE, Skoracki R, Goverman JG, et al. Microsurgery in the burn population: a review of the literature. *Ann Burns Fire Disasters*. 2015;28(1):39-45.
17. Jabir S, Frew Q, El-Muttardi N, et al. A systematic review of the applications of free tissue transfer in burns. *Burns*. 2014;40(6):1059-1070.
18. Jabir S, Frew Q, Magdum A, et al. Microvascular free tissue transfer in acute and secondary burn reconstruction. *Injury*. 2015;46(9):1821-1827.

57 Electrical Injury: Reconstructive Problems

PETER M. VOGT, ANDREAS D. NIEDERBICHLER, and ANDREAS JOKUSZIES

Introduction

Severe cases [of electrical injury] coming for reconstruction present a formidable problem of flexion contracture and loss of many tendons and nerves, new pedicled skin and grafted-in tendons and nerves usually being necessary. One encounters inside the limb the same type of destruction and cicatrix as is found after any severe infection.

STERLING BUNNELL, 1948

This chapter will focus on the multitude of surgical and reconstructive problems that result from electrical injury. The injury severity is complex due to various factors determining manifestation and the distribution of the resulting tissue damage. In common with other types of trauma, especially burn injuries, the consequences of electrical injury may affect a wide range of physiological functions. Its distinct features warrant a differentiated approach to this unique kind of trauma. The resulting tissue loss and the damage to essential structures of the involved body areas often require extensive plastic-reconstructive procedures.

Although the incidence of low-voltage burns has declined steadily over recent decades, most probably due to progress made in the field of home and occupational safety education and equipment, electrical injuries still account for 3–5% of all admissions to major burn centers.[1,2] Electrical fatalities are relatively uncommon, and most of them occur accidentally. Earlier reported limb amputation rates of up to 71% decreased over recent decades with the increasing ability to reconstruct anatomic parts and restore function, but limb salvage remains a surgical challenge.[3,4]

Physiological Basis of Tissue Destruction

The traditional pathophysiological understanding of electric injury was based on the assumption that the passage of electric current produces heat and triggers tissue damage.[5] Thus tissue-specific susceptibility (and vulnerability) is considered to increase progressively from nerve to blood vessels, muscle, skin, tendon, and fat to bone. As osseous tissue shows the highest electrical resistance, it will generate the most heat. Electric current will preferentially take the path of least resistance through the body so that the current will pass particularly along the neurovascular bundles. This theory further postulated that the lesions produced by the current would result in delayed vascular occlusion and progressive tissue necrosis.[6]

In high-voltage injuries, the internal milieu acts as a single uniform resistance.[7] Instead of conduction through specific preferential tissues, the body conducts the current with a composite resistance of all tissue components.[8] The crucial factor in determining the resistance and hence the magnitude of tissue damage is the cross-sectional diameter of the affected body part. Devastating injuries to the extremities occur with a significantly higher frequency than tissue damage to the thorax and abdomen[9] (Fig. 57.1). Because muscle tissue occupies the largest cross-sectional area in the limb it also carries the predominant electric current. Because joint areas are regions where the cross-sectional tissue composition changes from low-resistance muscle to high-resistance bone, tendon, and skin, a proportionally higher current and heat are produced in these areas according to Ohm's Law.[9]

Arcing describes the energy transmitted by a hot electrically conducting gas. However, this requires a voltage of more than 20,000 V to bridge even a short distance of 1 cm.[10] Effects on tissue vary from minimal skin wounds to charring and tissue vaporization.

The different trauma mechanisms of the burns induced by the arcing phenomenon are often referred to as "flush burns," heat burns that are induced by the massive heat generation. "Electrothermal burns" are caused by current passage through the body and the concomitant heat production.

Electrical damage to a large artery represents a grave prognostic sign for limb survival.[11] The reported risk of amputation is high, at between 37% and 65%.[12–14]

Further nonthermal mechanisms of cellular injury have been defined. This includes a voltage-induced loss of cell membrane semipermeability.[15–17] When the integrity of the cell membrane is lost, the impedance is markedly reduced, leading to a simultaneous increase in the area exposed to current flow.[18] In addition to breakdown in cellular integrity, electrical fields also induce denaturation of membrane proteins by altering their structural conformation and rendering them nonfunctional.[19] Both mechanisms are responsible for rhabdomyolysis and secondary myoglobin release, which depends directly on the imposed electric current and is not a thermal effect.[20]

The human body consists of about 60% water. The intra- and extracellular water content and their highly resistive plasma membrane separate these two compartments from each other.[21] Change in the current transporters from electrons to ions at the skin surface appears as metallic condensations of dark-grayish skin lesions that resemble eschar.[22]

Another central factor of the cellular effect of electrical current is its frequency, which can arbitrarily be divided

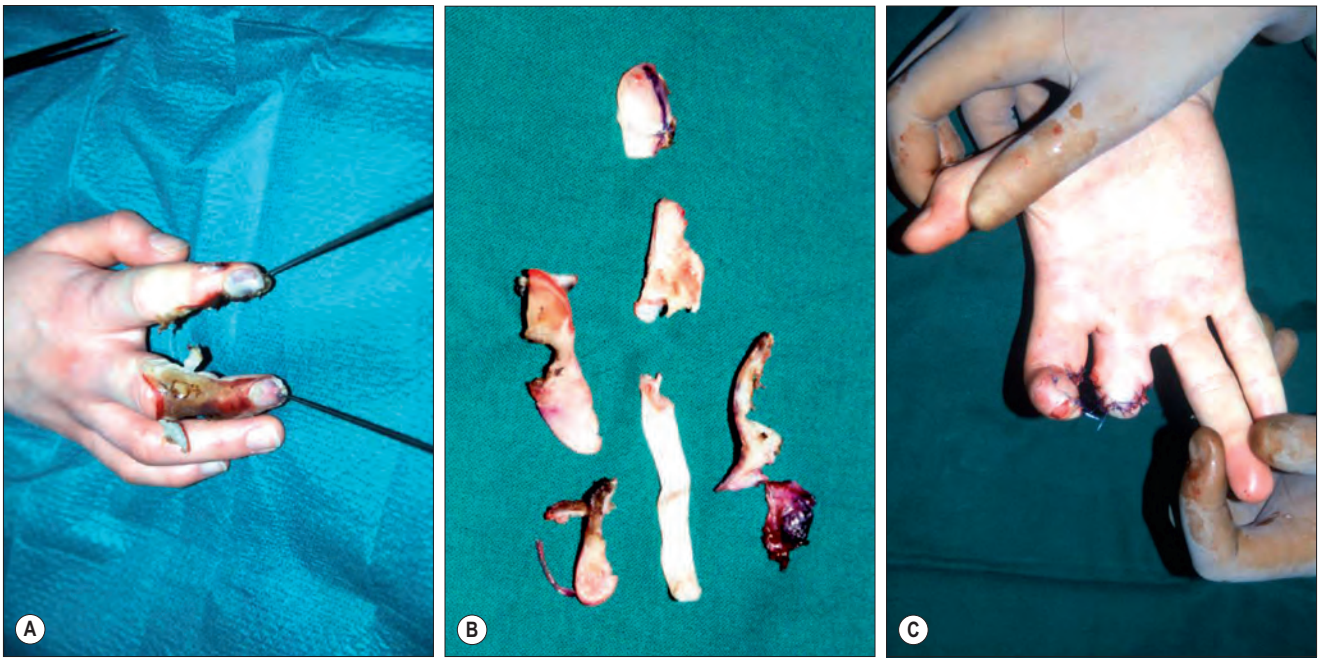


Fig. 57.1 Electrical burn from a domestic water heater (220 V). The 13-year-old girl manipulated the device while being immersed in the bathtub. She sustained third- and fourth-degree burns to the digits **(A)**. Debridement revealed full-thickness injuries involving tendons, nerves, and phalangeal bones **(B)**, which necessitated primary amputation **(C)**.

Table 57.1 Dependence of Cutaneous Resistance on Skin Moisture

	Resistance
Dry skin	100,000 Ω
Wet skin	2500 Ω
Skin immersion	1500 Ω
Rubber soles	70,000 Ω

Reproduced from Ohashi M, Koizumi J, Hosoda Y, et al. Correlation between magnetic resonance imaging and histopathology of an amputated forearm after an electrical injury. *Burns* 1998;24:362–368.

into low (<10 kHz) and high (>10 kHz, e.g., radio frequency, microwave, and ionizing frequencies).

Diagnosis and Acute Treatment

Diagnosis and acute treatment of electrical injury are described in Chapter 38.

Assessment of Tissue Damage

Accurate assessment of the extent of tissue damage is difficult. The percentage of burned body surface area grossly underestimates the injury to underlying tissue. Electrical burns may appear as mere pinpoint marks. In contrast, fatal electrocution may even take place without visible skin burns in the case of a large contact area (Table 57.1).

In contrast to thermal burns, deposition of metallic iron and copper is found on the epidermis after electrical injuries as electrolysis occurs in the extracellular fluid of the skin.[24–26]

Clinical determination of tissue viability is based on inspection and the demonstration of muscle contractility. As yet, there are no other diagnostic tools available to accurately assess the extent of tissue damage in the early phase following electrical injuries. The value of magnetic resonance imaging (MRI) for the detection of nonperfused nonedematous muscle is debated.[24–26] Angiography, although not providing information on tissue viability, demonstrates the absence of tissue perfusion and may lead to an early indication for limb amputation.[27]

Rhabdomyolysis and Myoglobinuria

Destroyed muscle cells release myoglobin, resulting in myoglobinemia. Hemolysis also often occurs with electrical injury. Serum levels of creatinine and creatinine phosphokinase (CPK) are used as indicators of rhabdomyolysis. After muscle injury CPK levels will peak by 24 h and return to baseline within 48–72 h.[28] This diminishes the diagnostic value of serum and urine chemistry testing.[29,30]

Renal Failure

Myoglobinuria has traditionally been considered a major risk factor for the development of acute renal failure. Recently patients with electrical injuries have been shown to have a surprisingly low risk for renal failure.[31] In 162

Table 57.2 Recommendation for Cardiac Monitoring in the Absence of Other Injuries

Admission and Cardiac Monitoring	Discharge
Loss of consciousness[59]	Asymptomatic patient[60]
Extensive burns[50]	Normal initial ECG[61]
Current passing through the thorax[52]	Uneventful 4-h observation[62]
Cardiac dysrhythmias[59]	Voltage less than 240/260 in adults[60,61]
	Voltage less than 120/240 in children[48,62]

patients, only 14% had myoglobinuria and none developed renal failure. Suggested criteria to evaluate the risk of acute renal failure after electrical injury include prehospital cardiac arrest, full-thickness burns, compartment syndrome, and high-voltage injury. The presence of at least two of these criteria should instigate immediate treatment because the timeframe to prevent progression to acute renal failure is limited to a few hours post injury.

Cardiac Monitoring

Among the estimated 1300 deaths that occur annually in the United States from electrical injury (including lightning strike), 30% of patients present with cardiac complications. The majority of electrocardiographic (ECG) abnormalities are sinus tachycardia and nonspecific changes in the ST-segment and T-wave.[32] Death from electric injury most commonly results from current-induced cardiac arrest.

However if an initial ECG shows no abnormalities, the delayed development of cardiac problems is very unlikely irrespective of whether the patient sustained high- or low-voltage injuries.[33–35]

Conversely, the presence of dysrhythmias or conduction abnormalities on initial presentation, electrical injury in children, or the projected path of the current flow crossing the thorax on initial presentation warrant prolonged cardiac monitoring.[36–39] Depending on the nature of the current-induced arrhythmia, pharmacotherapeutic and/or invasive interventions may be necessary. Table 57.2 outlines recommendations for cardiac monitoring of electrically injured patients based on central clinical findings and specific features of the trauma mechanism.[42]

Apart from specific therapeutic measures for cardiac complications, acute treatment of patients with electrical injuries adheres to guidelines of advanced burn life support (ABLS), advanced trauma life support (ATLS), and the current practice of intensive care medicine. The patient must be continuously monitored for signs of neurovascular compromise and deranged tissue perfusion and oxygenation.

Surgical Debridement

In recent decades the concept of progressive tissue necrosis has led to the treatment strategy of early debridement and fasciotomy, followed by serial debridement and delayed wound closure.[41] The observed changes may likely be explained by vascular changes similar to ischemia-reperfusion injury with immediate cessation of capillary blood flow in response to current passage. This event is followed by vascular spasms lasting for an extended period, with subsequent vasodilatation and restoration of flow.[43–45] Although still controversial, these findings may alter the acute treatment paradigm.

Although there is little discussion about the early time point of debridement, several recent studies question the need for extensive and total necrectomy and advocate the approach of delayed soft tissue coverage. *Conservative debridement* consisting of removal of charred and obviously necrotic tissue was promoted in a study on 40 patients.[46] In this study partially damaged tendons, muscles, and nerves were preserved, and wound closure was achieved by immediate flap coverage. Patients treated in this manner with immediate soft tissue coverage had a significantly better outcome than a control group who underwent serial debridement procedures. Similar results were found in a study using early free-flap coverage for electrical injuries, suggesting that careful limited initial debridement is an adequate measure.[47,48] According to this study overly extensive and repeated debridement to ensure viability of all remaining tissue appears not only unnecessary but quite likely harmful. It appears safe to abandon these strategies and to perform an early, extensive but selective debridement in order to preserve continuity of functionally important structures (Fig. 57.2). Limb salvage with functional preservation of vital structures should be attempted and may require revascularization using segmental vein grafts or segmental cable grafting of nerves. Pedicled flaps should be considered in cases of suspected arterial compromise.

Despite the encouraging results of the studies recommending early soft tissue reconstruction, by all means it should be noted that for the extent of electrical injury no scoring system has so far been established. Alternative approaches to salvage upper-extremity function, such as the temporary ectopic implantation of an undamaged hand, have been reported but cannot be considered standard of care.[49]

Compartment Syndrome

Muscle compartment pressure should be monitored clinically and by invasive pressure measurements. In contrast to blunt trauma, pain is not a reliable indicator of increased compartment pressure owing to the high incidence of electrical nerve injury. When compartment pressures exceed 30 mm Hg surgical decompression by open fasciotomy becomes necessary to prevent ischemic muscle injury. In the case of lower compartment pressure, progression may be prevented by administration of nonsteroidal antiinflammatory drugs (NSAIDs) and antioxidants, protective splinting, and rest without elevation of the affected extremities. However general operative decompression in high-voltage injuries to extremities appears not to be warranted. In a cohort study, Mann et al. found an increased amputation rate of 45% with immediate operative decompression compared to patients undergoing selective fasciotomy, and they recommend fasciotomy only in cases of progressive

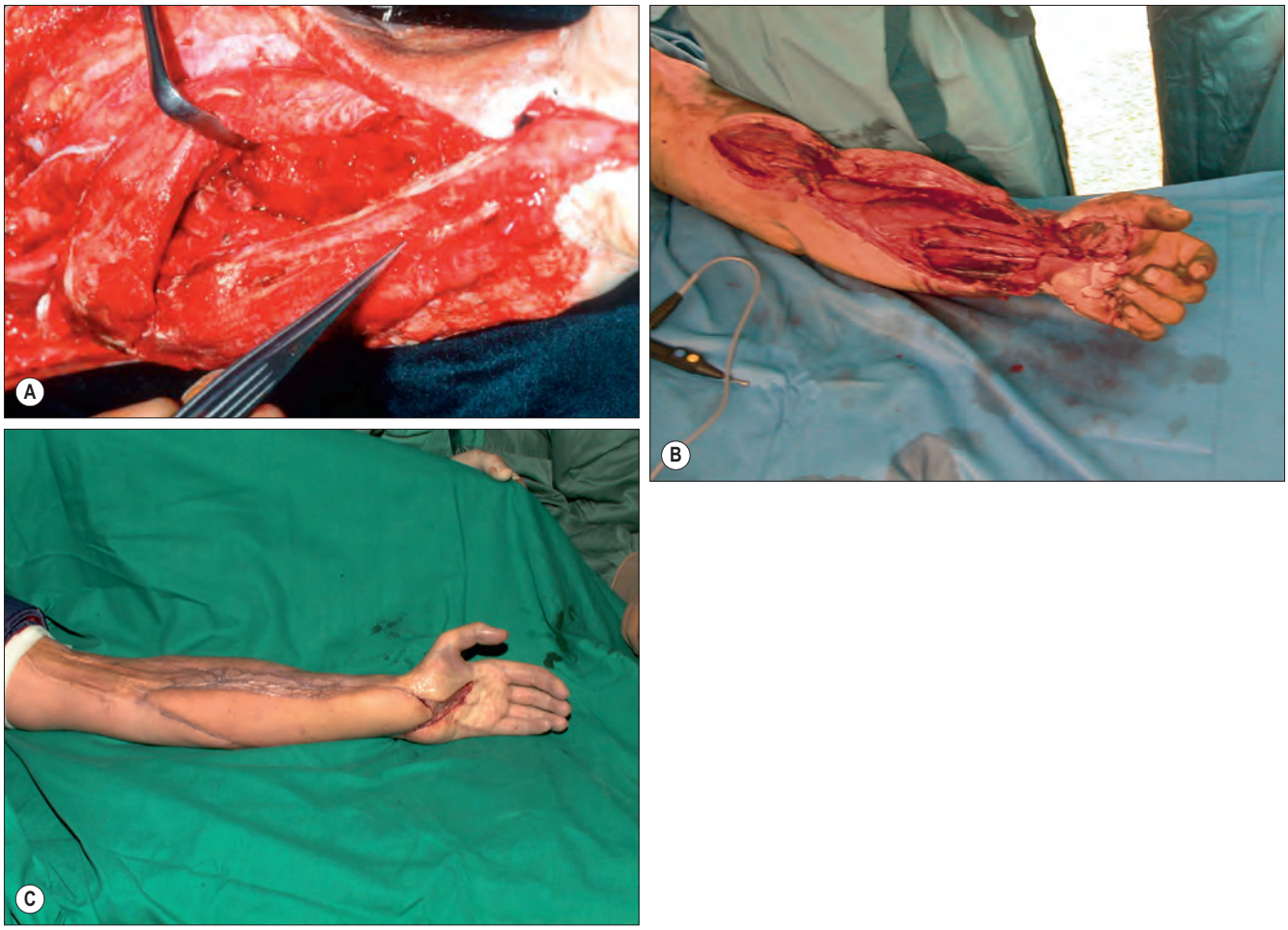


Fig. 57.2 High-voltage injury from an overhead power line (30,000 V). The teenager climbed a train and was struck by an arc without touching the power line. The spectrum of injury included third- and fourth-degree burns and deep tissue necrosis of the forearm **(A)**. After fasciotomy because of impending compartment syndrome **(B)**. Coverage with free latissimus dorsi flap after conservative debridement. Significant functional deficits after 4 years **(C)**.

peripheral nerve dysfunction, manifested compartment syndrome, or other major injuries[40] (Figs. 57.2 and. 57.3). With a fixed neurological deficit, however, surgical decompression shows no influence on outcome.[50] If the clinical situation remains doubtful, however, the performance of open fasciotomy with early debridement may be preferred.

Head: Scalp, Skull, and Mouth

Exposure and necrosis of osseous structures may lead to osteomyelitis and epidural abscess formation. Treatment strategies depend on the extent of the injury to the bone. In the case of only a partial necrosis of the bone, the outer table of the skull can be tangentially removed and the viable diploic cavity exposed. In cases of sufficient vascularization, the exposed bone can be grafted immediately or, when blood supply is questionable, grafted when suitable granulation tissue has developed.[51] Vacuum sealing of the wound can be of significant efficacy in growing adequate amounts of granulation tissue. When the initial wound debridement is delayed, necrotic and infected bone potentially becomes the source of a full-thickness skull defect. Full-thickness injury of the skull theoretically requires complete excision of the necrotic bone to prevent infectious complications.[69] Another approach suggested is partial debridement followed by definitive flap coverage of the exposed bone. This, however, requires early debridement and the prevention of localized bacterial colonization and infection.[52,53]

In a series of 10 male patients with nonviable cranial bone after class IV electrical burns, 3 weeks after initial soft-tissue debridement multiple burr holes in the nonviable and preserved bone were made and scalp flap coverage was performed.[54] Leaving the necrotic osseous structures in situ serves as a scaffold of substitution for bone regeneration.[55–57]

Skull contour was maintained in all 10 patients, making a secondary cranioplasty unnecessary. During a follow-up period of at least 1 year no postoperative infection, osteomyelitis, or cranial bone sequestration occurred.[54]

Another option is the use of glycerol-preserved allografts (GPAs).[58] The growth of spontaneous sufficient granulation tissue is promoted by its angiogenetic capacity, and split-skin autografts can be performed at a later stage. Further beneficial properties of GPA appear to be related to their permeable epidermal barrier, the subjacent network of dermal collagen, and protection of the bone by restoration

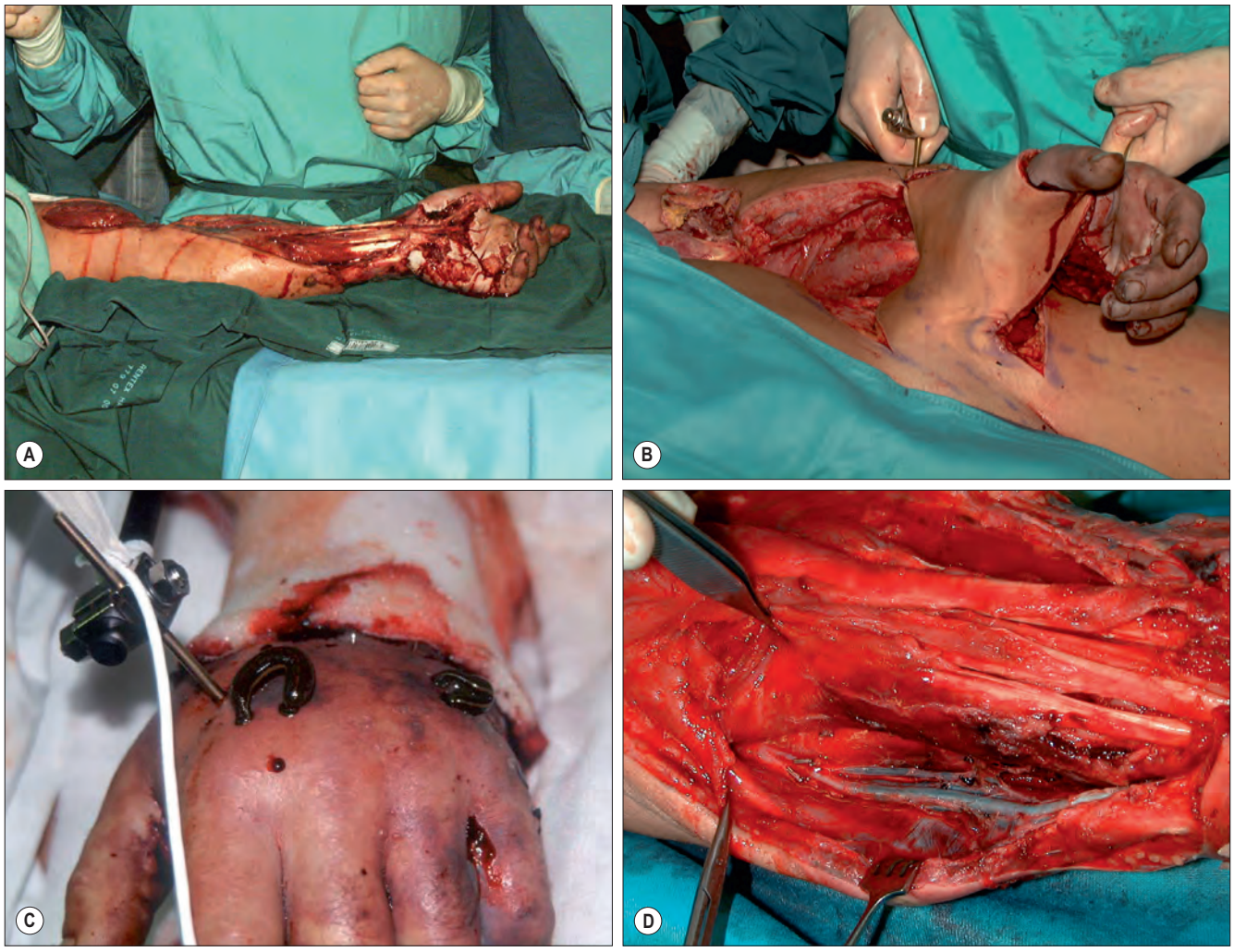


Fig. 57.3 High-voltage injury from a power line (50,000 V). Presentation with primary loss of perfusion, loss of function, and compartment syndrome. Initial operation with fasciotomy, revascularization of the radial artery, and necrectomies. On the following days, adequate perfusion with a patent radial artery without coexisting veins. Coverage with groin flap on day 6. Venous congestion and subsequent malperfusion was temporarily treated with leeches. Secondary amputation on day 10 due to late occlusion of the radial artery.

of a physical barrier that prevents drying out and reduces the risk of infection. With these allografts, the average healing time could be shortened to 6 weeks.

Fortunately, involvement of the dura occurs rarely. This usually requires an extensive free flap procedure.[59] We prefer to use the latissimus flap connected to cervical vessels, occasionally using interpositional vein grafts. This reduces the risk of perfusion problems considerably. When these options are not available, the use of acellular human dermis to reconstruct the dural defect followed by split-thickness skin grafting after vascularization may be an option.[60]

In children, especially toddlers, common sites of low-tension injury include the mouth, usually in the area of the oral commissure, affecting the commissure, the lips, and the tongue. The injury usually results in a localized partial necrosis of the lips and the commissure, and the subsequent contracture results in microstomia. The treatment strategies, conservative versus early surgical intervention, are debated. The more aggressive early approach of excision and reconstruction results in faster healing, a shorter hospital stay, and fewer surgical procedures.[61,62] However, in this sensitive age group early excision and reconstruction may also result in a tightened lower lip and consequent inhibition of normal mandible growth.[63,64]

The conservative management approach, which we prefer, performs the reconstructive procedure after maturation of the burn wound scar. Thus the extent of the damage is more apparent and the reconstruction can be performed electively.[65] Oral splinting has been advocated during the initial healing period to reduce the need for reconstructive surgery. However this more likely reduces scar contractures, so the planned reconstructive procedure can be performed after scar maturation.[66–68]

Thorax and Abdomen

Electrical injury to the trunk is generally a minor concern. However high-tension injuries can cause damage to underlying parenchymatous organs such as the lung. Clinically

this may lead to atelectasis and edema requiring aggressive ventilator support. Intra-abdominal injuries are uncommon but may require treatment as for penetrating injury. When exploration during escharectomy and debridement reveals necrotic underlying muscle and fascia, exploratory laparotomy may be indicated. Reconstructive options for the closure of chest or abdominal wall defects include direct closure or placement of a synthetic mesh covered by local fasciocutaneous or musculocutaneous flaps. However the potential negative effects of direct closure on intra-abdominal pressure and the subsequent development of an abdominal compartment syndrome or compromise of respiratory function must be considered.

Extremities

Electrical injuries to the extremities, especially to the arms and hand, are more common in adult members of the workforce. Electrical burns account for 3–5% of all admissions to burn units and approximately 1000 deaths per year in the United States.[70] There are three patterns of injury: direct, arc, and flash-type injuries. Direct injuries are associated with entry and exit wounds, and nearly 90% of these injuries involve the upper extremity.[71] Because the resistance and hence the local energy production are dependent on the tissue mass and the cross-sectional diameter of the injured body part, high-tension injuries often lead to extensive tissue damage and loss of the involved extremity. Despite aggressive treatment strategies with early debridement and decompression of neurovascular structures, the likelihood of amputation is high.[22–24,72] In the current literature the amputation rates for electrical injuries affecting the upper extremities range from 24% to 49%.[73,74] Even if amputation can be avoided the resulting outcome may be a nonfunctioning extremity. With the phenomenon of "kissing" lesions, extensive tissue damage may occur, with resulting thermal necrosis of muscle, tendon, nerves, and blood vessel. The superficial injury may appear innocuous, but debridement shows deep tissue destruction often mandating limb amputation. The importance of initial debridement cannot be overstated, as remaining nonviable tissue leads to infection and tissue loss. In our view the early debridement of nonviable tissue prevents this fatal development. When distal limb ischemia becomes obvious one can assume that the involved vessels have been severely injured. In these cases early vascular grafting of upper-extremity arteries may be indicated to salvage an ischemic upper limb.[75] Imminent or suspected compartment syndrome should always trigger open fasciotomy to prevent further compromise to the involved extremity. Sometimes it appears wise to perform a simple skin grafting procedure followed by elective secondary flap coverage and nerve cable grafting.

In high-voltage injuries (>1000 V) the point of entrance of the electrical current is usually located on the distal extremity. Tissue destruction decreases from distal to proximal. Zelt et al. described specific regions or so-called choke points, such as the wrist and elbow. These are characterized by smaller cross-sectional areas and highly resistant tissue components (tendinous and bony configuration) that result in increased heat production and more severe damage.[76]

The main area of reconstruction is the forearm, and limb salvage is the sole cause of free flap coverage.[77]

Fascial flaps provide thin, pliable coverage for reconstruction of the dorsum of the hand.

The serratus fascia flap is the flap of choice for larger defects; for smaller defects the temporoparietal fascial flap is preferred.[78]

Other regions of selective destruction in the upper extremity are the elbow and axilla. Debridement often leaves a vast tissue defect, which may be covered by rotation flaps from the anterior or posterior chest wall in the axilla. Microvascular free flaps at the level of the elbow are rarely used. For extensive defects on the hand and forearm pedicled groin flaps provide good coverage and an independent blood supply. The groin flap also avoids a vascular "steal phenomenon" as can be seen after microvascular free flaps in such severely injured extremities.

Newer approaches comprising early wound excision, coverage, and revascularization of damaged vasculature with flow-through free flaps and aggressive endovascular interventions will offer an opportunity to improve outcomes for these devastating injuries.[79–82]

Saint-Cyr and Daigle compared the use of free flaps with conventional multistage procedures and found a statistically significantly reduction in the number of operations, the time required to achieve wound closure, and the duration of hospitalization in the microsurgical group.[83]

The flap survival rate as described in the current literature is lower in the high-voltage injury group than in the burn injury group. It ranges from 62% to 100% and is lowest when performed early, within 5–21 days of trauma.[83–85]

In conclusion, free flaps play a key role in treating high-voltage electrical injuries to the extremities by reducing morbidity and functional impairment, which are characteristically high after these injuries.[83]

Amputations

Although distressing to the patient, amputation often remains the only option. As already mentioned, the amputation rates for electrical injuries affecting the upper extremities range from 24% to 49% in the current literature.[73,74] Despite an increased awareness of the potential danger of electrical burns, devastating outcomes with four-limb and penis amputations are still presented in the literature.[86–88] Although very rare, Haik and colleagues presented a case of a 5-week-old girl undergoing MRI for evaluation of spina bifida. She sustained a full-thickness burn encompassing her right forearm and wrist in the area where a non-MR-compatible pulse oximeter was attached. A possible cause for this incident could have been an electrical injury due to an exposed wire segment in direct skin contact. Despite immediate escharotomy, this injury led to amputation of the forearm and hand.[89]

The optimal level of amputation is determined by the extent of remaining viable tissue and the intention to create sufficient stump length for function and cosmetic appearance of a prosthesis. In electrical injury involving the lower extremity, this often requires higher amputation than initially anticipated in order to achieve sufficient stability of

the stump and thus allow early prosthetic fitting and ambulation. However, open (guillotine) amputation should be avoided whenever possible. Split-thickness skin grafting onto open stumps is an additional but less preferable approach because skin breakdown occurs more often in grafted areas, especially at graft borders or at points where grafts adhere to underlying bone, and further surgical interventions will be required. However, if valuable stump length can be maintained by skin grafting it should be attempted because secondary plastic surgical correction and specific prosthetic fitting are available.

In the upper extremity, more length should be preserved because the resulting weightbearing load on the stump is less than in the lower extremity. This allows for better control of the prosthesis by the patient and thus enhanced functionality. In the forearm, the muscle length of the flexor–extensor system should be preserved to improve function. In long forearm stumps, atraumatic handling of tendons and muscles is necessary to preserve pronation and supination. Upper-arm amputations should preserve as much length as possible as this eases subsequent kineplastic procedures for a functional prosthesis. As in the forearm, muscular length of the flexor–extensor system is maintained by joining them over the bone end. Although it is technically feasible to maintain extremity length by coverage with a free flap, this appears only useful in upper-extremity amputation where the functional implications warrant such large-scale surgery and the load on the stump is reduced.

Despite the availability of sophisticated modern myoelectric prostheses, the old techniques of surgical rehabilitation should be kept in mind. This includes the Sauerbruch kinemato-myoplasty of the biceps humeri muscle and the Krukenberg plasty of the forearm, which provides sensible chopstick-like stumps. Especially for upper-arm amputations, distraction osteogenesis procedures (Ilizarov technique) provide a valuable option to lengthen a short amputation stump.

Peripheral Nerve Injury

Peripheral nerves are very sensitive to electric alterations, and even minor injury may cause transient dysfunction. Clinical findings may be anesthesia, paresthesia, or dysesthesia of usually short-term duration. In rare cases minor electrical injury may cause temporary autonomic dysfunction and trigger a complex regional pain syndrome (sympathetic reflex dystrophy). Treatment for reflex sympathetic dystrophy should be initiated early and include elevation of the extremity to reduce edema formation, active exercise, NSAIDs, and adequate pain relief. The autonomic dysfunction may be influenced by α-adrenergic antagonists, calcium-channel blockers, and low-dose diazepam or may require intravenous regional blocks and sympathetic ganglion blockade.[90]

Electrical injury to the upper extremity commonly results in peripheral nerve injury to the median and ulnar nerves. The clinical findings may resemble upper-extremity compression syndromes or peripheral neuropathy.[91,92] Nerve lesions may be caused by secondary factors such as incorrect positioning and splinting, constricting dressings, or delayed inadequate escharotomy or fasciotomy. Owing to the accompanying severe muscle loss and scarring, the extent of pure nerve damage is sometimes difficult to determine.

Direct damage to peripheral nerves occurs following the above-mentioned mechanisms of local heat production, depending on cross-sectional resistance and the proximity of peripheral nerves to underlying bone. The local thermal effect affects vascularity and perfusion of perineural tissue by producing thrombosis, necrosis, or hemorrhage of epineural vessels. Delayed development of fibrosis and therefore a delayed onset of symptoms are not uncommon. Especially in areas of minimal cross-sectional area, the peripheral nerve is in close proximity to bone and fibrous tissue, which results in perineural fibrosis and symptoms of a compressive peripheral neuropathy. The treatment of choice to gain nerve recovery is decompressive corrective surgery.[93] Other mechanisms of nerve injury are the development of focal axonal degeneration following axonal excitation,[94] or electroporation, which more likely affects myelinated axons, and collagen type I deposition.[95–98]

Complications

CENTRAL NERVOUS SYSTEM

Approximately 60% of all patients with high-voltage injury present with immediate neurological complications, predominantly loss of consciousness.[99] Involvement of the spinal cord has been described in 2–27% of patients with an entry point of the current located in the head region.[100–102] The incidence of a delayed paralysis progressing to tetraplegia followed by partial remission has been described.[103] Although mortality in patients with neurological complications from electrical burns is not high, these patients are at great risk of permanent disability. The neurological sequelae were classified in 1964 by Silverside into immediate, secondary, and late effects.[104]

Immediate spinal cord injury is transient, and symptoms usually clear within 24 h after the accident. The late effects are characterized by progressive traits where complete recovery is not the rule. The ischemic injury in the distal area of the sulcal branch, the longest branch originating from the anterior spinal artery, is due to the susceptibility of the anterior horn cell and the spinal cord at T4–T8 to ischemic injury. Early administration of prostaglandin E_1 or steroid treatment is recommended to reduce ischemic spinal cord injury in cases of electrical burns.[105] The neuropsychological effects of electric injury have been described, mainly in case reports and retrospective studies. Typical consequences and complaints are related to physical, cognitive, and emotional changes.[106,107] In a study of 481 professional electricians, 97% reported having experienced an electrical shock at some point in their career.[108] The low incidence of neuropsychological dysfunction in this study differed from other findings about the nature and progression of a characteristic neuropsychological syndrome of electrical injury.[107,109] Although the development of transient and progressive neuropsychiatric complications is possible and undisputed, the actual specific effects of electrical injury are difficult to determine.

OCULAR MANIFESTATIONS OF ELECTRICAL INJURY

An increased incidence of cataract formation has been described after electrical injury, varying from 1% to 8% in different reports.[110,111] Patients with head and neck wounds appear to be most at risk. However the path of the current and the location of the entry point were not related to the development of ocular sequelae. Cataracts may also occur without injury to the head and appear even years after injury. Common initial complaints are blurred vision or diminished visual acuity.[112]

Cataracts usually develop from 1 month to 2 years after injury but may occur as soon as within several hours.[113] The mechanisms for formation are debated and several theories have been proposed, such as decreased permeability of the lens capsule, direct coagulative effect on the lens proteins, a disturbance in nutritional mechanisms of the lens cells due to iritis or impaired circulation, and exposure to ultraviolet and infrared radiation.[114]

Lightning strikes are a common cause of ophthalmic injuries, and the most common permanent sequela by far is lightning-induced cataract.[115] The lens of the eye is seemingly very sensitive to electrical current or the resultant heat, and prompt evaluation by an ophthalmologist is imperative.[116] Iritis and uveitis have also been described as possible sequelae after electrical injury.[117] Visual prognosis in patients with lightning-induced ocular injury will depend on the extent of irreversible retinal damage and optic nerve damage. Long-term follow-up of these patients is recommended according to the late onset of pigmentary changes at the fovea and papillomacular bundle, which may further prevent visual improvement.[118]

Patients should undergo serial ophthalmologic examinations, and treatment should be started immediately when abnormalities are recognized.

Skeletal Injury

In addition to direct tissue destruction through electrical energy, additional trauma can be indirectly inflicted by electric current. Fractures occur due to secondary falls or with forceful tetanic muscle contractions. These are mostly seen in the shoulder,[119] wrists,[120,124,125] femurs,[121,123] and spine[122] and may require open reduction and internal fixation. Late sequelae of electrical injury similar to severe thermal burns include major joint contractures and limited function of the extremities.

Another common late complication of electrical burns is heterotopic calcifications in periarticular tissue of large joints, especially the elbows. Causative factors include forced passive mobilization, secondary articular bleeding, and calcium precipitation and deposition in damaged or degenerating muscle and connective tissue. Particularly for electrical injury, heterotopic bone formation also occurs in amputation stumps of long bones. This, as well as the common formation of bone cysts in the amputation stump, may lead to secondary skin erosion, inflammation, and difficult adjustment to a prosthesis. In both situations surgical excision and wound closure may be adequate therapy.[126]

Conclusion

Electrical injuries result in deceptively large tissue loss often leading to amputation of involved extremities. After initial resuscitation, early debridement, necessary decompression of neurovascular structures, and early wound closure are essential to successful restoration of function. Extensive surgical procedures including free soft-tissue transfer may be necessary to achieve wound closure and to save and restore limb function. Sometimes, however, early amputation may provide easier and earlier recovery and reintegration into daily life. Long-term complications such as central nervous sequelae, cataracts, and heterotopic ossification must be considered and addressed early in the rehabilitation process.

Complete references available online at http://www.expertconsult.inkling.com

Further Reading

Brumback RA, Feedback DL, Leech RW. Rhabdomyolysis following electrical injury. *Sem Neurol.* 1995;15:329-334.

Saint-Cyr M, Daigle JP. Early free tissue transfer for extremity reconstruction following high-voltage electrical burn injuries. *J Reconstr Microsurg.* 2008;24(4):259-266.

Sauerbier M, Ofer N, Germann G, et al. Microvascular reconstruction in burn and electrical burn injuries of the severely traumatized upper extremity. *Plast Reconstr Surg.* 2007;119(2):605-615.

Smith M, Muehlberger T, Dellon AL. Peripheral nerve compression associated with low-voltage electrical injury without associated significant cutaneous burn. *Plast Reconstr Surg.* 2002;109:137-143.

Spies C, Trohman RG. Narrative review: electrocution and life-threatening electrical injuries. *Ann Intern Med.* 2006;145:531-537.

References

1. Rai J, Jeschke MG, Barrow RE, et al. Electrical injuries: a 30-year review. *J Trauma*. 1999;46:933-936.
2. Tredget EE, Shankowsky HA, Tilley WA. Electrical injuries in Canadian burn care. *Ann N Y Acad Sci*. 1999;888:75-87.
3. Rouge RG, Dimick AR. The treatment of electrical injury compared to burn injury: a review of pathophysiology and comparison of patient management protocols. *J Trauma*. 1978;18:43.
4. Edlich RF, Farinholt HM, Winters KL, et al. Modern concepts of treatment and prevention of electrical burns. *J Long Term Eff Med Implants*. 2005;15(5):511-532.
5. Lewis GK. Trauma resulting from electricity. *J Int Coll Surg*. 1957;28: 724-727.
6. Artz CP. Electrical injury simulates crush injury. *Surg Gynecol Obstet*. 1967;125:1316-1317.
7. Wehrmacher WH. The dual challenge of electric injury. *Compr Ther*. 1995;21:308-312.
8. Daniel RK, Ballard PA, Heroux P, et al. High voltage electrical injury: acute pathophysiology. *J Hand Surg*. 1988;13A:44-49.
9. Zelt RG, Daniel RK, Ballard PA, et al. High-voltage electrical injury: chronic wound evaluation. *Plast Reconstr Surg*. 1988;82:1027-1041.
10. Marc B, Baudry F, Douceron H, et al. Suicide by electrocution with low-voltage current. *J Forensic Sci*. 2000;45:216-222.
11. Vedung S, Arturson G, Wadin K, et al. Angiographic findings and need for amputation in high tension electrical injuries. *Scand J Plast Reconstr Hand Surg*. 1990;24:225-231.
12. Butler ED, Grant TD. Electrical injuries with special reference to the upper extremities. *Am J Surg*. 1977;134:95-99.
13. Hunt JL, Mason AD, Masterson TS, et al. The pathophysiology of acute electrical injuries. *J Trauma*. 1976;16:335-340.
14. Lee RC, Capelli-Schellpfeffer M. Electrical and lightning injuries. In: Cameron JL, ed. *Current Surgical Therapy*. St Louis, MO: Mosby; 1998:1021-1023.
15. Sugar IP, Foster W, Neumann E. Model of cell electrofusion: membrane electroporation, pore coalescence and percolation. *Biophys Chem*. 1987;26:321-335.
16. Tsong TY. Electroporation of cell membranes. *Biophys J*. 1991;60: 297-306.
17. Coster HG. A quantitative analysis of the voltage-current relationships of fixed charge membranes and the associated property of 'punch-through. *Biophys J*. 1965;5:669-686.
18. Lee RC, Gaylor DC, Bhatt D, et al. Role of cell membrane rupture in the pathogenesis of electrical trauma. *J Surg Res*. 1988;44:709-719.
19. DeBono R. A histological analysis of a high-voltage electric current injury to an upper limb. *Burns*. 1999;25:541-547.
20. Bhatt DL, Gaylor DC, Lee RC. Rhabdomyolysis due to pulsed electric fields. *Plast Reconstr Surg*. 1990;86:1-11.
21. Duling BR. Thekidney. In: Berne RM, Levy MN, eds. *Physiology*. St. Louis, MO: Mosby; 1983:821-892.
22. Jacobsen H. Electrically induced deposition of metal on the human skin. *Forensic Sci Int*. 1997;90:85-92.
23. Ferreiro I, Melendez J, Ragalado J, et al. Factors influencing the sequelae of high-tension electrical injuries. *Burns*. 1998;24:649-653.
24. Ohashi M, Koizumi J, Hosoda Y, et al. Correlation between magnetic resonance imaging and histopathology of an amputated forearm after an electrical injury. *Burns*. 1998;24:362-368.
25. Fleckenstein JL, Chason DP, Bonte FJ, et al. High voltage electric injury: assessment of muscle viability with MR imaging and Tc-99m pyrophosphate scintigraphy. *Radiology*. 1995;195:205-210.
26. Sayman HB, Urgancioglu I, Uslu I, et al. Prediction of muscle viability after electrical burn necrosis. *Burns*. 1998;24:649-653.
27. Vedung S, Arturson G, Wadin K, et al. Angiographic findings and need for amputation in high tension electrical injuries. *Scand J Plast Reconstr Hand Surg*. 1990;24(3):225-231.
28. Brumback RA, Feedback DL, Leech RW. Rhabdomyolysis following electrical injury. *Sem Neurol*. 1995;15:329-334.
29. Feinfeld DA, Cheng JT, Beysolow TD, et al. A prospective study of urine and serum myoglobin levels in patients with acute rhabdomyolysis. *Clin Nephrol*. 1992;38:193-195.
30. Grossmann RA, Hamilton RW, Morse BM, et al. Nontraumatic rhabdomyolysis and acute renal failure. *N Eng J Med*. 1974;291:807-811.
31. Rosen CL, Adler JN, Rabban JT, et al. Early predictors of myoglobinuria and acute renal failure following electrical injury. *J Emerg Med*. 1999;17:783-789.
32. Cooper MA. Emergent care of lightning and electrical injuries. *Semin Neurol*. 1995;15:268-278.
33. Bailey B, Gaudreault P, Thivierge RL, et al. Cardiac monitoring of children with household electrical injuries. *Ann Emerg Med*. 1995;25:612-617.
34. Arrowsmith J, Usgaocar RP, Dickson WA. Electrical injury and the frequency of cardiac complications. *Burns*. 1997;23:576-578.
35. Fish RM. Electric injury, part III: cardiac monitoring indication, the pregnant patient, and lightning. *J Emerg Med*. 2000;18:181-187.
36. Purdue GF, Hunt JL. Electrocardiographic monitoring after electrical injury: necessity or luxury. *J Trauma*. 1986;26:166-167.
37. Cunningham PA. The need for cardiac monitoring after electrical injury. *Med J Aust*. 1991;154:765-766.
38. Guinard JP, Chiolero R, Buchser E, et al. Myocardial injury after electrical burns: short and long term study. *Scand J Plast Reconstr Hand Surg*. 1987;21:301-302.
39. Wilson CM, Fatovich DM. Do children need to be monitored after electric shocks? *J Paediatr Child Health*. 1998;34:474-476.
40. Mann R, Gibran N, Engrav L, et al. Is immediate decompression of high-voltage electrical injuries to the upper extremities always necessary? *J Trauma*. 1996;40:584-587.
41. Luce EA, Gottlieb SE. True' high-tension electrical injuries. *Ann Plast Surg*. 1984;12:321-325.
42. Garcia C, Smith GA, Cohen DM, et al. Electrical injuries in a pediatric emergency department. *Ann Emerg Med*. 1995;26:604-608.
43. Jaffe RH, Willis D, Bachem A. The effect of electric currents on the arteries. *Arch Pathol*. 1929;7:244-249.
44. Hussmann J, Zamboni WA, Russell RC, et al. A model for recording the microcirculatory changes associated with standardized electrical injury of skeletal muscle. *J Surg Res*. 1995;59:725-732.
45. Ponten B, Erikson U, Johansson SH, et al. New observations on tissue changes along the pathway of the current in an electrical injury. *Scand J Plast Reconstr Surg*. 1970;4:75-82.
46. Zhi-Xiang Z, Yuan-Tie Z, Xu-Yuan L, et al. Urgent repair of electrical injuries: analysis of 40 cases. *Acta Chir Plast*. 1990;32:142-151.
47. Chick LR, Lister GD, Sowder L. Early free-flap coverage of electrical and thermal burns. *Plast Reconstr Surg*. 1992;89:1013-1019.
48. Yang JY, Noordhoff MS. Early adipofascial flap coverage of deep electrical burn wounds of upper extremities. *Plast Reconstr Surg*. 1993;91:819-825.
49. Godina M, Bajec J, Baraga A. Salvage of the mutilated upper extremity with temporary ectopic implantation of the undamaged part. *Plast Reconstr Surg*. 1986;78:295-299.
50. Engrav LH, Gottlieb JR, Walkinshaw MD, et al. Outcome and treatment of electrical injury with immediate median and ulnar nerve palsy at the wrist: a retrospective review and a survey of members of the American Burn Association. *Ann Plast Surg*. 1990;25:166-168.
51. Sheridan RL, Choucair RJ, Donclean MB. Management of massive calvarial exposure in young children. *J Burn Care Rehabil*. 1998;19:29-32.
52. Luce EA, Hoopes JE. Electrical burns of the scalp and the skull. *Plast Reconstr Surg*. 1974;54:359.
53. Bizhkol P, Slesarenko SV. Operative treatment of deep burns of the scalp and skull. *Burns*. 1992;18:220-223.
54. Cruz NI, Saavedra FM. Preservation of nonviable cranial bone after class IV electrical burns. *P R Health Sci J*. 2010;29(1):83-85.
55. Rockwell WB, Bodily KD. Fate of free muscle transfer covering chronically infected burned skull. *J Burn Care Rehabil*. 2001;22(4):288-291.
56. Norkus T, Klebanovas J, Viksraitis S, et al. Deep electrical burns of the calvarium: early or delayed reconstruction? *Burns*. 1998;24(6): 569-572.
57. Gümüs N, Coban YK, Reyhan M. Cranial bone sequestration 3 years after electrical burn. *Burns*. 2006;32:780-782.
58. Groenevelt F, Van Trier AJM, Khouw N. The use of allografts in the management of exposed calvarial electrical burn wounds of the skull. *Ann N Y Acad Sci*. 1999;888:109-112.
59. Miyamoto Y, Harada K, Kodama Y, et al. Cranial coverage involving scalp, bone and dura using free inferior epigastric flap. *Br J Plast Surg*. 1986;39:483-490.
60. Barret JP, Dziewulski P, McCauley RL, et al. Dural reconstruction of a class IV calvarial burn with decellularized human dermis. *Burns*. 1999;25:459-462.
61. Zarem HA, Greer DM. Tongue flap for reconstruction of the lip after electrical burns. *Plast Reconstr Surg*. 1974;53:310.
62. DeLaPlaza R, Quetgals A, Rodriguez E. Treatment of electrical burns of the mouth. *Burns*. 1983;10:49.

63. Hartford CD, Kealy GP, Lavelle WE, et al. An appliance to prevent and treat microstomia from burns. *J Trauma*. 1975;15:356.
64. Ortiz-Monasterio F, Factor R. Early definitive treatment of electric burns of the mouth. *Plast Reconstr Surg*. 1980;65:169.
65. Pensler JM, Rosenthal A. Reconstruction of the oral commissure after an electrical burn. *J Burn Care Rehabil*. 1990;11:50-53.
66. Leake JE, Curtin JW. Electrical burns of the mouth in children. *Clin Plast Surg*. 1984;11:669.
67. Dado DV, Polley W, Kernahan DA. Splinting of oral commissure electrical burns in children. *J Pediatr*. 1985;107:92.
68. Silverglade D, Ruberg RL. Nonsurgical management of burns to the lips and commissures. *Clin Plast Surg*. 1986;13:87.
69. Wright HR, Drake DB, Gear AJL, et al. Industrial high-voltage electrical burn of the skull, a preventable injury. *J Emerg Med*. 1997; 15(5):345-349.
70. Koumbourlis AC. Electrical injuries. *Crit Care Med*. 2002;30:424-430.
71. Bingham H. Electrical burns. *Clin Plast Surg*. 1986;13:75-85.
72. Luce EA, Dowden WL, Su CT, et al. High tension electrical injury of the upper extremity. *Surg Gynecol Obstet*. 1978;147:38.
73. Handschin AE, Vetter S, Jung FJ, et al. A case-matched controlled study on high-voltage electrical injuries vs thermal burns. *J Burn Care Rehabil*. 2009;30:400-407.
74. Yakuboff KP, Kurtzman LC, Stern PJ. Acute management of thermal and electrical burns of the upper extremity. *Orthop Clin North Am*. 1992;23:161-169.
75. Wang XW, Wei JN, Sung YH, et al. Early vascular grafting to prevent upper extremity necrosis after electrical burns. *Burns Incl Therm Inj*. 1982;8:303-312.
76. Zelt RG, Daniel RK, Ballard P, et al. High-voltage electrical injury: chronic wound evolution. *Plast Reconstr Surg*. 1988;82:1027.
77. Sauerbier M, Ofer N, Germann G, et al. Microvascular reconstruction in burn and electrical burn injuries of the severely traumatized upper extremity. *Plast Reconstr Surg*. 2007;119(2):605-615.
78. Flügel A, Kehrer A, Heitmann C, et al. Coverage of soft-tissue defects of the hand with free fascial flaps. *Microsurgery*. 2005;25:47.
79. Ansel GM, Silver MJ, Botti CF. Critical limb ischemia – a contemporary review of reperfusion techniques. *Vasc Dis Manag*. 2006;3:305-306.
80. Sauerbier M, Ofer N, Germann G, et al. Microvascular reconstruction in burn and electrical burn injuries of the severely traumatized upper extremity. *Plast Reconstr Surg*. 2007;119:605-615.
81. Titley OG, Chester DL, Park AJ. A-A type, arterialized, venous, flow-through, free flaps for simultaneous digital revascularization and soft tissue reconstruction – revisited. *Ann Plast Surg*. 2004;53:185-191.
82. Zeller T, Tepe G. Drug-eluting stents and drug-coated balloons in peripheral interventions. *Vasc Dis Manag*. 2008;5:171-175.
83. Saint-Cyr M, Daigle JP. Early free tissue transfer for extremity reconstruction following high-voltage electrical burn injuries. *J Reconstr Microsurg*. 2008;24(4):259-266.
84. Baumeister S, Koller M, Dragu A, et al. Principles of microvascular reconstruction in burn and electrical burn injuries. *Burns*. 2005;31:92-98.
85. Ofer N, Baumeister S, Megerle K, et al. Current concepts of microvascular reconstruction for limb salvage in electrical burn injuries. *J Plast Reconstr Aesthet Surg*. 2007;60:724-730.
86. Mohammadi AA, Johari HG. Four limb amputations: a tragic end of electrical burn. *J Burn Care Res*. 2009;30(3):541.
87. Prakash V. Amputation of the penis due to electrical burn – role of prefabricated urethra in penile reconstruction. *Burns*. 2008;34:119-121.
88. Landecker A, Macieria L. Penile and upper extremity amputation following high-voltage electrical trauma: case report. *Burns*. 2002;28:806-810.
89. Haik J, Daniel S, Tessone A, et al. MRI induced fourth-degree burn in an extremity, leading to amputation. *Burns*. 2009;35:294-296.
90. Gellman H, Nichols D. Reflex sympathetic dystrophy in the upper extremity. *J Am Acad Orthop Surg*. 1997;5:313-322.
91. Still JM, Law EJ, Duncan W, et al. Long thoracic nerve injury due to an electric burn. *J Burn Care Rehabil*. 1996;17:562-564.
92. Haberal MA, Gürer S, Akman N, et al. Persistent peripheral nerve pathologies in patients with electric burns. *J Burn Care Rehabil*. 1996;17:147-149.
93. Smith M, Muehlberger T, Dellon AL. Peripheral nerve compression associated with low-voltage electrical injury without associated significant cutaneous burn. *Plast Reconstr Surg*. 2002;109:137-143.
94. Agnew WF, McCreery DB, Yuen TG, et al. Local anaesthetic block protects against electrically induced damage in peripheral nerve. *J Biomed Eng*. 1990;12:301-308.
95. Wang ZG, Li XY, Li YJ, et al. The changes in blood flow in sciatic nerve after electrical injury in rabbit. *Zhonghua Shao Shang Za Zhi*. 2007;23(3):201-203.
96. Abramov GS, Bier M, Capelli-Schellpfeffer M, et al. Alteration in sensory nerve function following electrical shock. *Burns*. 1996;22: 602-606.
97. Gaylor DC, Prakah-Asante K, Lee RC. Significance of cell size and tissue structure in electrical trauma. *J Theoret Biol*. 1988;133:223-237.
98. Fan KW, Zhu ZX, Den ZY. An experimental model of an electrical injury to the peripheral nerve. *Burns*. 2005;31:731-736.
99. Grube BJ, Heimbach DM, Engrav LH, et al. Neurologic consequences of electrical burns. *J Trauma*. 1990;30:254-257.
100. Koller J, Orsagh J. Delayed neurological sequelae of high tension electrical burns. *Burns*. 1989;15:175-178.
101. Varghese G, Mani H, Redford SH. Spinal cord injuries following electric accident. *Paraplegia*. 1986;24:159-162.
102. Levine NS, Atkins A, McKeel DW, et al. Spinal cord injury following electrical accidents: case reports. *J Trauma*. 1975;15:459-463.
103. Breugem CC, van Hertum W, Groenevelt F. High voltage electrical injury leading to a delayed onset tetraplegia, with recovery. *Ann N Y Acad Sci*. 1999;888:131-136.
104. Silversides J. The neurological sequelae of electrical injury. *Can Med Assoc J*. 1964;91:195-204.
105. Ko SH, Chun W, Kim HC. Delayed spinal cord injury following electrical burns: a 7-year experience. *Burns*. 2004;30:691-695.
106. Janus TJ, Barrash J. Neurologic and neurobehavioural effects of electric and lightning injuries. *J Burn Care Rehabil*. 1996;17:409-415.
107. Pliskin NH, Capelli-Schellpfeffer M, Law RT, et al. Neuropsychological symptom presentation after electrical injury. *J Trauma*. 1998;44:709-715.
108. Tkachenko TA, Kelley KM, Pliskin NH, et al. Electrical injury through the eyes of professional electricians. *Ann N Y Acad Sci*. 1999;888:42-59.
109. Pliskin NH, Fink J, Malina A, et al. The neuropsychological effects of electrical injury. *Ann N Y Acad Sci*. 1999;888:140-149.
110. Boozalis GT, Purdue GF, Hunt JL, et al. Ocular changes from electrical burn injuries: a literature review and report of cases. *J Burn Care Rehabil*. 1991;12:458-462.
111. Solem L, Fisher R, Strate R. The natural history of electrical injury. *J Trauma*. 1977;17:487-492.
112. Saffle JR, Crandall A, Warden GD. Cataracts: a long-term complication of electrical injury. *J Trauma*. 1985;25:17.
113. Kobernick M. Electrical injuries: pathophysiology and emergency management. *Ann Emerg Med*. 1982;11:633-638.
114. Reddy SC. Electric cataract: a case report and review of the literature. *Eur J Ophthalmol*. 1999;9(2):134-138.
115. Cazabon S, Dabbs TR. Lightning-induced cataract. *Eye*. 2000;14:903.
116. Norman M, Albertson D, Younge BR. Ophthalmic manifestations of lightning strike. *Surv Ophthalmol*. 2001;46(1):19-24.
117. Miller B, Goldstein MH, Monshizadeh R, et al. Ocular manifestations of electrical injury: a case report and review of the literature. *The CLAO J*. 2002;28(4):224-227.
118. Moon SJ, Kim JE, Han DP. Lightning-induced maculopathy. *Retina*. 2005;25(3):382.
119. Dumas JL, Walker N. Bilateral scapular fractures secondary to electrical shock. *Arch Orthop Trauma Surg*. 1992;111:287-288.
120. Adams AJ, Beckett MW. Bilateral wrist fractures from accidental electric shock. *Injury*. 1997;28:227-228.
121. Tompkins GS, Henderson RC, Peterson HD. Bilateral simultaneous fractures of the femoral neck: case report. *J Trauma*. 1990;30:1415-1416.
122. van den Brink WA, van Leeuwen O. Lumbar burst fracture due to low voltage shock. A case report. *Acta Orthop Scand*. 1995;66:374-375.
123. Spies C, Trohman RG. Narrative review: electrocution and life-threatening electrical injuries. *Ann Intern Med*. 2006;145:531-537.
124. Pappano D. Radius fracture from an electrical injury involving an electric guitar. *South Med J*. 2010;103(3):242-244.
125. Hostetler MA, Davis CO. Galeazzi fracture resulting from electrical shock. *Pediatr Emerg Care*. 2000;16(4):258-259.
126. Helm PA, Walker SC. New bone formation at amputation in electrically burn-injured patients. *Arch Phys Med Rehabil*. 1987;68:284-286.

58 The Role of Alternative Wound Substitutes in Major Burn Wounds and Burn Scar Resurfacing

NAIEM S. MOIEMEN and KWANG CHEAR LEE

Introduction

Early excision of major burns has been shown to improve patient outcomes. The lack of available donor sites from which to harvest conventional autologous skin grafts to achieve wound closure is challenging. Burke and Yannas in the early 1960s pioneered the introduction of alternative wound cover after burn excision. They invented a dermal scaffold composed of bovine collagen and shark glycosaminoglycan matrix with an epithelial equivalent, the silicon layer. This became known as Integra. During that same period, Rheinwald and Green, in 1975, described the technique of cultured epidermal autografts (CEA), which provided another alternative to help achieve wound cover. The first multicenter clinical trial using Integra was published in 1988.[1] Integra was eventually granted approval by the U.S. Food and Drug Administration (FDA) in 1996 for use in acute burns.

Alternative wound substitutes provide biological wound cover either on a temporary or permanent basis. Permanent substitutes are mostly in the form of scaffolds that become integrated into the wound and eventually are replaced by host cells, with the scaffold itself finally undergoing reabsorption. Temporary substitutes, on the other hand, do not integrate into the wound; they temporarily adhere to the wound bed and may induce growth and promote healing of the underlying wound.

Classification of Alternative Wound Substitutes

The wide variety of alternative wound cover products may be classified into temporary or permanent (Tables 58.1 and 58.2). Other classifications include autologous, allogenic, or xenograft; biological or synthetic; cellular or acellular, and single layer or composite.

Clinical Applications of Alternative Wound Substitutes in Major Burn Wounds

Temporary alternative wound substitutes are used to cover partial-thickness burns, full-thickness excised burn wounds, widely meshed skin grafts, and, occasionally, skin graft donor sites.

For partial-thickness burns, temporary substitutes, in contrast to traditional wound dressings, provide a biological wound cover that promotes healing by reducing moisture loss and accelerating epithelialization. However they are not incorporated into the architecture of the healed wound, as in the case of permanent substitutes. In addition, most of these products (such as Biobrane, Suprathel, and amniotic membrane) are applied only once. This is a significant advantage, especially for children, because it avoids the pain and associated psychological trauma of repeated wound dressing changes.

For full-thickness excised burn wounds, temporary alternative substitutes can provide cover if skin grafting or application of a permanent substitute is planned as a staged procedure. In certain circumstances, to allow for a reduction in wound exudate and to ensure complete hemostasis, this may be delayed for 24–48 hours after wound excision in a major burn. Due to lack of available donor sites for skin graft harvest, it may be decided to apply a permanent substitute, and "take" can be optimized by staging the procedure; during this time a temporary substitute can be very helpful.

Temporary substitutes are very valuable for covering widely meshed skin grafts (the Alexander technique). Alexander described applying allograft on top of widely meshed autograft to provide biological wound closure that protects the open wound within the interstices (gaps) of the meshed graft. While allograft tends to adhere to the wound bed and may in fact interfere with epithelization of the interstices, E-Z Derm dries out after a week of its application with almost complete epithelization underneath. This may also represent a cost saving.

Rapid healing of skin graft donor sites is critical to patients with major burns. Expanded pre-confluent autologous epidermal cells (ReCell) or sprayed CEA may accelerate epithelization and allow more frequent harvesting from the limited donor sites in these situations. However wider use is prohibited by cost and efficacy. ReCell has also been shown to accelerate healing of partial-thickness burn wounds when covered with widely meshed skin grafts.

Permanent alternative wound substitutes are used to cover full-thickness wounds after burn excision. One example of a bilayer acellular substitute is Integra, which has been used for decades in patients with major burns and has

Table 58.1 List of Temporary Skin Substitutes and Their Biological Value

Example	Structure	Biological Value/Mechanism of Action
Amniotic membrane	The innermost layer of the placenta; it consists of a single epithelial layer, a basement layer, and an avascular stroma. Available in frozen or glycerol-preserved forms	Promotes migration and adhesion of epithelial cells. It has high concentration of hyaluronan and Decorin and has anti-inflammatory, antiangiogenic, antimicrobial, and antiscarring actions
Allograft	Human cadaveric split-thickness skin grafts. Can be either cryo- or glycerol-preserved	Allogenic skin graft vascularizes initially as per autograft; however, it is eventually rejected by the host within 3–4 weeks
Xenograft	Animal-derived skin graft (usually porcine, although frog skin has been used). Examples include EZ Derm (acellular dermis)	Used as an alternative to allografts. It does not vascularize. It adheres to wounds and provides temporary coverage
Biobrane (Smith & Nephew, London and Hull, United Kingdom)	Consists of a silicone membrane bonded to a nylon mesh that is impregnated with porcine dermal collagen peptides	The collagen peptide coating enhances adherence to the wound. Biobrane has no inherent antimicrobial properties
Suprathel (PolyMedics Innovations GmbH, Denkendorf, Germany)	Entirely synthetic and composed of synthetic copolymers, mostly polylactic acid	This has similar indications to Biobrane and is used for temporary cover of partial-thickness burns and donor sites
Oasis (Smith & Nephew, London and Hull, United Kingdom)	Acellular porcine intestinal submucosa	Indicated as a single-application dressings for deep dermal burns
Omiderm (Omikron Scientific Ltd., Rehovot, Israel)	Synthetic polymer made from hydrophilized polyurethane	Indications are similar to Biobrane and Suprathel

Table 58.2 List of Permanent Skin Substitutes and Their Biological Value

Example	Structure	Biological Value/Mechanism of Action
Epicel (Vericel Corporation, Ann Arbor, Michigan, United States)	Consists of a petroleum gauze and autologous keratinocyte sheets that have been co-cultured with murine cells	Indicated for deep dermal and full-thickness burns; sheets are 2–8 cell layers thick
ReCell (Avita Medical, Cambridge, United Kingdom)	Pre-confluent autologous keratinocytes obtained by trypsinizing a small biopsy and directly sprayed onto the wound	Other cells such as fibroblasts and melanocytes are also delivered
Alloderm (Lifecell Corporation, Branchburg Township, New Jersey, United States)	Donated human skin that is processed to remove the epidermis and cells leaving an acellular matrix	Acellular dermis acts as a scaffold for fibroblast and vascular ingrowth, split-thickness skin grafts are applied over it during the same procedure
PriMatrix (TEI Biosciences Inc., South Boston, United States)	Acellular fetal bovine dermal scaffold	A scaffold to support new dermis formation
Matriderm (Medskin solutions, Billerbeck, Germany)	A single layer of matrix of non-crosslinked bovine collagen and tendon-derived elastin hydrolysate. Available in 1- and 2-mm thicknesses	A scaffold that promotes the regeneration of a new dermis. Split-thickness skin graft is applied on top as a single-stage procedure
Orcel (Forticell Bioscience Inc., New York, United States)	Bilayered collagen constructs seeded with allogenic keratinocytes and fibroblasts derived from neonatal foreskin	The matrix acts as a scaffold, and the allogenic cells produce growth factors and are eventually replaced by the host own cells within a few weeks
Apligraf (Organogenesis Inc., Massachusetts, United States)	Similar to Orcel, it is formed from collagen type I constructs seeded with allogenic keratinocytes and fibroblasts derived from neonatal foreskin	As with Orcel, the matrix acts as a scaffold and the cells induce a suitable environment for host cells to migrate into and populate. However, unlike Orcel, the top layer of keratinocytes is exposed to the atmosphere during manufacture, forming a stratified layer with better barrier function
Stratagraft (Stratatech Corporation, Madison, Wisconsin, United States)	Bilayered construct with a dermal layer with human dermal fibroblasts and an epidermal layer that is produced by near-diploid immortalized keratinocyte S (NIKS) cells	A fully stratified multilayered epidermal equivalent is generated by the NIKS cells, which are a pathogen-free keratinocyte cell line. The substitute releases bioactive molecules that condition the wound for healing
Permaderm (Regenicin Inc., New Jersey, United States)	Bilayered collagen matrix with basement membrane seeded with autologous keratinocytes and fibroblasts	A permanent alternate substitute that can provide complete wound cover and closure. Only a small autologous skin biopsy can potentially be used to cover the entire body after 3–4 weeks. It has been used in major burns
Integra (Integra LifeSciences, New Jersey, United States)	These consist of an outer silicone epidermal equivalent and a lower cross-linked bovine collagen and shark glycosaminoglycan. Single layer of collagen only is also available	The bilayered dermal template is widely used in burns. This requires a two-stage procedure while the single layer is used as a single-stage procedure. The single layer is used both in acute burns and in reconstruction. Cross-linked collagen provides the stability of the dermal construct
Pelnac (Gunze Limited, Kyoto, Japan)	Consists of cross-linked calf collagen with a thin silicon outer layer	Very similar to Integra but the silicon layer is thinner for better pliability and conformity to the wound bed

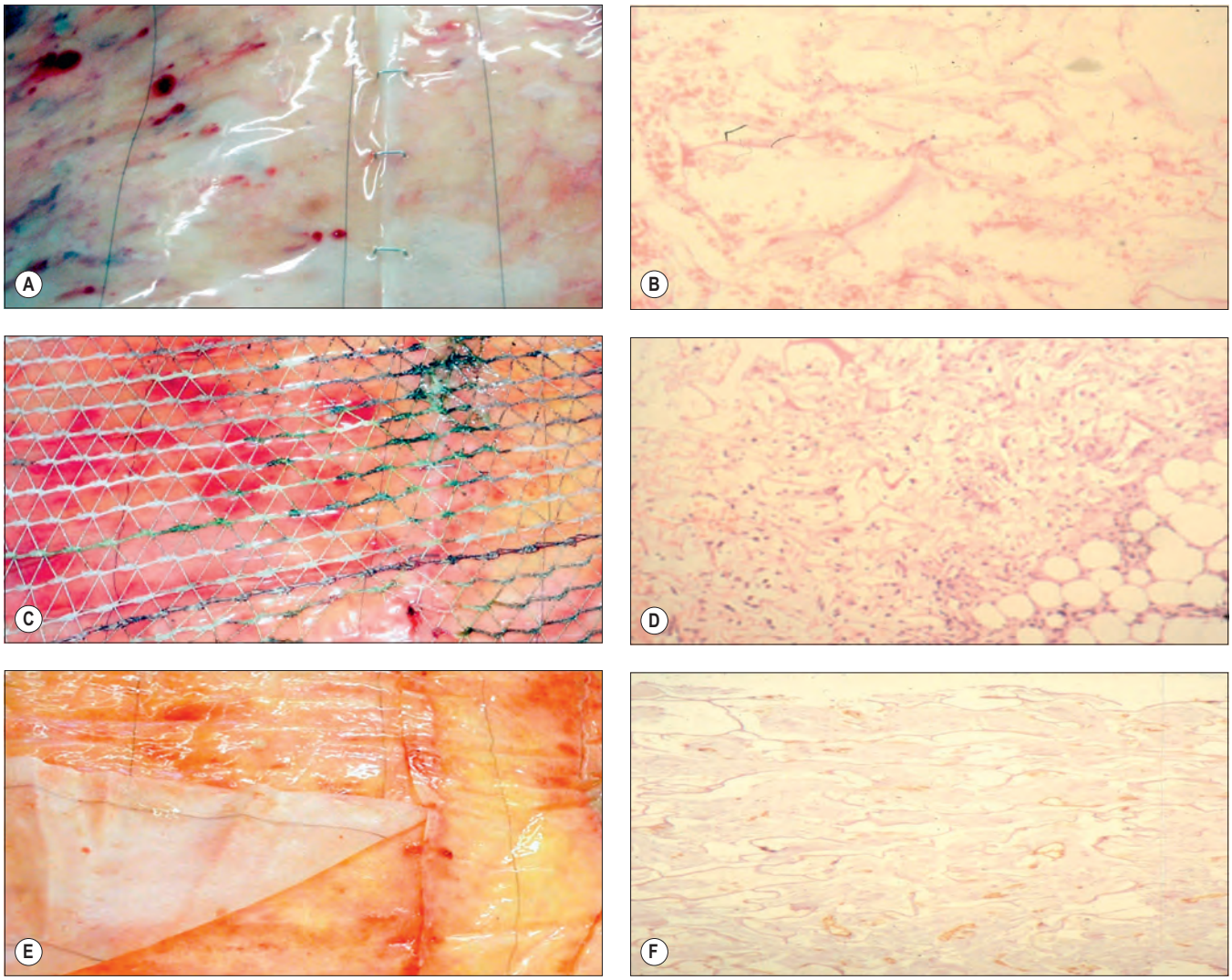


Fig. 58.1 Stages of Integra vascularization. Matrix color is correlated with the stage of vascularization. Clinical (*left*) and histological appearances (*right*). Appearance at first stage, day 0 with pale colored matrix **(A,B)**; matrix developing a pinkish color at day 21 **(C,D)**; and a peachy color at 4 weeks **(E,F)**. CD31-stained endothelial cells in the superficial layer of the neodermis **(F)**. (From Moiemen NS, Vlachou E, Staiano JJ, Thawy Y, Frame JD. Reconstructive surgery with Integra dermal regeneration template: histologic study. Clinical evaluation and current practice. *Plast Reconstruct Surg*. 2006;117(7 Suppl.):160S–174S.)

yielded favorable short- and long-term outcomes.[2] The matrix vascularization and formation of the "neodermis" occurs over a period of 3–4 weeks (Fig. 58.1)[3] under the protective cover of the silicon epithelial-equivalent layer. This allows wound closure during the critical time of waiting for limited donor sites to heal and be ready for reharvesting. In fact, the fully matured vascularized matrix can be left in place, even for several further weeks, as long as the silicon layer remains adherent to it.

When Integra is used in acute major burns, immediate or early burn excision is important. This allows adherence of the matrix to the wound bed before wound colonization occurs, thus decreasing the risk of infection. If immediate excision has been performed, it is prudent to delay application of Integra for 24–48 hours, as mentioned earlier. Fibrin sealant may be useful to promote adherence and prevent hematoma formation. Integra may also be meshed at a 1:1 ratio with a noncrushing mesher (Brennen, Molnlycke Health Care, Gothenburg, Sweden.) to reduce the risk of hematoma and to allow antimicrobials to access the wound bed. Surgifix (BSN medical GmbH, Hamburg, Germany) applied directly onto the silicon layer can be very useful to prevent early silicon separation, especially if the second stage is to be delayed for several weeks until donor sites are available (Fig. 58.2). Antimicrobial dressings followed by an absorbent gauze layer are applied over the Surgifix, and a firm bandage completes the dressing. When compared to Integra application for scar resurfacing, wound care in acute burns is of paramount importance because early identification of complications can avoid disastrous consequences with loss of the entire Integra layer and the potential for sepsis. Frequent inspection of the matrix, especially during the first week, by a member of the team with experience in the use of Integra is crucial. To ensure successful Integra engraftment, the whole multidisciplinary team should be aware of how to mobilize

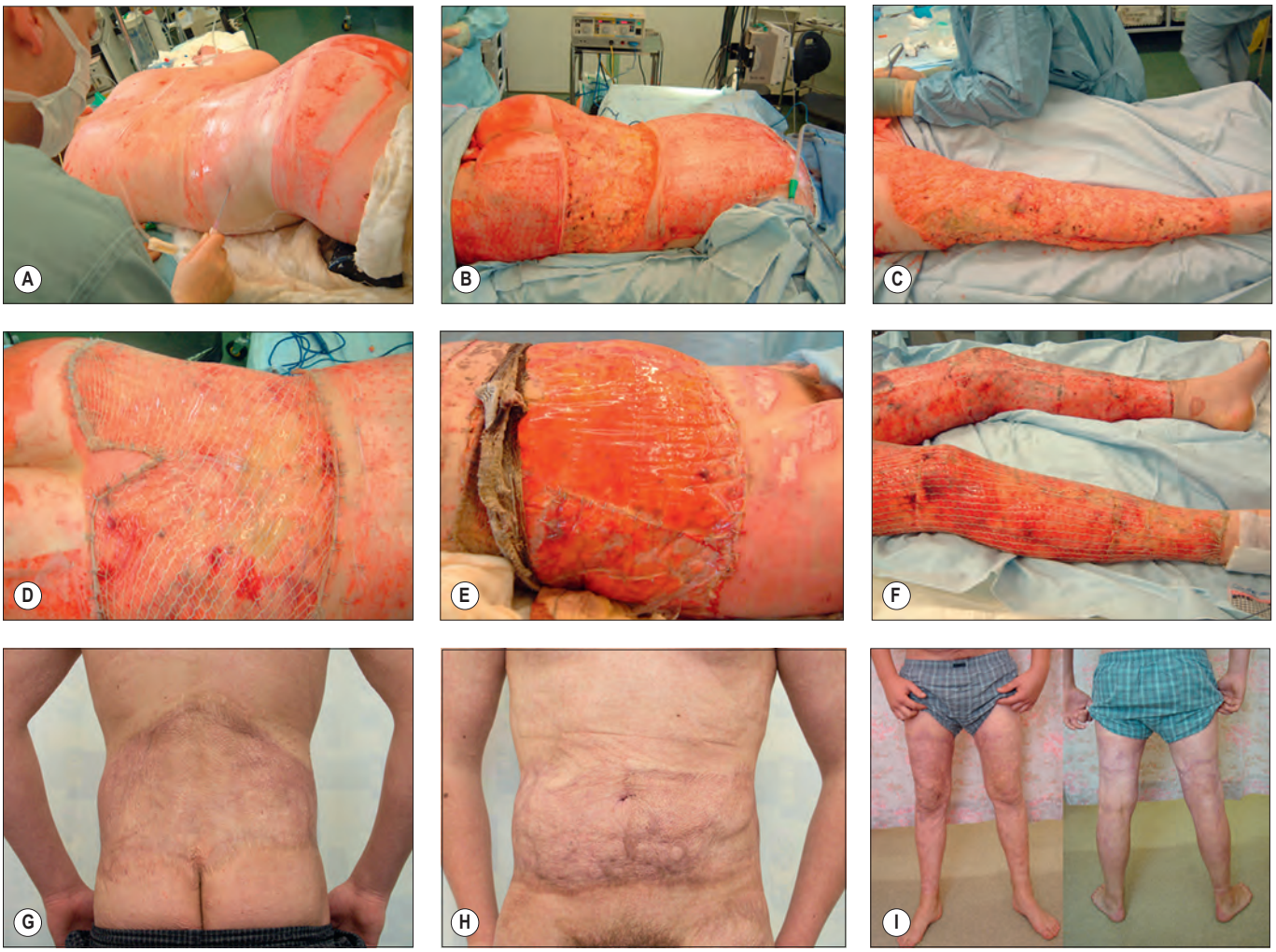


Fig. 58.2 Acute early burn excision and Integra application with 7-year follow-up. *Top row*: 14-year-old female with 60% total body surface area (TBSA) flame burn **(A)**, post-excision of burn on back **(B)** and legs **(C)**. *Middle row*: Day 9 post-excision appearance of burn wound and application of Integra on back **(D)**. Day 18 appearance of abdominal **(E)** and leg **(F)** burn wounds postexcision and application of Integra. *Bottom row*: Appearance of the healed burn wounds 7 years post burn of back **(G)**, abdominal area **(H)**, and lower limbs **(I)**.

and turn the patient and perform therapy, including chest therapy, without disturbing the matrix. Wound care after the second stage (removal of the silicon layer and application of partial-thickness grafts) is the same as in other major burns.

Matriderm is mainly used as a single-stage procedure, with the skin graft applied onto the matrix in the same operation. It has applications in burns where function and aesthetics are important (e.g., in the hand over joints or on the face). However the requirement for immediate grafting is a limitation in major burns when donor sites are sparse. Matriderm, being formed of noncross-linked collagen, is vascularized more quickly than Integra and also resorbs more quickly; however additional analysis of long-term results is still needed.

Other bilayer cellular substitutes include Apligraft, Orcel, and the Engineered Skin Substitute (ESS or Permaderm). Only ESS, which was first introduced by Steven Boyce of the Shriners Hospitals for Children, Cincinnati, contains autologous epithelial cells and fibroblasts that, once produced, allow complete wound cover of major burns and require only a very limited skin biopsy from the patient.[4] ESS has been granted orphan status by the FDA for use in acute burns and a phase II multicenter trial will soon be under way.

Clinical Applications of Alternative Wound Substitutes in Burn Scar Resurfacing

Resurfacing of extensive postburn hypertrophic scars has become possible with the availability of permanent alternative wound substitutes such as Integra. The outcome is superior to that of partial-thickness skin grafts, but it falls short of full-thickness skin grafts that are still the gold standard option for scar resurfacing. However, following major burns there can be limited availability of donor sites for full-thickness grafts.

The timing of scar resurfacing is important. The wisdom of experience has shown that extensive resurfacing

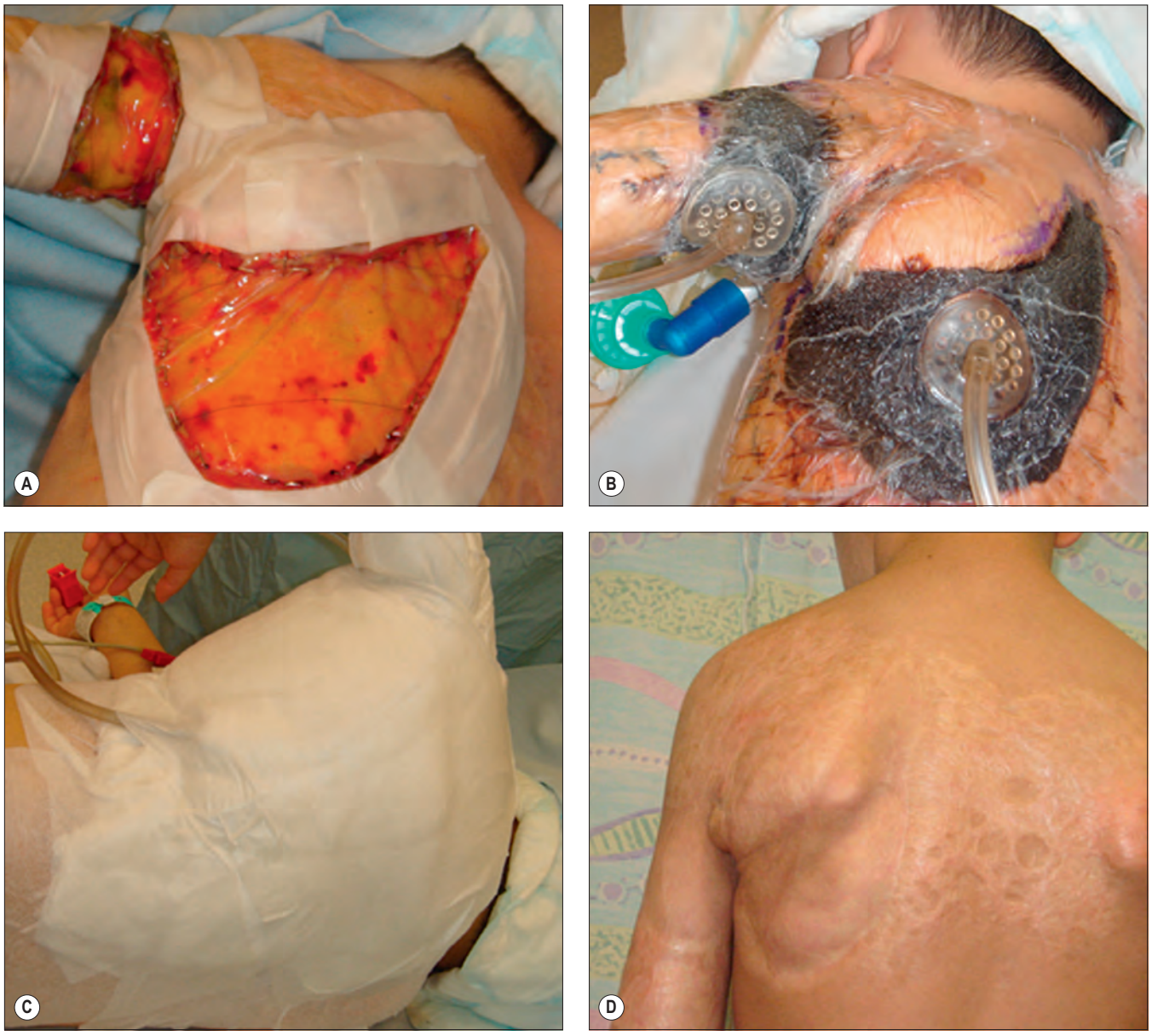


Fig. 58.3 Long-term outcome of Integra scar resurfacing. Post-excision of a scar on the back of a child and application of Integra **(A)**, which is further secured with negative-pressure dressing **(B)**, and final appearance of dressing **(C)**. Appearance of resurfaced burn wound scar 4 years postop **(D)**.

procedures are more successful when the scars have matured and become pale in color. At early stages of post-burn scarring, other surgical approaches including flaps or modalities such as laser may be more appropriate. Radical excision of all scar tissue, especially at the depth of the excised wound bed, is important to achieve good results with skin substitutes and to avoid recurrence of any contracture. Certain anatomical areas are challenging to reconstruct, such as the neck, axillae, and groin. Transposition flaps, if possible, may be used to avoid applying Integra directly over joints. Negative-pressure therapy (NPT) can assist with adherence and minimize shear; whether or not it accelerates vascularization and cell migration is debatable (Fig. 58.3). The skin substitute is covered with an antimicrobial dressing (e.g., Acticoat, Smith & Nephew, London and Hull, United Kingdom), then a layer of gauze (Kerlix, Medtronic, Dublin, Republic of Ireland) and a bandage. For resurfacing on the limbs, a foam circumferential cylinder firmly applied provides gentle pressure and may prevent complications including shear and hematoma formation.

Aftercare following surgery is very important to detect any early signs of infection. In the author's practice, patients are usually discharged home the day following surgery in extensive resurfacing or on the day of surgery in smaller cases. Patients are reviewed by a member of the team with experience in dealing with Integra. Readmission for the second stage to apply the partial-thickness skin graft (0.008–0.010 inch) occurs 3–4 weeks after the first stage. The same dressings are applied as at the first stage for 1 week, and the patient is followed-up weekly. Patients are seen regularly by the therapy team during the postoperative period, and the same splinting and scar management as for conventional skin grafts is applied.

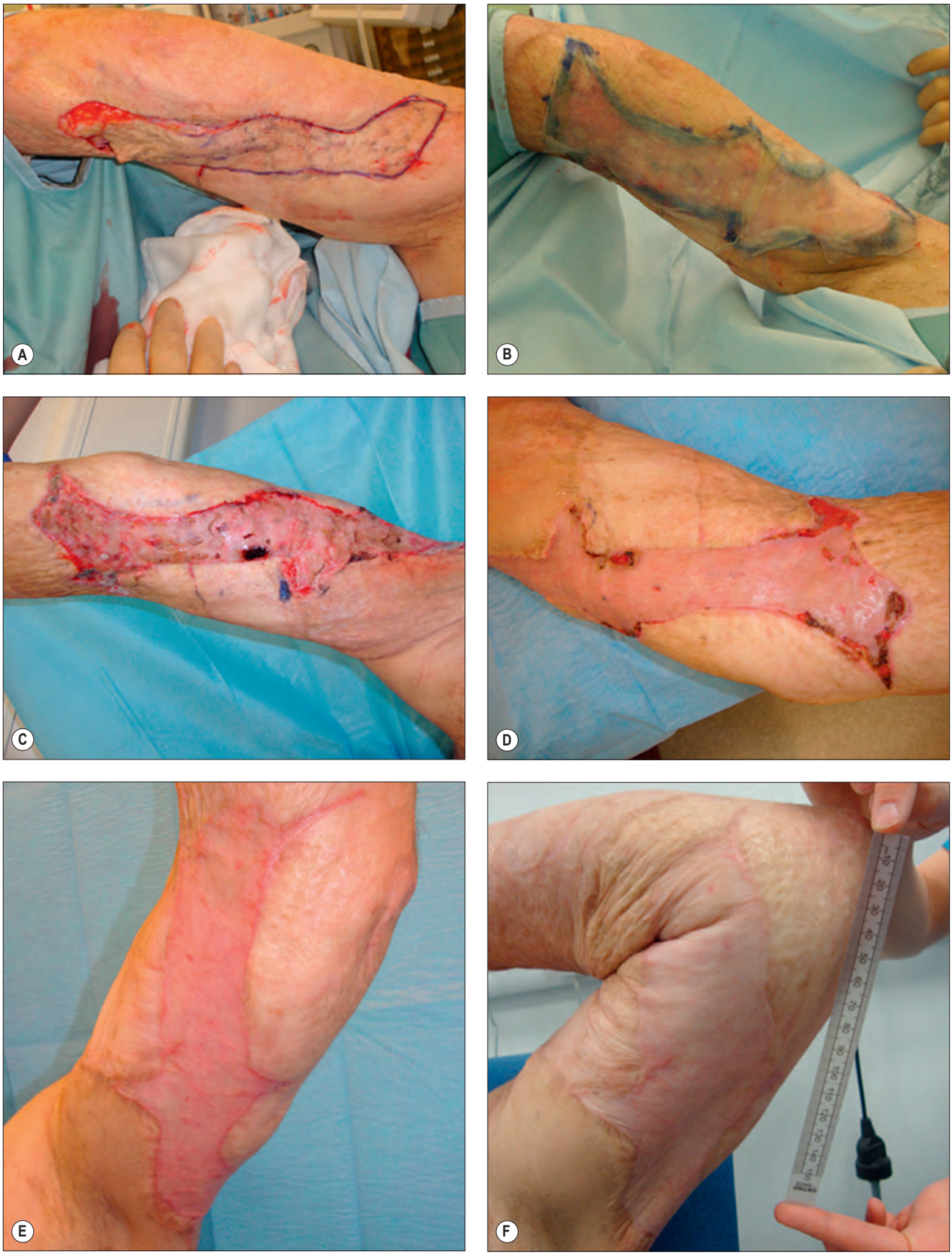


Fig. 58.4 Long-term outcome of Matriderm resurfacing. Excision of hypertrophic burn scar **(A)**, post application of Matriderm and split-thickness skin graft **(B)**, appearance at 2 weeks **(C)**, appearance at 3 weeks **(D)**, and appearance of healed scar at 3 months **(E)** and 9 months with good range of motion at the elbow joint **(F)**.

Matriderm operative and postoperative care is similar to that of Integra; however occlusive dressings that are not disturbed for 1 week usually give good results because the skin graft overlying the Matriderm requires a moist environment until vascularization occurs (Fig. 58.4). Since Matriderm does not have a silicon layer, NPT should be used with caution because it may shrink the matrix.

Future Directions

Permanent alternative wound substitutes can improve survival and outcome in burn patients but remain prohibitively expensive. Ninety-five percent of patients with major burns live in low- and middle-income countries where these products are not easily affordable. New products that could be produced less expensively on a large scale may reduce the cost and help these patients.

Unlocking the regenerative potential of skin, together with new innovations such as scaffolds that deliver molecules to the wound bed to promote healing and reduce scarring, are exciting directions for the future.

Complete references available online at
www.expertconsult.inkling.com

References

1. Heimbach D, Luterman A, Burke J, et al. Artificial dermis for major burns. A multi-center randomized clinical trial. *Ann Surg*. 1988;208(3):313-320.
2. Branski LK, Herndon DN, Pereira C, et al. Longitudinal assessment of Integra in primary burn management: a randomized pediatric clinical trial. *Crit Care Med*. 2007;35(11):2615-2623.
3. Moiemen NS, Vlachou E, Staiano JJ, et al. Reconstructive surgery with Integra dermal regeneration template: histologic study, clinical evaluation, and current practice. *Plast Reconstr Surg*. 2006;117(7 suppl):160S-174S.
4. Boyce STKR, Meyer NA, Yakuboff KP, et al. The 1999 clinical research award. Cultured skin substitutes combined with Integra Artificial Skin to replace native skin autograft and allograft for the closure of excised full-thickness burns. *J Burn Care Rehabil*. 1999;20(6):453-461.

59 Aesthetic Reconstruction in Burn Patients

JUAN P. BARRET

Introduction

The severity of injury and deformity from burn trauma range from relatively minor to severe.[1] The psychological and social impact of sequelae do not parallel the severity of the deformity; even minor disfigurements can have severe psychologic and social impacts on the patient. Basic concerns common to all burned patients include function, comfort, and appearance.[2] The approach is that of total patient care; it must include all healthcare team members and it is predicated on aesthetic and functional reconstruction. Burn reconstruction is a complex and long process that starts when the patient is admitted in the acute phase and lasts until the patient's expectations have been reached and/or there is nothing more to offer. It is normally a lifelong commitment, and, even if there may be no other possibilities to offer at that point, the patient–surgeon relationship still continues. It is preferable, although not imperative, that burn reconstruction be performed in close vicinity to the burn center and that it has the constant support of and coordinated treatment with the multidisciplinary burn team. If this is not the case, good communication with the team referring the patient is desirable.[3]

Preventing and minimizing scarring and deformity in burn patients starts during the acute phase. Reducing the inflammatory and catabolic responses after burn injury using a team approach and early closure of the burn wound is paramount to control wound healing in these patients.[4]

It is preferable that the surgeon managing the acute injury be responsible for later reconstruction. If this is not the case, the reconstructive surgeon should be consulted early on so that the needs for reconstruction enter into the plan of the acute care.[5]

Different procedures are important during the acute phase to minimize later reconstruction. Splints, face masks, silicone gel sheets, early pressure therapy and ambulation, and skeletal traction and fixation are of great importance to produce the best result and avoid future operations (Fig. 59.1).

Burn trauma requires aggressive intervention by rehabilitation services to prevent debilitating deformities. Burn distribution as well as burn depth is a good predictor of rehabilitation outcomes. Prevention of burn deformities includes proper positioning with or without splints, exercise to maintain joint range of motion, maintenance of muscle strength and muscle tone, and early mobilization. All this is true not only for the acute period, but also for the reconstructive period.[6,7]

Burn patients tend to assume the position of comfort, which is often responsible for deformities that require reconstructive surgery later during the recovery phase (Box 59.1). Thus, positioning in bed is one of the most important ways to prevent deformities (Box 59.2). It is not the responsibility only of rehabilitation services, but of the whole burn team as well. Exercise reduces edema, maintains joint motion and strength, reduces scars, and, in the pediatric patient, maintains development level. Ambulation can begin as soon as the patient is deemed medically stable, with wounds properly dressed and doubly wrapped lower limbs.

Prevention by positioning and splinting affects many problems in the care of burned patients. Static and dynamic splints are used for either immobilization or mobilization, respectively. Initially splints are used at all times except for exercise and immediately postop during the immobilization period. As active range of motion increases and is maintained, the protocol changes to night-only splinting. Skeletal traction and fixation also are used on a limited basis to prevent and correct burn scar contracture formation and are always tailored to the patient's needs.[8]

Timing of Reconstruction

It has been advocated that definitive correction of burn scarring should be delayed for 1 year or longer after healing in the acute period. It is certainly true that unaesthetic and ugly scars mature over time, and, with the effect of pressure and splints, many of them do not require surgery once the acute phase of scar maturation has taken place. Patience is often the best tool of the reconstructive surgeon. However some problems encountered early during the recovery phase must be dealt with and operated on before the golden period of scar maturation is over. In these circumstances it must be absolutely certain that an operation is needed to correct the deformity. Urgent procedures must be planned to correct functions that are not amenable to other treatments, often because time is of the essence. An eyelid release to protect an exposed cornea, correction of distracted or entrapped neurovascular bundles, severe fourth-degree contractures, and severe microstomia fall into this group. Intense rehabilitation, splinting, and pressure therapy are mandatory after correction of these deformities. In some patients deformity may be addressed nonoperatively, but if this approach does not lead to appropriate results, an operation may be considered. In this section fall all burn scar contractures that do not respond to rehabilitation and hypertrophic scarring and contractures that prevent the patient from eating, bathing, moving, and performing activities of daily living.

Most of the problems that patients may present are aesthetic ones and scar contractures that, although not

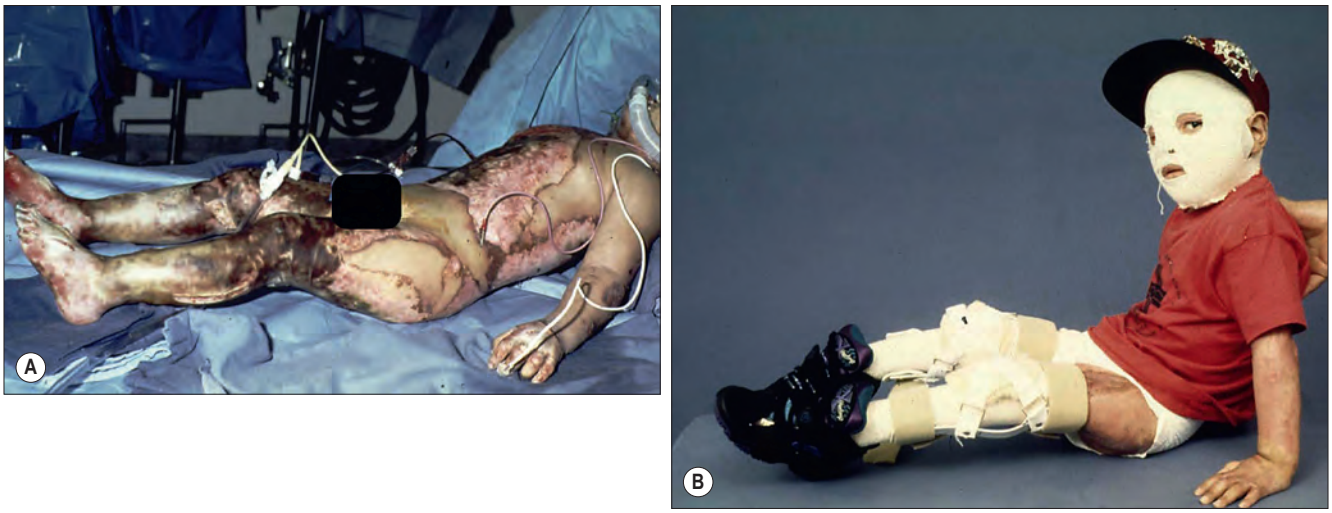


Fig. 59.1 **(A)** Sixty percent full-thickness total body surface area (TBSA) burn. **(B)** A comprehensive rehabilitation team approach is necessary to achieve good functional and aesthetic outcomes.

Box 59.1 Position of Comfort After Burn Trauma (to be Avoided)

1. Neck flexion
2. Shoulder protraction
3. Elbow flexion
4. Metacarpal extension
5. Interphalangeal flexion
6. Wrist flexion
7. Hip flexion
8. Knee flexion
9. Ankle plantar flexion

Box 59.2 Prevention of Deformity: Positioning in Bed

1. Maintain straight alignment of the trunk and neck
2. Neck should be in slight extension
3. Arms should be elevated in the neutral plane or in line with the glenoid at approximately 15–20 degrees of horizontal flexion and 80 degrees of abduction
4. Elbow should be in full extension
5. Hand should be in the intrinsic plus position with the thumb in flexion and abduction
6. Hips should be in extension and abduction
7. Knees should be in full extension
8. Foot should be in neutral position and with 90 degrees or greater dorsiflexion

prominent, produce great discomfort. Many of these problems disappear in the first 2 years postburn with appropriate care, and these problems benefit most from patience and time. Many important deformities seen a few months post burn improve with time and can be treated with simple or less extensive procedures later (Fig. 59.2).

Many factors other than scar maturation, however, affect the decision of whether to operate on burn scars. Psychologic and socioeconomic factors are very important when making this decision. The patient's mood plays an important role because an unmotivated or depressed patient will not appreciate the procedure as much as a healthy patient. Moreover, operating on such a patient may produce discomfort and discouragement that, eventually, can jeopardize the patient's compliance and prevent further reconstruction. The social status of the patient is also of great relevance. Emotional support received from friends, family, and co-workers is important, as is the patient's economic status. When making a treatment plan, all these particular circumstances need to be taken into account when considering the number of procedures to be done at a time, recovery time, family support in the recovery phase, and what is to be done first.[5]

Patient–Surgeon Relationship

Burn patients require an intense and good relationship with their surgeon. The relationship is normally a long-lasting one, many times extending to a lifetime. Patients require a surgeon's professional expertise, but also the surgeon's time, a good dose of optimism, and compassion. The initial meeting is one of the most important events in burn reconstruction. A patient presents with a set of complaints that have to be evaluated together with the patient's motivation for surgery and his or her psychologic status. Chief complaints, patient motivation, and expectations are evaluated. Limitations of surgery and any relevant technique are explained, together with the master plan for reconstruction and the order of reconstructive priorities. Photographic workup is extremely important to document the case, assist in definitive preoperative planning, and for documentation. When dealing with long-term scars and burn deformities, different problems may be encountered intraoperatively that might require a complementary technique. These specific issues of burn reconstructive surgery have to be explained in detail to the patient, and the surgeon needs to foresee and include them in the preoperative planning and

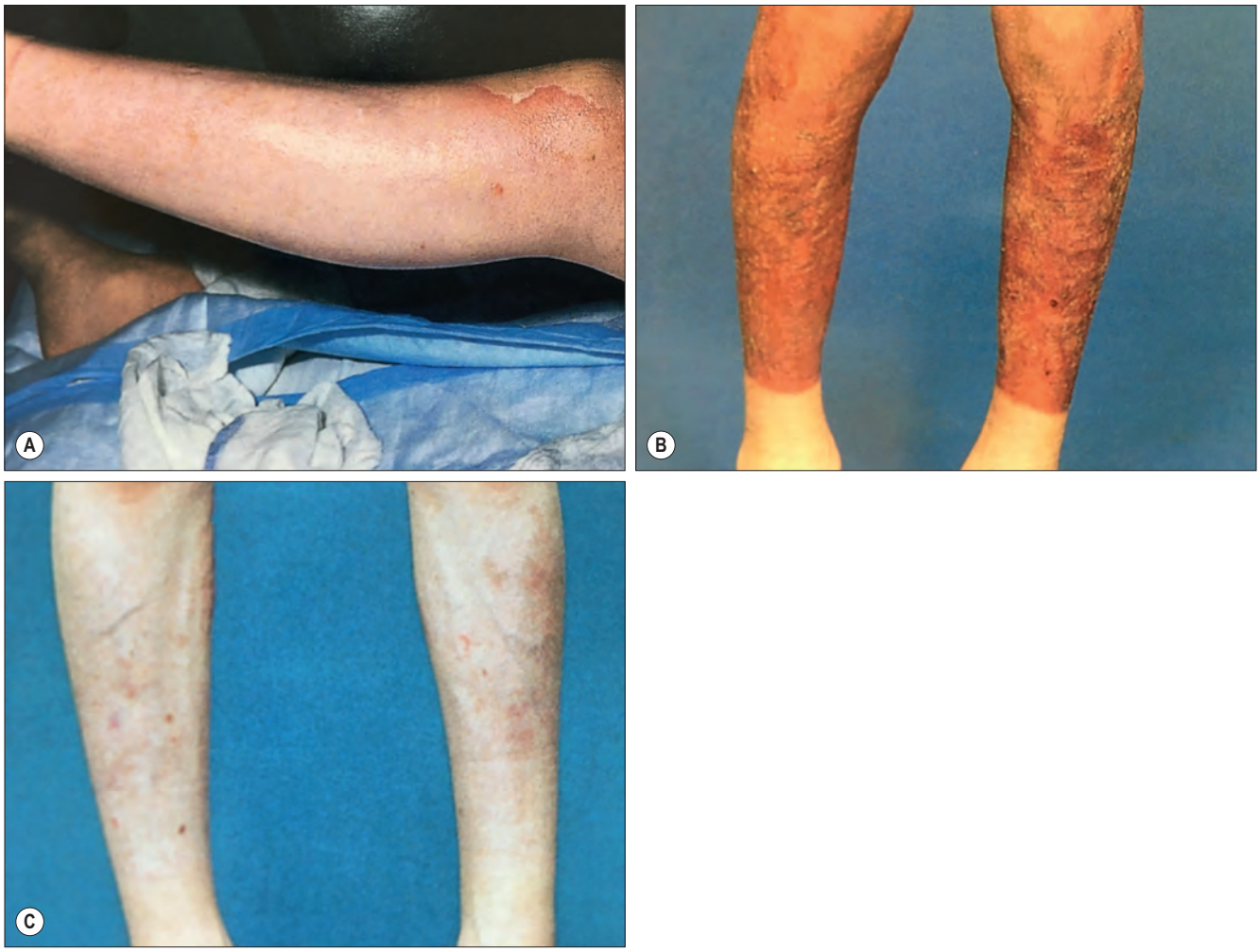


Fig. 59.2 (A) Second-degree burn to the lower extremities. **(B)** Same patient at 2 months. Erythema, hyperpigmentation, and scarring are present. **(C)** Result at 18 months with conservative treatment. Scarring is minimal with good overall result. In many cases scar maturation renders optimal outcomes and allows good planning for reconstructive planning if necessary. (From *Color atlas of burn care*, London 2001, First Edition, Elsevier.)

the informed consent meetings so that unpleasant surprises are not encountered later.[9]

Patients need to be reassured frequently. A burn reconstruction project involves several operations, many clinic visits, and often a long time to make a final assessment. The patient's feelings and impressions must be addressed continuously and any trouble, minor disappointment, or depression detected early on and treated as needed (Box 59.3).

Box 59.3 Characteristics of Burn Reconstructive Plastic Surgery

1. Starts during acute period
2. Strong patient–surgeon relationship
3. Development of a "master plan"
4. Involvement of the burn team using a multidisciplinary approach
5. Long and staged procedures
6. Complex and technological implications
7. Involvement of plastic surgery and aesthetic surgery/medicine techniques

Pre- and Postoperative Care in Burn Reconstruction

A complete record of all encountered problems has to be performed during the initial and any follow-up visits before surgery. Quality and color of the skin in the affected areas must be noted, including abnormal scars, hyper- or hypopigmentation, contractures, atrophy, and open wounds. Function has to be addressed next: all involved joints are explored, range of motion noted, and skeletal deformities addressed. Often scar contractures distract joints and the body maintains an abnormal position to overcome the deformity. A complete X-ray workup must be obtained to explore the status of bones and joints. In severe restriction of function, good radiological imaging must be obtained to rule out heterotopic calcification.

The needs for physiotherapy, occupational therapy, and pressure garments have to be considered at this time. The

Box 59.4 Essentials of Burn Reconstruction

1. Strong patient–surgeon relationship
2. Psychological support
3. Clarify expectations
4. Explain priorities
5. Note all available donor sites
6. Start with a "winner" (easy and quick operation)
7. As many surgeries as possible in the preschool years
8. Offer multiple, simultaneous procedures
9. Reassure and support the patients

patient is referred to the rehabilitation department for consideration. Finally, an inventory of all possible sites for donor tissue is made.

All reconstructive possibilities are discussed with the patient, and the timing and order of such procedures are outlined. All important points and pitfalls are explained to the patient. The importance of addressing all urgent, essential, and functional problems first has to be understood by the patient. This is essential because the patient can become extremely upset when important cosmetic problems are disregarded at the beginning while other not so obvious problems (to them) are addressed first.

Finally, in children, it is also important to perform as many procedures as possible during the preschool years and to offer the patient multiple, simultaneous procedures. Time, effort, and money are then best invested. Essentials of burn reconstruction are summarized in Box 59.4.

Pre-, intra-, and postoperative care of burn reconstructive patients include all techniques and special treatments of general plastic surgery and any state-of-the-art special plastic surgery techniques. The scope of procedures performed in burn reconstructive surgery ranges from split-thickness grafts to tissue expansion and microsurgery. More recently composite vascularized allotransplantation has emerged as a new technique for catastrophic burn deformities.

The plastic surgeon operating on burn patients works most of the time with scarred and injured skin. In this particular setting, it is very important to handle all tissues with extreme care because vascularization in the area is normally altered. Patients are instructed to stop smoking for at least 3 weeks before surgery. All meals and drinks containing active vascular substances need to be tapered and any medications noted so that all unnecessary drugs can be stopped. The patient is instructed also to avoid medications such as aspirin that may increase intraoperative and postoperative bleeding. Uncontrolled hypertension, cough, nausea, and disorders of coagulation need to be known by the surgeon and treated as needed since they are known to increase the risk for hematoma. It is always advisable that the patient presents for surgery with a responsible adult to take care of them after surgery.

The evening before surgery the patient is instructed to have the skin cleansed with bacteria-reducing soap, and a light dinner is advised. Burn patients normally have hypertrophic scarring, seams, and intradermal cysts that are prone to a high bacterial load. It is also advisable to include in the operative planning the perioperative use of antistaphylococcal agents. If a skin flap or introduction of alloplastic material is to be performed, antibiotics should be continued in the postoperative period for at least two more doses.

Probiotics are also advised to avoid any antibiotic side effect. Intraoperatively large doses of local anesthetics are to be avoided, and the extensive use of electric coagulation is minimized because it increases the risk of necrosis of scarred skin. Similarly the use of subcutaneous epinephrine is limited because of the same risks.

A smooth emergence from general anesthesia, one free of coughing and vomiting, is essential in burn reconstructive surgery, as are controlling high or low blood pressure episodes, nausea, and vomiting. Hyperactive and anxious patients may benefit from anxiolytic medication to avoid sudden and uncontrolled movements in the immediate postoperative period. Light dressings are applied after surgery and any high pressure avoided since it can injure burned tissue. When aesthetic procedures are planned (such as fat grafting, CO_2 laser therapy, chemical peels, aesthetic surgery), patients are left without dressings to allow accurate and correct wound healing. Immobilization is kept to a minimum, and passive and active range of motion is started as soon as possible in the postoperative period. Movement helps to avoid edema formation, congestion, and recurrence of contractures. Splints, prostheses, and pressure garments must be used either immediately or very soon after the operation. Rehabilitation is normally part of the reconstructive master plan, so it must be included and started after surgery. Silicone inserts in grafted areas have been found helpful in controlling the early phase of scar maturation because they apply gentle and uniform pressure to the wounds and position joints properly.

It is also very important to administer good pain control because having a comfortable and cooperative patient helps positioning, rehabilitation, and the success of any operation. Patient-assisted analgesia is the best option if the patient is able to use it. Other than that, scheduled hydrocodone and morphine are good alternatives. Anxiolytics must always be considered as part of the pain control program, and the addition of antiitch medications and antiemetics such as diphenhydramine and droperidol is very helpful.

Finally, providing the patient and family an environment that is cozy and relaxing helps them and the burn reconstructive team to cope better with periodic admissions and decreases fear and anxiety before every step in the progress of the reconstructive plan.[10,11]

Surgical Approach to the Burn Reconstructive Patient: The Role of the Reconstructive Ladder

Some progress has been made in burn reconstructive surgery in the past decades, although its impact is not as dramatic as in other areas of plastic surgery. Burn reconstructive surgery involved for many decades incisional or excisional releases of the affected scars and skin autografting. Today, however, the first approaches that the reconstructive surgeon should bear in mind are local or regional

Box 59.5 Techniques Available for Aesthetic Burn Reconstruction

1. Classic workhorse techniques: skin grafts, cartilage grafts, z-plasty, local and regional flaps, keystone flaps
2. Dermal regeneration templates
3. Tissue expansion with or without flap prelamination/prefabrication
4. Free flaps, with or without prelamination
5. Fractional CO_2 laser and others
6. Fat grafting and stem cell therapy/keratinocytes
7. Aesthetic plastic surgery techniques: liposuction, rhinoplasty, facelifts, breast surgery, etc.
8. Chemical peels
9. Hair transplantation
10. Osseointegration and dental surgery
11. Micropigmentation
12. Composite vascularized allotransplantation

flaps.[5] They provide new and vascularized tissue to the area, they grow in children, and they render the best functional and cosmetic results. These flaps can be raised either with normal skin or burn scar. Even though it is generally true that burned tissues present a high tendency to congestion, ischemia, and necrosis, such tissue can be used as a reliable flap if extreme care is used while raising the flap and the injured skin is left attached to the underlying tissues.[12] This expands burn reconstruction into new territories and techniques.

Moreover, tissue expansion offers reconstructive surgeons the possibility to produce new pre-expanded flaps that may be transferred as free flaps or tailored or prefabricated flaps.[13–15]

For years surgeons used to evaluate the chief complaint or complaints and wait for immature scars or increasing deformities to mature with time and the use of pressure garments. Only then, after the deformity was stable, would they begin with simple techniques. At that point, depending on the type of deformity, skin grafts or simple techniques such as z-plasties or the like were used. Today, the burn reconstruction plan needs to be tailored to the individual patient, and complex and advanced techniques are utilized since they offer better function and cosmesis.[5]

Aesthetic Reconstruction of Burned Patients

The evaluation of reconstructive needs in burn victims should follow a holistic approach. In the best hands, the approach is developed under the umbrella of a group of experienced plastic, reconstructive, and aesthetic physicians in which all techniques are mastered. Not only have simple, traditional plastic surgery operations to be contemplated, but also new additions in aesthetic surgery and aesthetic medicine (Box 59.5). These include skin grafts to free flaps, composite vascularized allotransplantation, fat grafting, hair transplantation, and laser treatments or chemical peels.[16] Fig. 59.3 summarizes a master aesthetic burn reconstructive plan.

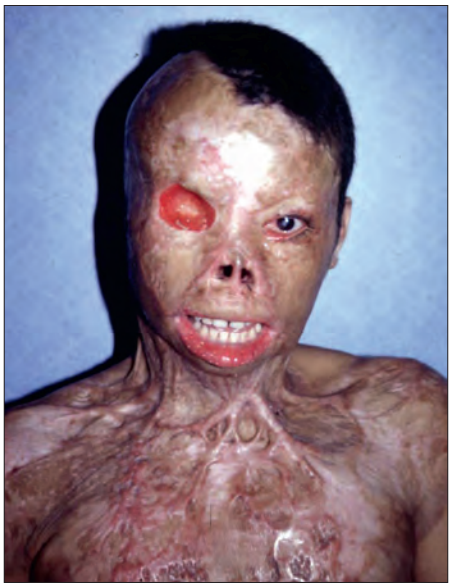


Fig. 59.3 Burn wound sequelae to the face. Aesthetic master plan includes pre-expanded flaps, full-thickness skin grafts, scar revision, commissuroplasties and lip correction, fat grafting, vertical subperiosteal mid face lift, monofollicular hair transplantation, ear reconstruction, osseointegrated implants, CO_2 fractional laser treatment, and micropigmentation. Mastering all techniques of reconstructive surgery, aesthetic surgery, and aesthetic medicine is a must to provide excellent outcomes.

HEAD AND NECK

Burns to the head and neck are still a challenge to the burn team. Residual deformities produce severe distortion, with disfigurement and functional limitations. Bridging scars from chin to neck to anterior shoulder result in exaggerated kyphosis with neck flexion and protraction of the shoulders. The most frequent deformity in the periorbital area is ectropion, although more severe cases present distraction of the canthal folds, fusion of part of the eyelids, and distortion of the lacrimal punctate. Release of upper and lower eyelid contractures has to be performed separately, with undermining of the surrounding tissues. Full-thickness grafts are most suitable for lower eyelids where stability is the goal, while split-thickness skin autografts are used on upper eyelids to improve mobility.[17] Fat grafting has been successfully used to restore the aesthetic appearance of the upper eyelid. Lower eyelid ectropion may also benefit from fat grafting. Good repositioning of deep structures can be achieved by this technique, often solving difficult ectropion problems.[18] Eyelashes and eyebrows can be restored by monofollicular or multiple-follicular hair transplantation, rendering in many situations better outcomes than traditional techniques. Micropigmentation is another good solution in selected patients, restoring normal appearance and even providing the disguising look of three-dimensional facial architecture.[19,20]

The nose anatomy deserves careful attention. Small deformities may be corrected by secondary rhinoplasty and dermabrasion with or without sprayed keratinocyte cells. More extreme deformities (destruction of the columella or alar rims) are good indications for helical rim free flaps, whereas subtotal or total destruction of the nose calls for a

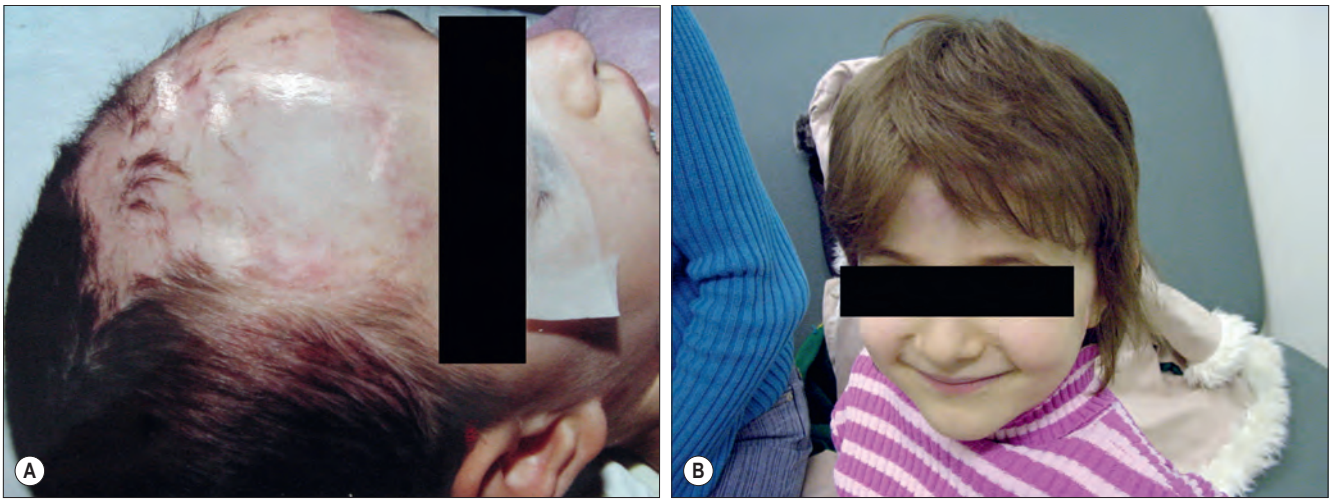


Fig. 59.4 (A) Burn scar alopecia, including the anterior hairline. **(B)** Result after reconstruction with scalp tissue expansion with rectangular tissue expanders.

traditional nose reconstruction with paramedian forehead flap (if this donor site is absent, a prelaminated free flap is a good option).[21]

Lip deformities and microstomia are normally addressed with local flaps, commissuroplasties, and skin grafts. Micropigmentation is a good aid to finish the reconstruction and to restore the vermilion border. Fat grafting can be utilized for lip volume, whereas laser treatment and dermabrasion clear superficial irregularities. Loss of hair follicles in male patients has been traditionally reconstructed by means of scalp grafts or flaps, but monofollicular hair restoration is the ultimate solution for this problem.[22]

Another area that deserves aesthetic (and indeed functional) attention is dental malocclusion. It is not uncommon for burn patients to lose teeth and present with an altered smile and poor projection. The growing child deserves extra attention too. Tight scars, inelastic skin, and scar contractures may alter the correct growth of facial bones and produce malocclusion. If these anomalies are detected, orthodontics, tooth replacement, osseointegrated implants, and even orthognathic surgery may be required.[23]

Other passive deformities include ear deformities. Ear reconstruction in burned patients can be done with rib cartilage grafts. If there is no suitable subcutaneous pocket, a superficial temporalis fascial flap can be used to wrap the framework, with a split-thickness skin graft on top. Other times, tissue expansion to the retroauricular area can be performed prior to the creation of a rib cartilage framework.[24]

BURN ALOPECIA

One of the areas where the effects of burn injury are most noticeable is the scalp. Healing of deep partial- and full-thickness burns very often leads to areas of scalp alopecia. This produces an important psychologic impact for the patient because it affects self-esteem and image. Small areas of patchy alopecia can be effectively treated with excision and direct closure; however, tissue expansion is still the gold standard of treatment for burn alopecia (Fig. 59.4).

Box 59.6 Classification of Burn Alopecia (after McCauley et al.)

Type 1: Single alopecia segment
- A, <25%
- B, 25–50%
- C, 50–75%
- D, 75%

Type 2: Multiple alopecia segments amenable for tissue expansion
Type 3: Patchy burn alopecia
Type 4: Total alopecia

McCauley et al. classified burned scalp alopecia in terms of the pattern and extension (Box 59.6). This classification has proved very useful in our approach. Patchy burn alopecia extending across the entire scalp or total alopecia are not suitable for classical reconstruction.[25] However micropigmentation or even monofollicular hair transplantation has produced great results and provided new tools for burn reconstruction of these difficult problems.[19] On the other hand, alopecia extending to up to 50% of the scalp can be corrected with single expansion and closure, whereas larger areas of alopecia or different concomitant segments of alopecia can be managed with sequential expansion. Many times overinflation of the expander is necessary, and it is important to bear in mind that expanded tissue normally contracts by 20% of the initial surface. Care of these patients is similar to that of any patient undergoing tissue expansion. In our hands rectangular tissue expanders with overexpansion are the best possible solution for these types of problems.

Selected patients with good-quality scars and limited areas of burn alopecia may be offered hair transplantation. If this technique is selected, the same tenets and aftercare utilized in male pattern alopecia restoration apply. It is important to recognize the male pattern alopecia areas in the subject of relatives to select the appropriate donor site.[26]

Fig. 59.5 Typical hand deformity. A comprehensive approach with a program of functional reconstruction and aesthetic consideration of skin coverage is advocated.

UPPER EXTREMITY

Hypertrophic scars and contractures to the upper extremity promote the position of comfort: protraction and adduction of the shoulder, elbow in flexion, and the "burned hand position" with wrist in flexion, metacarpophalangeal extension, interphalangeal flexion, and first metacarpal extension and adduction. The overall appearance of the hand is that of a "claw deformity" (Fig. 59.5). Many of these problems can be prevented with correct acute care and splinting, which include the arm elevated in the neutral plane or in line with the glenoid at approximately 15–20 degrees of horizontal flexion and 80 degrees of abduction, elbow in full extension, and hand in intrinsic plus position with thumb in flexion and abduction.

Linear contractures to the shoulder can be addressed with local flaps, keystone flaps, or two-staged dermal regeneration burn reconstruction techniques. The addition of fat grafting and stem cell therapy are promising grounds for best outcomes and clinical research. Often four- and five-flap z-plasties are very useful. When the contracture extends to all or nearly all of the axilla, incisional release and autografting is preferable, although regional rotational flaps or free flaps can be used if available. It has to be noted, however, that a contracture to the axilla cannot be released at the same time a neck release is performed since it is not possible to maintain correct neck hyperextension while abducting the shoulders in the postoperative period. The neck needs to be addressed first, followed by the shoulder release, thus allowing a perfect result in each operation.

Contractures to the elbow normally include flexion deformity, which is best addressed with local z-plasties or, when not possible, incisional release and autografting. It must be noted, however, that heterotopic calcification has to be ruled out when dealing with limitations of extension. In some cases, peripheral nerves, in particular the ulnar nerve, need to be transposed for complete functional correction of the deformity.

The most common deformities of the hand are wrist and dorsal contractures with extension, web space contractures, and boutonniere deformities. Extension deformity to the wrist and dorsum of the hand normally requires an incisional release and autografting, whereas web space contractures are best reconstructed with local flaps. Fascial free flaps are also often utilized, covered with dermal regeneration templates in a two-stage operation. Occasionally a skin autograft is necessary to add length to the reconstruction of the linear contractures. Boutonniere deformities need reconstruction of the extensor mechanism. If contracture to the palmar surface co-exists, a full-thickness graft or a cross-finger flap is necessary. However, in our experience, full release of the contracture followed by a fascial free flap and skin graft, versus a single- or two-stage dermal regeneration template procedure, together with the injection of platelet-rich plasma is a great solution. Extensor tendon destruction or adhesion is normally treated with tenolysis, and, if tendon repair is necessary, a flap must be considered. Stem cell therapy often helps in controlling excessive scarring, although future clinical research will show its real indications in burn care reconstruction. Finger transfers, thumb lengthening, and internal and external fixation are to be considered in severe and selected problems.[5]

Other available techniques that provide better cosmetic outcomes include fat grafting, chemical peels, and fractional ablative CO_2 laser therapy.[27]

One of the most important parts of the reconstruction of the burned hand is the rehabilitation plan. It must be started as soon as the skin coverage is stable. Pressure therapy, web spacers, and night splints are necessary to achieve the expected results.[28]

BREASTS

Breast deformity, asymmetry, and displacement of the nipple areola complex (NAC) is a commonly encountered deformity. Even though they may affect both genders, the presence of a breast deformity and NAC alteration has a deeper emotional and psychosocial impact in the female population.

Traditional techniques for treatment include release and autografting. Novel additions to the reconstructive armamentarium are integral and other dermal templates, which provide pliability and elasticity with good recreation of the breast mound and submammary fold. They also aid in the growing breast, allowing for better symmetry and good aesthetic outcome.

Other patients require augmentation mammoplasty with breast implants or fat grafting. In this situation it is not uncommon for patients to require the temporary placement of a breast tissue expander to augment the tissue envelope and better accommodate a definitive implant with enhanced symmetry and breast aesthetics.[24]

LOWER EXTREMITY

Severe burns to the lower extremity can be a source of important morbidity. Deformity to the feet can affect gait and normal living. Severe destruction may even prevent the patient from standing. Patients are often concerned about the appearance and correct positioning of the feet, plus the correction of nail deformities; fractional ablative laser therapy and fat grafting are parts of an integral functional and cosmetic reconstruction. A good and durable skin covering must be supplied to these areas to improve weight-bearing and ambulation. Good acute care can prevent some

of the deformities to this area, and excision and grafting to all full-thickness burns with early ambulation and physical therapy are also important. When in bed, the feet should be in neutral position and at 90 degrees or greater dorsiflexion. Orthopedic shoes and metatarsal bars are helpful in positioning foot burns in infants and small children.

Common deformities in the lower extremity include hip and knee flexion, whether anterior or posterior, and most often impose the position of knee flexion, equinovarus deformity of the foot, and extreme extension of the toes from dorsal foot burns. In all deformities, the overall functional goal is restoring anatomy, which in turn provides good cosmetic appearance.

Other relevant techniques that improve functional outcomes and overall cosmesis in lower extremities are free flaps and keystone flaps. The former are often utilized as fascial free flaps with dermal regeneration templates or full-thickness skin grafts. Fat grafting and stem cell therapy help in improving function and aesthetic appearance through a modulation of the inflammatory response and reduced scar deposition.[5,24]

Complete references available online at
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References

1. Lawrence JW, Mason ST, Aschomer K, Klein MB. Epidemiology and impact of scarring after burn injury: a systematic review of the literature. *J Burn Care Res*. 2012;33:136-140.
2. Burd A. Burns: treatment and outcomes. *Semin Plast Surg*. 2010;24:262-280.
3. Goverman J, Mathews K, Nadler D, et al. Satisfaction with life after burn: a burn model system national database study. *Burns*. 2016;42:1067-1073.
4. Finnerty CC, Jeschke MG, Branski LK, et al. Hypertrophic scarring: the greatest unmet challenge after burn injury. *Lancet*. 2016;388:1427-1436.
5. Barret JP. Burns reconstruction. *BMJ*. 2004;329:274-276.
6. Stoddard FJ, Ryan CM, Schneider JC. Physical and psychiatric recovery from burns. *Surg Clin North Am*. 2014;94:863-878.
7. Rowan MP, Cancio LC, Elster EA, et al. Burn wound healing and treatment: review and advancements. *Crit Care*. 2015;12:243.
8. Bezuhly M, Fish JS. Acute burn care. *Plast Reconstr Surg*. 2012;130:349e-358e.
9. Orgill DP, Ogawa R. Current methods of burn reconstruction. *Plast Reconstr Surg*. 2013;131:827e-836e.
10. Klein MB. Burn reconstruction. *Phys Med Rehabil Clin N Am*. 2011;22:311-325.
11. Wainwright DJ. Burn reconstruction: the problems, the techniques, and the applications. *Clin Plast Surg*. 2009;36:687-700.
12. Barret JP, Herndon DN, McCauley RL. Use of previously burned skin as random cutaneous local flaps in pediatric burn reconstruction. *Burns*. 2002;28:500-502.
13. Huang X, Qu X, Li Q. Risk factors for complications of tissue expansion: a 20-year systematic review and meta-analysis. *Plast Reconstr Surg*. 2011;128:787-797.
14. Bozkurt A, Groger A, O'dey D, et al. Retrospective analysis of tissue expansion in reconstructive burn surgery: evaluation of complication rates. *Burns*. 2008;34:1113-1118.
15. Guo L, Pribaz JJ. Clinical flap prefabrication. *Plast Reconstr Surg*. 2009;124:e340-e350.
16. Rose EH. Aesthetic reconstruction of the severely disfigured burned face: a creative strategy for a "natural" appearance using prepatterned autogenous free flaps. *Burns Trauma*. 2015;3:16.
17. Ahrenholz DH, Clayton MC, Solem LD. Burns and wound management. *Otolaryngol Clin North Am*. 1995;28:1939-1955.
18. Barret JP, Sarobe N, Grande N, et al. Maximizing results for lipofilling in facial reconstruction. *Clin Plast Surg*. 2009;36:487-492.
19. Barr L, Barrera A. Use of hair grafting in scar camouflage. *Facial Plast Surg Clin North Am*. 2011;19:559-568.
20. Garg G, Thami GP. Micropigmentation: tattooing for medical purposes. *Dermatol Surg*. 2005;31:928-931.
21. Bernard SL. Reconstruction of the burned nose and ear. *Clin Plast Surg*. 2000;27:97-112.
22. Robson MC, Barnett RA, Leitch IO, Hayward PG. Prevention and treatment of postburn scars and contracture. *World J Surg*. 1992;16:87-96.
23. Kung TA, Gosain AK. Pediatric facial burns. *J Craniofac Surg*. 2008;19:951-959.
24. Cartotto R, Cicuto BJ, Kiwanuka HN, et al. Common postburn deformities and their management. *Surg Clin North Am*. 2014;94:817-837.
25. MacLennan SE, Corcoran JF, Neale HW. Tissue expansion in head and neck burn reconstruction. *Clin Plast Surg*. 2000;27:121-132.
26. Gho CG, Neumann HA. Advances in hair transplantation: longitudinal partial follicular unit transplantation. *Curr Probl Dermatol*. 2015;47:150-157.
27. Ho D, Jagdeo J. Excellent aesthetic and functional outcome after fractionated carbon dioxide laser skin graft revision surgery: case report and review of laser skin graft revision techniques. *J Drugs Dermatol*. 2015;14:1285-1288.
28. Klein MD. Burn reconstruction. *Phys Med Rehabil Clin N Am*. 2011;22:311-325.

60 Laser for Burn Scar Treatment

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History of Laser and Intense Pulse Light

Albert Einstein was the first to describe the theoretical physics of the laser in 1917. He described the interaction of atoms and molecules with electromagnetic energy in terms of the spontaneous absorption and emission of energy and concluded that stimulated emission of energy was also possible. In 1959, the first instrument was developed by Drs. Townes and Schawlow based on those concepts. It was known as the microwave amplification through the stimulated emission of radiation (MASER). Shortly thereafter, in 1960, Theodore Maimon developed the first laser light with use of a ruby crystal. Early clinical studies with the ruby laser began in 1964, with Dr. Leon Goldman, a dermatologist considered by many to be the father of laser medicine. The rapid development of additional lasers occurred with the helium-neon laser appearing in 1961, the argon laser in 1962, the carbon dioxide (CO_2) laser in 1964, the Nd:YAG laser in 1964, and the erbium-YAG laser in the mid-1990s.[1]

However, early lasers had limited control of energy parameters, leading to frequent thermal injury and scarring. The concept of selective photothermolysis (SPTL) introduced by Anderson[2] led to the development of the first laser that was specifically designed to treat a medical condition; it was named the *pulsed dye laser* (PDL) and was almost instantly accepted in treating port wine stains in very young patients, a condition that had hitherto been very problematic.[3]

Further developments over the ensuing decades included the introduction of pulsed energy resulting in decreased laser exposure time.[1] Reliant technologies unveiled the ability to split the treated zone into specific area, resulting in multiple microtreatment zones within the target area; this was termed *fractionated laser treatment.*[4] The advent of short-duration Er:YAG lasers in the mid-1990s offered an additional option for resurfacing, either alone or in combination with the CO_2 laser. Around the same time, high-intensity flashlamp exposure was presented as a suitable tool for treating vascular lesions;[5] this resulted in the release of intense pulsed light (IPL) as a medical device. In the following years, multiple technical modifications allowed easier handling, increased safety, and widened the spectrum of potential indications.[5]

Physics of Laser

Lasers are devices that rely on the stimulated emission of radiation to produce a beam of light. The word LASER is an acronym for the term *light amplification by stimulated emission of radiation*. The device itself consists of an active medium, an energy source, and a resonating chamber.

In most lasers, there is a population of atoms known as an *active medium*. The active medium of a laser is a material of controlled purity, size, concentration, and shape. This material can be of any state: gas, liquid, solid, or plasma. The gas lasers consist of the argon, copper vapor, helium-neon, krypton, and CO_2 devices. One of the most common liquid lasers, the PDL, contains a fluid with rhodamine dye. The solid lasers are represented by the ruby, neodymium:yttrium-aluminum-garnet (Nd:YAG), alexandrite, erbium, and diode lasers.[1]

In the atom's resting state, electrons orbit around the nucleus at their ground state or lowest energy levels, in orbitals. When an electron absorbs energy from an energy source, electrons become excited and orbit into higher orbitals. The energy source used to excite the electrons can be a light source, an electrical field, or a chemical. When these excited electrons fall back into their resting orbitals, energy is released, generating photons (electromagnetic radiation). Photons have wavelengths specific to the atom excited. Since lasers have a consistent population of atoms, the photons emitted are all identical. These identical photons are considered monochromatic, meaning that all photons in a laser beam are of the same wavelength. By contrast, IPL consists of many different wavelengths.

The resonant chamber consists of two reflective mirrors between which photons reflect back and forth. If a photon collides with an excited electron, that electron falls back to its resting orbital, releasing another photon of the same wavelength. The two photons are "in phase" or "coherent," meaning their wave patterns are synchronized and reinforce each other. By comparison, the photons in conventional light travel randomly. As these photons hit other excited electrons, more photons are released and the light energy increases. The resonant chamber allows for more and more atoms to become excited and then return to ground state, thereby amplifying the energy produced (amplification of stimulated emission) and allowing for photon coherence.

One of the mirrors is only partially reflective and partially transparent. Those photons traveling in a perfectly parallel direction will exit the transparent portion of the mirror, also known as the optical resonator, taking the form of the "laser beam."

Light energy can be visible or invisible depending on its wavelength. The spectrum of electromagnetic radiation ranges from long radio waves (wavelength >10 cm) to extremely short γ rays ($<10^{-11}$ m). The entire spectrum includes radio, microwave, infrared, visible (400–700 nm), ultraviolet, X-ray, and γ rays.

The specific wavelength emitted by a laser will determine how the laser beam interacts with tissue. When the laser strikes tissue, a variety of desirable and undesirable effects result as the laser is reflected, scattered, transmitted, or absorbed.

Reflection is the proportion of laser that bounces off the surface and is redirected in a different direction. When laser is directed perpendicular to the skin, approximately 5% of the laser is reflected. Reflection of laser is one of the reasons why it is imperative to wear appropriate safety goggles at all times when performing laser treatments.

Scatter is the increase in spatial distribution of a laser beam as it passes farther through tissue, leading to irradiation over a larger area of tissue. The main scattering wavelengths are between 400 and 1200 nm (those where tissue water absorption is poor).

Absorption can be described as the conversion of the energy of the laser to heat when its photons strike a specific molecular target, known as a *chromophore*. The mechanism by which lasers are used to target specific tissue is called *selective photothermolysis* (photo = light and thermolysis = decomposition by heat).

Transmission occurs when a laser that has not been absorbed is transmitted into deeper tissue beyond the chromophore.

Multiple variables must be considered when selecting a type of therapeutic laser, in addition to the appropriate wavelength. The additional laser parameters that optimize the result are *fluence*, or power density (joules/cm^2); pulse width or duration; mode of delivery; and spot size (increasing spot size increases penetration).

The theory of selective photothermolysis first described by Anderson and Parrish explains the principles behind the clinical application of photothermal lasers.[2] The wavelength of laser light chosen must be selective and appropriate for the target tissue, which must be destroyed without damaging the surrounding tissues. The pulse width or duration of the laser pulse must be within the thermal relaxation time of the treated tissues. Thermal relaxation time is the amount of time it takes to transfer two-thirds of the resultant heat to the surrounding tissues.

The laser's effect on the epidermis can further be classified as ablative or nonablative depending on whether or not the epidermis is left intact. Fractional lasers treat only a portion (or fraction) of the tissue. Nonablative lasers will thermally injure the tissue, whereas ablative lasers will destroy entire columns of tissue, including epidermis.

Overview of Lasers in Hypertrophic Burn Scar

The ultimate goal in the treatment of hypertrophic scars is to make improvements both aesthetically and functionally, as well as reduce itching and pain related to the scars. Traditional and emerging laser- and light-based technologies offer new hope for patients with burn scars.

GENERAL CONSIDERATIONS

An important tool in the evaluation of the patient for a resurfacing procedure is Fitzpatrick's scale of sun-reactive skin types, and this should be assessed prior to laser treatment.

The type of anesthesia employed prior to laser therapy depends on several factors, including the mode of laser treatment (e.g., ablative lasers are more painful than nonablative lasers), size of the scar, and the age of the patient. Children may require general anesthesia, whereas adults can be treated with topical anesthesia. This is more often required when treating areas of hyperpigmentation. Pain response can be assessed during a test patch procedure. If necessary, Eutectic mixture of local anesthetic (EMLA; lidocaine 2.5%/prilocaine 2.5%; AstraZeneca AB, Södertälje, Sweden) cream can be applied to reduce the stimulation of the procedure and reduce postoperative pain. The use of topical anesthetic as part of multimodal analgesia for fractionated laser treatment of burn scars significantly decreases the requirement for opioid analgesia and reduces procedure to discharge times.[6] Similarly an opioid sparing regime in children has been shown to have the potential to provide adequate post-operative pain following laser treatment under general anaesthesia.[7]

Patients undergoing ablative fractional laser treatment routinely receive perioperative antibiotic prophylaxis, which is typically not indicated for patients undergoing nonablative laser treatments. Patients undergoing fractional ablative laser are routinely washed with chlorhexidine and thoroughly dried prior to initiation of laser treatment. All patients receiving fractional ablative laser to the face are given acyclovir for herpes simplex prophylaxis.

Ice packs are used on the skin immediately following treatment. Wound care after laser treatment is initiated on the first postoperative day and includes a topical antiseptic wash and application of a generous amount of emollient for several days. Wound care for IPL consists of aloe vera cream applied every 15 min for a couple of days or until the stimulating effect has receded. Hydrocortisone 1% cream is also provided to those patients undergoing fractional laser treatment to help with itching. Analgesia is usually achieved with over-the-counter pain medications; however, some patients may require a short course of narcotic medication. Patients may resume normal activity almost immediately, including physical or occupational therapy. Depending on the discomfort level and the desired type of activity, patients may return to school or work after 1–3 days. Compression garments may be worn once wounds reepithelialize. Sun avoidance and use of broad-spectrum sunscreens with a sun protection factor (SPF) of at least 30 are mandatory for 12 months postoperatively to reduce the likelihood of postinflammatory hyperpigmentation.

PULSED DYE LASER THERAPY

The PDL is the most studied laser for hypertrophic scarring.[8] Over the past decade, the PDL has been shown in multiple studies to provide significant and long-term improvement in hypertrophic scars.[9] However, further studies have yielded conflicting data, with some more recent investigations finding no difference in PDL-irradiated hypertrophic scars over untreated controls.[10,11] Developed several decades ago, the vascular-specific, flashlamp-pumped 585- and 595-nm PDLs became the standard of care in the treatment of port wine stains, capillary malformations, and some hemangiomas.[9] This laser selectively targets hemoglobin and coagulates microvasculature in the papillary and reticular dermis up to a depth of 1.2 mm. Although the mechanism of action for scar improvements is unknown, most theories are based on the principle that vascular proliferation plays a key role in hypertrophic scars. The PDL

causes photothermolysis, in which light energy is absorbed by hemoglobin leading to coagulation necrosis.[9] Beneficial effects of PDL on burn scar pruritus have also been observed. This may be secondary to either decreased mast cell count following PDL treatment or decreased amounts of substance P and calcitonin gene-related peptide (CGRP), which mediate the vascular response of the skin.[11] The settings for PDL in the treatment of hypertrophic burn scar are found in Table 60.1.

ABLATIVE/NONABLATIVE FRACTIONAL LASERS

Fractional resurfacing leads to controlled destruction of tissue columns, also known as microscopic treatment zones (MTZs), without significant collateral damage. Similar to a z-plasty, the laser breaks up the thick, disorganized collagen fibrils that created the scar, allowing these regions to repair in a more organized fashion. However, a significant amount of epidermis and dermis remains intact, which assists in wound healing.

Fractional laser injury has also been shown to induce a molecular cascade including heat shock proteins and matrix metalloproteinases as well as inflammatory processes that lead to a rapid healing response and prolonged neocollagenesis.

ERBIUM-YAG LASER

In a prospective, single-arm, pilot study, treatment with a nonablative fractional erbium laser resulted in at least mild improvement in scar appearance in 90% of subjects and moderate to excellent improvement in 60% of subjects.[13] However, this study did not separate out patients who had hypertrophic burn scars versus scars from other etiologies. Two additional studies also investigated 1540-nm nonablative fractional erbium laser in mature burn scars and found a similar lack of improvement in thick scars.[14,15] Based on findings in these studies, it is likely that hypertrophic burn scars benefit from even deeper penetrating laser energy. There is a significantly greater potential depth of thermal injury with ablative fractional laser when compared with nonablative fractional laser devices (approximately 4.0 and 1.8 mm, respectively).[16] Ablative erbium:YAG laser emits infrared light with a wavelength of 2940 nm. The major innovation of the erbium:YAG laser over the CO_2 laser is its shorter wavelength, which increases its absorption coefficient through water 10- to 16-fold. Also, there is less thermal necrosis at the treatment site. One study cited improvement in hypertrophic burn scars in 24 patients on face, neck, or low neckline, and eight on the hands.[14] The settings for ablative erbium:YAG lasers in the treatment of hypertrophic burn scar are found in Table 60.1.

CO_2 LASER

The CO_2 laser has a wavelength of 10,600 nm and is used to target water in abnormal collagen several millimeters below the surface of the skin. The absorption of CO_2 laser by tissue water is significantly less than that of erbium:YAG leading to a relatively greater potential for surrounding tissue ablation. However, the increased ablation appears to induce a modest immediate photomechanical release of tension in some restrictive scars and appears to facilitate the subsequent remodeling response more effectively. In fractional ablative CO_2 laser-treated skin specimens, a collagen subtype (types I and III collagen) profile resembling that of nonwounded skin was found.[18] Also, pinpoint bleeding after ablative fractional laser is much less problematic with the fractional ablative CO_2 laser because of the increased zone of coagulation when compared to the erbium:YAG laser. The fractional ablative CO_2 laser has been shown to be highly effective in the treatment of hypertrophic scars,[12,18-28] including cosmetic and functional enhancement of traumatic scars and contractures, with treatment ranging between one and six sessions. Improvement of tactile sensation after treatment of burn scars of the palm has also been reported. Patients who underwent fractional ablative CO_2 laser procedures for treatment of symptomatic burn scars also had a 49% decrease in pruritus after laser treatment.[19] Our institution (UTMB, Galveston) recently performed a review[29] of the patient cohort who underwent treatment with fractional ablative CO_2 laser therapy for postburn hypertrophic scarring. A total of 452 fractional ablative CO_2 laser treatments were performed in 245 pediatric patients (126 females and 119 males) in 3 years. Fractional ablative CO_2 laser was used 256 times on the face, 103 on the neck, 164 on the torso, 164 on the upper limbs, and 74 on the lower limbs. Treatment providers have seen a reduction in scar thickness and improvement in scar pigmentation, as well as improvement in burn scar itch in patients treated with fractional CO_2 laser.

In 2012, Lumenis introduced a modification to the high-energy CO_2 laser (UltraPulse Encore; Lumenis, Santa Clara, CA) by adding a module for the treatment of scars—Synergistic Coagulation and Ablation for Advanced Resurfacing (SCAAR FX). The device generates hundreds of very deep microchannels that penetrate up to 4 mm. Usually after the first procedure patients feel a reduction of tension and softening of the scar. This is now the mainstay of the CO_2 laser treatment at our institution for thick hypertrophic scars (for more details on laser settings refer to Table 60.1).

LASERS TO TARGET PIGMENT

There are several lasers available that target pigment including the Ruby laser which is near infra-red (wavelength 694 nm) and targets pigment. A long pulse is used for hair removal (by destroying hair follicle stem cells) and ultra short (nano-second) pulse for interfollicular and follicular melanocyte destruction. Combination lasers include the TriVantage and GentleMAX (Candela Laser Corporation, USA), which both combine an alexandrite laser (755 nm) and Ng:YAG capabilities (1064 nm. This creates a broad spectrum of different wavelengths to enable targeting of different pigments and depths of melanocytes. They are thus useful for the removal of pigmentation and pigmented hairs to treat burn scar folliculitis.

INTENSE PULSED LIGHT

Although not technically a laser, IPL delivers focused, controlled light energy through a coupling gel across the 515–1200 nm (visible to near infrared) spectrum and at a fluence of up to 40 J/cm^2. IPL sources are filtered xenon

Table 60.1 Common Laser/IPL Settings

PULSE DYE LASER		
Wavelength		585–595 nm
Handpiece (spot size)		7-mm or 10-mm spot
Pulse duration		1.5 ms
Cryogenic cooling settings		30-ms spray and 20-ms delay
Fluence (7 mm)		6.0–11.0 J/cm^2
Fluence (10 mm)		4.0–5.0 J/cm^2
Overlap		Yes
Endpoint		Purpuric skin change
ERBIUM:YAG LASER		
Wavelength		2940 nm
Spot size		3–6 mm
Frequency		4–8 Hz
Fluence		11–12 J/cm^2
Overlap		No
Endpoint		Pinpoint bleeding
CO_2 LASER		
Wavelength		10,600 nm
DeepFX Handpiece	**SCAARFX**	**DeepFX**
Indication	Severely thickened hypertrophic scar	Intermediate-thickness hypertrophic scar or atrophic scar
Energy	70–100 mJ	15–20 mJ
Frequency	250 Hz	600 Hz
Pattern	2	2
Size	10	10
Density	1%–3%	10%
Overlap	No	No
Endpoint	Pinpoint bleeding	Pinpoint bleeding
Ultrascan CPG	**ActiveFX Central**	**ActiveFX Peripheral**
Indication	All central scar	All peripheral scar (feathering)
Energy	60–100 mJ	50 mJ
Frequency	125 Hz	125 Hz
Pattern	3	3
Size	7	5
Density	3%	3%
Overlap	Yes	Yes
Endpoint	Full coverage of scar	Full coverage of peripheral scar
INTENSE PULSED LIGHT		
Wavelength Filter		590 nm
Pulse Duration		5 ms
Delay		20 ms
Fluence		15–17 J/cm^2
Guide		Large rectangular light guide

flashlamps that release pulses of noncoherent polychromatic light. The mechanism of IPL is not fully understood, but it probably targets the vascular proliferation essential to collagen overgrowth and its effect on pigmentation (both melanin and artificial pigments) that results in scar development (hyperpigmented, erythematous, and proliferative scars).[10] Specific filters in the handpiece allow the user to select a window of wavelengths, such as 755 nm for collagen stimulation, 695 nm to remove superficial leg veins, and 515 nm to treat rosacea.[12] Multiple studies have shown IPL to be helpful in the management of burn scar dyschromia, long-standing hypervascularity, and chronic folliculitis without the risks or downtime of PDL photothermolysis or laser resurfacing.[10,12] The settings that we use for IPL in the treatment of hypertrophic burn scars are found in Table 60.1.

Treatment of Specific Post Burn Scar Conditions

FOUR-YEAR REVIEW

A recent review (2011–2014) in our unit (St Anderws, Chelmsford) demonstrated a wide use of different lasers for the treatment of various post burn scar conditions.[30] We carried out 194 procedures on 40 patients with an age range of 3–73 years. The fractionated CO_2 laser was used for 66 (34%) procedures alone and 112 in total, combined with other lasers in the same sitting. Indications included hypertrophic scar, contracture bands, unstable or thick, cracked scars. The PDL was used for 19 (10%) procedures, 137 in total. The main indications were red, itchy symptomatic scars. It was also used to soften scars prior to injection with dermal steroids. The Ruby laser was used for 30 (15%) of procedures alone and 51 procedures in total, with indications being hyperpigmentation and folliculitis. In 2014 this was replaced by the TriVantage and Gentlemax. These were used for 4 procedures alone and 27 in total. Indications were hyperpigmentation (TriVantage short pulse) and folliculitis (GentleMAX long pulse).

VASCULAR AND HYPERTROPHIC SCARS

Red scars with visible telangiectasia which blanch on touch are common in the months and years following healing of a burn. These are often lumpy and thick, or cracked and shiny, unstable or non-healing. The patient often complains of pruritus and pain. We have found that these scars respond well to PDL to reduce the erythema, followed by CO_2 to flatten the scar and enable stable healing Intradermal steroids may also be applied.

Folliculitis

Commonly, hair becomes trapped under scars or grafts causing irritation and repeated localized infections, This can be particularly problematic in the beard area of men. Fig. 60.1 illustrates this 25 months following a burn. We use the PDL to soften the scar in order to access the hair and decrease erythema. Following this a laser targeted at pigment (in this case Alexandrite laser) is used to remove the hair. As tight, thickened scar is usually also present, we would use the CO_2 laser in addition to address areas of tightness.

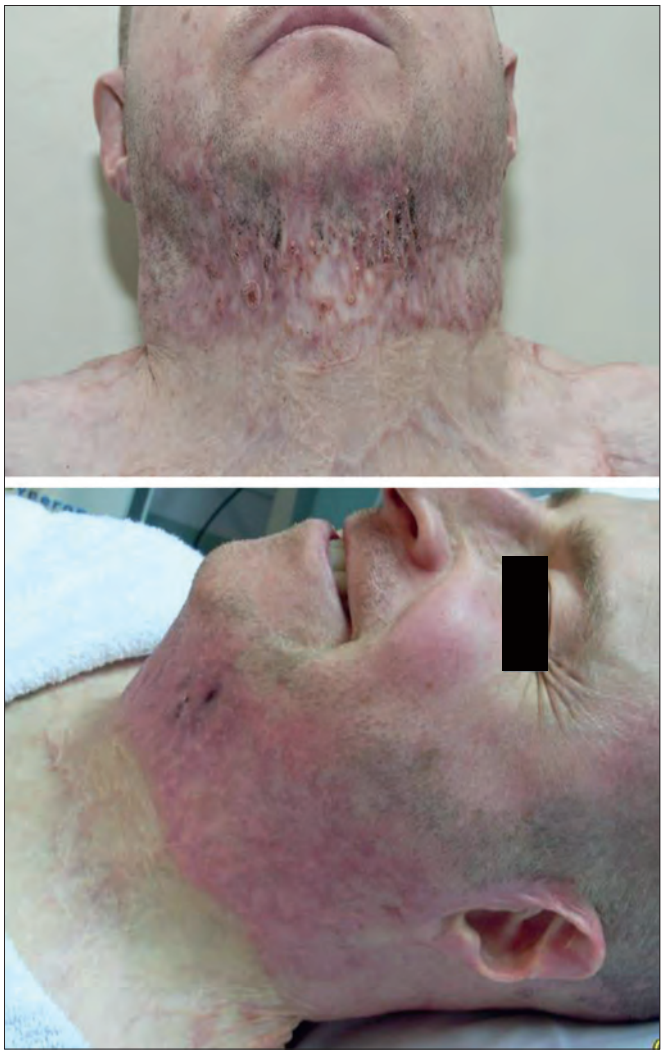

Fig. 60.1 Before (above) and after (below) photographs of a man with hypertrophic scars and follocilitis to the beard area, 25 months following burn injury, who was treated with PDL, Alexandrite and CO_2 lasers.

SCAR CONTRACTURE

Wide contracture bands and thick sheets of scar contracture can be well addressed with fractionated CO_2 laser, with the addition of steroid injections. This allows the relaxation of tissues, enabling release of skin around the neck and in the webspaces of the hand.

HYPERPIGMENTATION

Patients with darker skin types may develop areas of hyperpigmentation following burns or on donor sites. This is very unpredictable. Lasers to target pigmentation such as the Alexandrite or ND:YAG laser can be used to address these areas. Patients must be comprehensively consented, as the laser will cause hypopigmentation which may be equally distressing.

Laser Complications and Laser Safety

LASER COMPLICATIONS

Although infrequent, complications do occur. Common complications of PDL therapy include transient purpura and mild to moderate erythema or edema that usually resolves in 7–10 days. However, in some cases, a mild erythema can persist up to 3 months posttreatment. Occasionally skin blistering or crusting may occur in the early posttreatment phase. Hypo- or hyperpigmentation may also occur, especially in patients with darker skin types. Overtreatment of burn scars may induce scarring exacerbation, especially in skin with darker pigmentation, in which melanin acts as a competing chromophore. Intraprocedural cryogenic cooling of the skin may limit these adverse reactions.[31]

Fractional ablative lasers have an improved adverse effect profile compared with nonfractional ablative devices. However, delayed wound healing, ulceration, postinflammatory hyperpigmentation (PIH), and scarring, particularly in areas of thinner skin and in decreased adnexal structures such as the neck, have also been reported with fractional lasers. Postoperative topical application of ascorbic acid has been shown to decrease the duration as well as the severity of erythema. Because PIH can be a major problem for those undergoing fractional laser therapy, some units attempt to reduce pigmentation within the target zone prior to application of laser therapy using hydroquinone. If a patient is likely to elicit PIH, then a treatment we have found to be successful is Azelaic acid gel (15%); this has a tyrosine kinase inhibitory action that reduces the recurrence of PIH. (I emphasize that it is not a treatment for PIH but a preventative measure.) Those wishing to treat PIH with topical therapy often use a combination of steroid, hydroquinone, and tretinoin. Patients with a history of herpes who undergo laser treatment around the face may experience an outbreak if not pretreated as discussed earlier in the chapter.

LASER SAFETY

When performed by properly trained medical personnel, laser therapy has low risks for harmful outcomes and can be executed safely. National safety requirements are based on the American National Standards Institute (ANSI) Z136.3, Guide to the Safe Use of Lasers in Healthcare. This document is a benchmark standard for safe practice in the United States. Although not regulatory and without legal enforcement, this document is evidence-based and is considered best practice; as such, it is the foundation for state laws, Occupational Safety and Health Administration (OSHA) guidance, the Joint Commission (TJC) surveys, and professional recommended practices.[32] Proper handling and installation of lasers in hospitals and private practices is overseen by OSHA, which uses a set of standard guidelines issued by the American National Standard Institute. However, institutional guidelines and state regulations differ. These regulations determine the licensing requirements for who can operate a laser under the supervision of a physician.

The greatest risk when operating a laser is that of eye injury to either the medical personnel or the patient. Medical personnel operating lasers should be fully trained and should cover their skin and wear correct protective eyewear (different forms of eyewear filter different wavelengths; therefore it is important that appropriate eyewear is worn for each specific laser). The protective specifications (wavelengths and optical densities) are usually printed on the goggles, generally near the top of the unit. Protective eyewear should also be placed on the door(s) outside the laser operating room in case emergency entrance is required.

To help prevent eye injury, laser procedures should be restricted to dedicated rooms that are clearly labeled and only allow the necessary personnel. Those rooms should limit the amount of reflecting surfaces (e.g., mirrors, computer screens, windows) to avoid scattering laser beams inside and outside of the room.[33]

If the procedure is being performed on the head and neck, metal scleral eye shields that fit the patient's cornea are filled with an ocular lubricant and placed directly on the corneal surface. However, if the procedure is being done below the neck, burnished stainless steel eye cups are fitted over the eyelids and secured so that the entire periorbital area is covered.

Appropriate signage on the laser operating room door(s) is a requirement. The sign should describe the nature of the laser being used, its wavelength, and energy. Signs should only be posted when the laser is in actual use and removed or covered when the laser is turned off and the key removed.[32] All operating room windows should be closed and covered. Lasers that have foot pedals are helpful in allowing expeditious use of the laser. However, accidental activation of the foot pedal is one of the most commonly reported accidents.[32] Any repositioning of the foot pedal should take place when the laser is deactivated, and only the operator of the laser should use the foot pedal. The control panel of the laser should never be left activated and unattended. When not in use, the laser should be turned off and the key removed. The footswitch for activating the laser must be given only to the credentialed laser user.

Operating room fires and airway fires are both possible when using a laser. Production of a flame requires that the triad of heat source (laser), fuel source (patient's tissue), and an oxidizer (supplemental oxygen) be present. The risk of operating room or airway fire is rare, but most commonly occurs in patients undergoing laser treatment near the face. The risk is significant when patients who are under conscious sedation require supplemental oxygen via standard nasal cannula. Eliminating supplemental oxygen altogether is the safest way to prevent operating room or airway fire. However, the risk of fire is significantly reduced when supplemental oxygen is delivered directly to the posterior pharynx using the nasopharyngeal tube or when the patient is intubated.[32,34,35] Moist towels should cover areas around the treatment zone to avoid thermal radiation and damage to adjacent tissue. A moist towel can be safely wrapped around the endotracheal tube if present. Additionally moist gauzes should also be placed into the patient's nares and mouth when operating lasers in close proximity.

It is best to keep a fire extinguisher either inside or positioned just outside the room, so it is quickly available for

someone either inside or outside the room. All staff should be notified of its location and operation.

Along with ocular hazards and fire hazards, the laser smoke plume is a significant occupational hazard. Research has proved that thermal disruption of viable human cells, regardless of the instrument used, results in the release of mutagenic and carcinogenic materials, including carbon particles, viruses, bacteria, DNA, aerosolized blood, bloodborne pathogens, and more than 41 known hazardous gases such as benzene, formaldehyde, toluene, and acrolein.[32] Masks are not meant to be the first line of protective devices against plume exposure in the breathing zone. There are no masks on the market today, including N95 masks, that are capable of filtering out all airborne contaminants.[32] Laser masks can be used instead of standard surgical masks, but one should note that the filtration medium stops working when the mask becomes damp from breathing, thus defeating its purpose.[28] Instead the most effective way to prevent this occupational hazard is to utilize a high-efficiency ultra-low-particulate air filter. It should be rated to 99.999% efficiency and placed within 1–2 cm of the laser smoke plume source to be effective.

Logistical and Financial Considerations

Starting a laser practice dedicated to the treatment of burn patients with hypertrophic scar formation can be quite daunting.[12] The ability to collect revenue from these procedures is absolutely essential for the sustainability of the practice.[36] Third-party insurance carriers specify that hypertrophic burn scars that cause significant pain or result in a significant physical functional impairment are candidates for laser.[36] Critical to the success in obtaining preauthorization from insurance companies is a thorough history and physical, clinical photography, and the use of accurate, specific, and complete CPT and ICD-10 codes. Because specific CPT codes for the laser treatment of burn scars do not exist, Hultman et al. recommend using 17106, 17107, and 17108 (laser destruction of cutaneous vascular proliferative lesion, $<10\ cm^2$, 10–50 cm^2, and $>50\ cm^2$, respectively). The rationale for using these codes is that burn scars are hypervascular, hypertrophic, and hyperpigmented, all of which are due to a proliferative, neovascular, and hyperplastic response of the injured tissues. While not hemangiomas or vascular malformations, burn scars act like these lesions due to similar pathophysiologic mechanisms, resulting in similar endpoints.[12] Also important for documentation is using the correct ICD-10 diagnosis terminology to signify that these scars are from burns and corrosions of external body surfaces. Use T20 for head, face, and neck; T21 for trunk; T22 for shoulder and upper limb, except wrist and hand; T23 for wrist and hand; T24 for lower limb, except ankle and foot; and T25 for ankle and foot. Also utilize ICD-10 codes L91.0 to describe keloid or hypertrophic scars and L90.5 to describe scar conditions and fibrosis of skin.

Acquiring the laser platforms may be done through rental, lease, or purchase, but the capital requirement can be considerable.[12] Because laser technologies can become obsolete quickly, and because warranties can be quite expensive, at least in the beginning of the venture, leasing is one way to start a practice offering laser treatments.[36]

The clinician must also have access to an accredited surgical facility that includes all of the safety features of an operating room or surgical suite. Most patients require a large area of treatment that generally exceeds the area that could be covered by local anesthesia. These patients require treatment in an operating room with either monitored anesthesia or general anesthesia with supervision by an anesthesiologist.

One element that is particularly attractive to all stakeholders, patients, providers, and third-party payers is that laser therapy for hypertrophic burn scars has the potential to dramatically reduce the cost of care.[12] It is possible that laser treatments might preclude the need for invasive surgery in some patients with mild to moderate contractures and permit less aggressive and less costly procedures in patients with moderate to severe contractures.[36] From experience at our institution, patients expressed preference for the less-invasive laser treatment compared to a more invasive surgical scar release.[29] Laser treatments can decrease pharmacologic requirements for such medications as narcotics, antihistamines, anxiolytics, and antidepressants leading to decreased healthcare costs.[12] Also, patients who have had successful treatment of their hypertrophic burn scar may return to work or school sooner and require less clinic follow-up.

Future Investigations

Although the effect of lasers on hypertrophic burn scars has only been studied in the past few years, this work is very promising and therefore just beginning. High-quality, prospective, blinded, randomized, controlled trials are necessary to assess which lasers or light-based therapies are best for hypertrophic burn scar modulation, pruritus, and dysesthesias. Within each type of therapy, standardization of several different laser parameters, such as fluence, pulse time, density, and timing of surgery, will be developed. Any additional benefit from adding topical medications to the treatment area also needs to be standardized. Studies assessing economic benefits will allow for other institutions to adopt lasers for the treatment of hypertrophic scarring.

Conclusion

Lasers and light-based therapies are safe and effective treatment options for hypertrophic burn scars, and they are now becoming the standard of care for all burn patients. Although not a panacea for all scars, they are a worthy addition to the armamentarium of all burn reconstruction surgeons.

Although laser treatments are clearly effective, they have not yet been optimized. Prospective, randomized clinical studies are necessary to provide evidence-based and quality care for patients with hypertrophic burn scars.

Complete references available online at
www.expertconsult.inkling.com

References

1. Goldberg DJ. *Laser Dermatology*. 2nd ed. Berlin Heidelberg: Springer; 2013:142.
2. Anderson RR, Parrish JA. Selective photothermolysis: precise microsurgery by selective absorption of pulsed radiation. *Science*. 1983;220(4596):524-527.
3. Guyuron B, Eriksson E, Persing JA, et al. *Plastic Surgery Indications and Practice*. 1st ed. New York: Elsevier; 2009.
4. Neligan PC. *Plastic Surgery*. 3rd ed. New York: Elsevier Saunders; 2013.
5. Babilas P, Schreml S, Szeimies RM, Landthaler M. Intense pulsed light (IPL): a review. *Lasers Surg Med*. 2010;42(2):93-104.
6. Edkins RE, Hultman CS, Collins P, et al. Improving comfort and throughput for patients undergoing fractionated laser ablation of symptomatic burn scars. *Ann Plast Surg*. 2015;74(3):293-299.
7. Wong BM, Keilman J, Zuccaro J, et al. Anaesthetic practices for Laser rehabilitation of paediatric hypertrophic burn scars. *J Burn Care Res*. 2017;38(1):e36-e41.
8. Brewin MP, Lister TS. Prevention or treatment of hypertrophic burn scarring: A review of when and how to treat with the Pulsed Dye Laser. *Burns*. 2014;40(5):797-804.
9. Parrett BM, Donelan MB. Pulsed dye laser in burn scars: current concepts and future directions. *Burns*. 2010;36(4):443-449.
10. Erol OO, Gurlek A, Agaoglu G, Topcuoglu E, Oz H. Treatment of hypertrophic scars and keloids using intense pulsed light (IPL). *Aesthetic Plast Surg*. 2008;32(6):902-909.
11. Allison KP, Kiernan MN, Waters RA, Clement RM. Pulsed dye laser treatment of burn scars. Alleviation or irritation? *Burns*. 2003;29(3):207-213.
12. Hultman CS, Edkins RE, Lee CN, Calvert CT, Cairns BA. Shine on: review of laser- and light-based therapies for the treatment of burn scars. *Dermatol Res Pract*. 2012;2012:243651.
13. Waibel J, Wulkan AJ, Lupo M, Beer K, Anderson RR. Treatment of burn scars with the 1,550 nm nonablative fractional erbium laser. *Lasers Surg Med*. 2012;44(6):441-446.
14. Taudorf EH, Danielsen PL, Paulsen IF, et al. Non-ablative fractional laser provides long-term improvement of mature burn scars: a randomized controlled trial with histological assessment. *Lasers Surg Med*. 2015;47(2):141-147.
15. Haedersdal M, Moreau KE, Beyer DM, Nymann P, Alsbjorn B. Fractional nonablative 1540 nm laser resurfacing for thermal burn scars: a randomized controlled trial. *Lasers Surg Med*. 2009;41(3):189-195.
16. Anderson RR, Donelan MB, Hivnor C, et al. Laser treatment of traumatic scars with an emphasis on ablative fractional laser resurfacing: consensus report. *JAMA Dermatol*. 2014;150(2):187-193.
17. Eberlein A, Schepler H, Spilker G, Altmeyer P, Hartmann B. Erbium:YAG laser treatment of post-burn scars: potentials and limitations. *Burns*. 2005;31(1):15-24.
18. El-Zawahry BM, Sobhi RM, Bassiouny DA, Tabak SA. Ablative CO_2 fractional resurfacing in treatment of thermal burn scars: an open-label controlled clinical and histopathological study. *J Cosmet Dermatol*. 2015;14(4):324-331.
19. Issler-Fisher AC, Fisher OM, Smialkowski AO, et al. Ablative fractional CO2 laser for burn scar reconstruction: an extensive subjective and objective short-term outcome analysis of a prospective treatment cohort. *Burns*. 2017;43(3):573-582.
20. Waibel J, Beer K. Ablative fractional laser resurfacing for the treatment of a third-degree burn. *J Drugs Dermatol*. 2009;8(3):294-297.
21. Hultman CS, Edkins RE, Wu C, Calvert CT, Cairns BA. Prospective, before-after cohort study to assess the efficacy of laser therapy on hypertrophic burn scars. *Ann Plast Surg*. 2013;70(5):521-526.
22. Hultman CS, Friedstat JS, Edkins RE, Cairns BA, Meyer AA. Laser resurfacing and remodeling of hypertrophic burn scars: the results of a large, prospective, before-after cohort study, with long-term follow-up. *Ann Surg*. 2014;260(3):519-529, discussion 529-532.
23. Lee SJ, Suh DH, Lee JM, Song KY, Ryu HJ. Dermal remodeling of burn scar by fractional CO_2 laser. *Aesthetic Plast Surg*. 2016;40(5):761-768.
24. Zadkowski T, Nachulewicz P, Mazgaj M, et al. A new CO_2 laser technique for the treatment of pediatric hypertrophic burn scars: an observational study. *Medicine (Baltimore)*. 2016;95(42):e5168.
25. Levi B, Ibrahim A, Mathews K, et al. The use of CO_2 fractional photothermolysis for the treatment of burn scars. *J Burn Care Res*. 2016;37(2):106-114.
26. Blome-Eberwein S, Gogal C, Weiss MJ, Boorse D, Pagella P. Prospective evaluation of fractional CO_2 laser treatment of mature burn scars. *J Burn Care Res*. 2016;37(6):379-387.
27. Azzam OA, Bassiouny DA, El-Hawary MS, et al. Treatment of hypertrophic scars and keloids by fractional carbon dioxide laser: a clinical, histological, and immunohistochemical study. *Lasers Med Sci*. 2016;31(1):9-18.
28. Ozog DM, Liu A, Chaffins ML, et al. Evaluation of clinical results, histological architecture, and collagen expression following treatment of mature burn scars with a fractional carbon dioxide laser. *JAMA Dermatol*. 2013;149(1):50-57.
29. Forbes AAWP, Branski LK, Finnerty CC, Herndon DH, Norbury WB. *Ablative CO_2 laser treatment of hypertrophic scars for severely burned children*. Austin: Texas Society of Plastic Surgery. 2015.
30. Bache SE, Chilton L, Mack T, Philp B. Using laser therapy to modify burn scars: a four year review. Presented at British Burns Association 48th Annual Meeting, Birmingham, UK, 2015.
31. Clayton JL, Edkins R, Cairns BA, Hultman CS. Incidence and management of adverse events after the use of laser therapies for the treatment of hypertrophic burn scars. *Ann Plast Surg*. 2013;70(5):500-505.
32. Goldman MP, Ross EV, Kilmer SL, Weiss RA. Lasers and energy devices for the skin; Boca Raton (FL): CRC Press; 2013.
33. Franck P, Henderson PW, Rothaus KO. Basics of lasers: history, physics, and clinical applications. *Clin Plast Surg*. 2016;43(3):505-513.
34. Engel SJ, Patel NK, Morrison CM, et al. Operating room fires: part II. optimizing safety. *Plast Reconstr Surg*. 2012;130(3):681-689.
35. Wald D, Michelow BJ, Guyuron B, Gibb AA. Fire hazards and CO_2 laser resurfacing. *Plast Reconstr Surg*. 1998;101(1):185-188.
36. Hultman CS, Edkins RE, Cairns BA, Meyer AA. Logistics of building a laser practice for the treatment of hypertrophic burn scars. *Ann Plast Surg*. 2013;70(5):581-586.

61 The Ethical Dimension of Burn Care

ARTHUR P. SANFORD and MICHELE A. CARTER

Introduction

Burns are a leading cause of accidental injury and death in the United States and worldwide, and they can often raise profound concerns about autonomy, mortality, quality of life, and suffering. In seeking optimum health for each patient, contemporary burn care aspires to integrate the highest standards of evidence-based medicine with excellence in patient care delivery and clinical research. Optimal care of patients with burns is a virtuous practice involving highly integrated, team-oriented, interdisciplinary,[1] and humanistic encounters. It includes adherence to certain norms of professional conduct as well as a process of reflection on how to incorporate those norms in individual patient care or research settings. It involves increasingly complex layers of technological and professional sophistication, clinical judgment, and expertise and sensitive attention to the ethical values at the core of medicine. Clinical situations can be complex, not simply because of the wide range of medical facts and situational factors that constitute burn care, but because of the diversity of human needs that lay coiled beneath the surface of illness or trauma. Given that patients with burns are among the most vulnerable of patients and have needs that expand the full range of the human condition, all members of the healthcare team are called upon to offer care that is tender, skillful, comprehensive, and ethically conscientious. The core ethical ingredient of these encounters is the doctor–patient relationship and the underlying expectations of trust that patients and their families bring to the clinical setting.[2]

Caring for the burned patient encompasses a long-standing commitment to the safety, healing, rehabilitation, and growth of patients. As such it is thoroughly infused with ethical values and goals. As conceived in ancient Athens and during most of its history, Western ethics involves the quest for achieving the good life, living it excellently, and setting forth ideals of human flourishing. In contemporary times, these ideals continue to inform the practice of medicine and contribute to the evolving field of clinical ethics. Clinical ethics is "the systematic identification, analysis, and resolution of ethical problems associated with the care of particular patients. Its goals include protecting the rights and interests of patients, assisting clinicians in ethical decision making, and encouraging cooperative relationships among patients and those close to patients, clinicians, and healthcare institutions."[3] Over the past several decades, the field of clinical ethics has become an essential part of hospital life and culture, reflecting the complexity and poignancy of the real-life ethical puzzles clinicians frequently encounter. It involves critical thinking about right and wrong and of what should or should not be done[4] in terms of our responsibilities to others. It also legitimates the importance of ethics teaching and ethics dialogue in all phases of professional practice, whether that is in the classroom, the board room, or on "ethics rounds at the bedside."[5] Clearly caring for burned patients invites moral reflection and imagination, and clinical ethicists increasingly are part of the integrated approach.

In general, most healthcare providers hold certain values in common and are thus not in doubt about what morality requires. That is, we hold firmly to the conviction that it is a good thing to preserve life, to cure disease, or to lessen someone's pain or suffering. For the most part, we are clear about what our ethical responsibilities are: to respect the values and dignity of human life, to tell the truth, to avoid harming patients, and to treat them and their families fairly and with compassion. Indeed ethical decision-making for some is therefore like breathing,[6] something we do without even thinking. At times however disagreements about what we ought to do or what we ought to value occur. That is, while we may be clear on the general principles of ethics, it is not always so clear how to apply them in a particular case. This uncertainty can give rise to ethical problems and dilemmas, some of which occur at the bedside of the patient and others that may involve questions of institutional policy, resource allocation, or even larger societal issues about how we ought to distribute goods and services.

What Is an Ethical Problem?

An ethical problem is present when it involves a conflict of two or more of the following: rights or rights-claims, obligations, goods, and/or values.[7] For example, disputes about writing a "comfort-measures-only" order for a patient without decision-making capacity and with a very low probability of survival commonly involve a conflict between an obligation and a good: the obligation not to abandon aggressive therapy prematurely and the good of a maximally pain-free and unprotracted death. In this case, the burn team and the patient/surrogate are ordinarily the major stakeholders and appropriate decision-makers, and they are addressing *a problem in clinical ethics*. On the other hand, consider the burn center's or healthcare organization's (HCO's) responsibility to ICU patients when a safe nurse-to-patient ratio cannot be consistently met despite the burn center's best efforts. If discerning what should be done in such circumstances requires decision-making at the managerial level of the burn center or HCO, *a problem in organizational ethics*[8] is the correct term to use.

As indicated, conflicts among rights, obligations, and the like are very common and vary greatly in difficulty. When should they be taken seriously? An ethical problem is serious when there are stakeholders involved who stand to be seriously affected by the problem or its outcome. Stakeholders working collaboratively without outside help can successfully manage the vast majority of such problems. When are such problems so serious that assistance should be sought from an ethics consultant or a healthcare ethics committee (HEC) or its equivalent? An ethical problem is serious enough to refer to an HEC:

a. When you suspect the Smell Test would be positive; that is, "What would the action or situation we are considering smell like if we read about it in a front page news article or in a popular blog? Would I be comfortable explaining it to my spouse, or my grandmother?" The problem with this, as the olfactory image reminds us, is that living with bad smells or unethical conduct for a long time may dull a person's ability to notice them.
b. When there is persistent disagreement among the major stakeholders and codes, rules, laws, and more discussions fail to lead to a resolution within generally acceptable ethical boundaries in a reasonable amount of time.

How Should Clinical Ethics Problems Be Managed?

In the United States, the informed consent process was developed by the American judiciary to safeguard the legal rights and welfare of all the stakeholders participating in bedside decision-making. Throughout the United States, this legal process has become the foundation of the healthcare provider's approach to avoiding and managing serious ethical problems at the bedside. Its application in the burn center was explained and diagrammed in detail in the first edition of this book,[9] and what follows should be considered an update and development of what is stated there.

On the vast majority of occasions, there is little or no difficulty achieving agreement and patient consent about a proposed course of burn management. There are many predictors of clinical outcomes that are without controversy.[10] Occasionally, however, the process of obtaining informed consent leads to problems involving disagreements, anxieties, and/or controversies about what should or should not be done. At this point, the participants must give careful attention to the quality of the discussion in attempting to resolve the problem, part of which requires respect for the patient's underlying values.

Increasingly, ethics consultants are seen as important stakeholders in optimizing the care of patients suffering from burns, especially when treatment decisions are ethically complex or psychologically difficult. Through facilitated dialogue, the rights, interests, and needs of the patient are brought to the center and deliberated upon, but the values and concerns of the team are honored as well. Additionally, ethics consultants facilitate the process of making and justifying moral judgments on the basis of certain ethical principles that transcend individual personal opinion or perspective. That is, a judgment that a certain act—say, withdrawing life-saving treatment for a dying patient—is to be performed or not is justified on the basis of some rule or standard applicable in all relevantly similar cases. In this way, ethical dialogue becomes more than simply ensuring that a patient has provided an informed consent for treatment. Instead ethical dialogue becomes the means by which we examine the full range of our ethical responsibilities to others, drawing on principles of trust, autonomy, dignity, beneficence, justice, and care (Fig. 61.1).

THE ROLE OF THE CARE-PROVIDER IN ETHICAL DIALOGUE

Approaching the resolution of ethical conflict through dialogue fosters in the burn team a sense of moral inquiry and agency and makes explicit the process of respecting the patient and family. At its best, ethical discourse begins by establishing an interpersonal "relationship" made safe for transparent and self-critical honesty and furthered by active listening and openness to learning about the relevant norms that constitute good care.[11]

To do this the care-provider should explore the bio-psycho-social-economic and cultural/religious information required to approach the patient and his family and/or surrogate with empathy for their lives and values. One of the strongest ways we show respect for the patient and family is to honor religious values, even when such values may differ from those of the healthcare team. For instance, Western religions often proclaim that there are certain limitations to earthly life and advocate adherents to look to a future beyond the present for ultimate value and meaning. By contrast, Eastern religions hold that our present lives are reflective of past deeds and future conditions, that life is oriented to the present. Many confer extreme respect on the spirit of departed ancestors and live their lives in service to their honor. Finally, some individuals do not have religious affiliations at all and may live for different goals or ideals. These belief perspectives illuminate diverse ways of deriving meaning in life and understanding those ends that make life worth living. At times, this diversity can render decision-making about treatment decisions more challenging and can give rise to ethical uncertainty or moral distress in members of the healthcare team. Many patients, based on personal values and beliefs, may decide against life-prolonging treatments in hopes of not burdening their family with large hospital bills. Other patients may demand care that is arguably futile, care that has no possibility of conferring any physiological benefit to the patient. For some practitioners, such reasoning patterns may appear to be fundamentally flawed and can spawn difficult emotional contests. In these situations, the ethical dialogue may expand beyond the doctor–patient relationship and involve policy-makers, legislators, practice plans, and regulators, all of whom are stakeholders in the system of trust that society relies upon. Given that patients with burns reflect the diversity of the American population and a plurality of values regarding life and death, care of the burned patient is complex and challenging. Consideration of patient values and preferences should occur early on in the plan of care so that proper respect for patient autonomy, culture, and religious perspectives can occur.

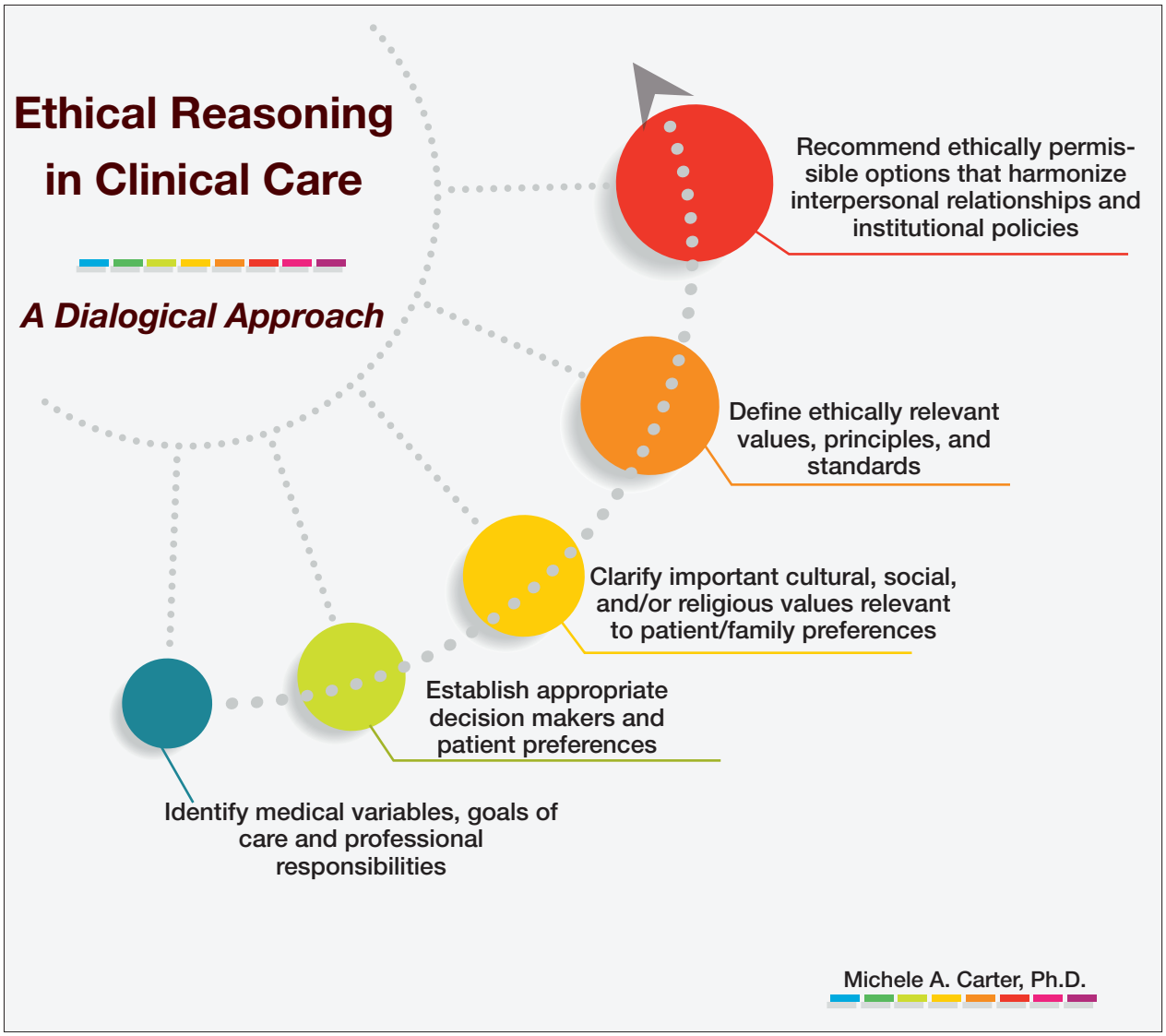

Fig. 61.1 Ethical Reasoning in Clinical Care—A dialogical approach.

The care-provider must assess the patient's capacity for decision-making. To have decision-making capacity, the patient should be able to understand proposed treatments and their relevant risks and benefits, comprehend the consequences of various actions and/or alternatives, and evaluate whether they accord with his or her personal values. Also patients should be able to meaningfully deliberate and express their preferences regarding recommended treatments; this standard is often difficult to meet in the emergency or intensive care setting and appropriate surrogate decision-makers should be identified early in the hospital course.[12] Decision-making capacity is enhanced by optimizing the patient's physiological stability, consciousness, and pain control as much as possible. It is typically verified by ascertaining orientation and by asking the patient to rephrase the information provided in his or her own words and to offer a reason or rationale for the decision. In general, the physician is authorized to determine whether or not a patient is capacitated sufficiently to make a health-related decision. Determination of decision-making capacity by judicial process (i.e., determination of legal competency) is rarely necessary. If despite all efforts the patient is found to lack decision-making capacity, an appropriate surrogate should be sought among the patient's family or friends, depending on local laws to determine priority.

The care-provider has a duty to provide accurate information pertaining to the patient's diagnosis, prognosis, and treatment plan so that the capacitated patient or appropriate surrogate can properly deliberate. This includes relevant information about plausible alternatives, including the option of forgoing proposed therapies. This duty is part of the ethical standard of care and is an ongoing responsibility throughout the hospital course. In providing optimal care for burned patients, allegiance to this ethical norm is an essential ingredient of the doctor–patient relationship and the foundation of trust.

THE ROLE OF THE PATIENT OR SURROGATE IN ETHICAL DIALOGUE

Patients and families bring to the clinical encounter previous experiences with loss and suffering, and these experiences influence decisions about their goals for care and recovery. The role of the patient is to assimilate information provided by caregivers into their own value system and to participate honestly and sincerely in conversations about their preferences and concerns. One cannot expect an acutely injured patient to fully understand medical information, and most often they will require assistance from the team before they are able to render a values-based decision. Behavioral therapists, nurses, social workers, and clergy are often needed to provide support and counsel, and they often help patients discover internal resources needed to meet or revise their life goals. In addition, critically burned patients are often unable to participate meaningfully in treatment decisions and must have their right of self-determination carried out by a surrogate decision-maker. By entering the patient's personal world and participating in the unfolding narrative of his or her experience, care-providers are better able to arrive at ethically sound decisions.[13] Patients and their surrogates thus are essential participants in the integrated approach to optimal burn care, and, without their involvement and solicited participation, the ethics dialogue is incomplete.

HOW SHOULD PERSISTENT ETHICAL CONFLICT BE MANAGED?

Even when participants make a sincere effort to establish consensus about treatment decisions, disagreements occasionally persist. To resolve them, a patient care conference is needed and ideally should include all major stakeholders. The goal of these conferences is to collaboratively arrive at ethically appropriate solutions that respect the values of the patient and accord with appropriate standards of care. Patient and family conferences are important components to managing conflict in patient care decision-making. These conferences usually involve representatives from multiple disciplines who are involved in the care of the patient and often are organized to help resolve ethical disagreements or dilemmas. In any serious ethical inquiry, three questions must be answered: What seems to be the problem? What can be done? What should be done? A seven-step decision-making model has been found helpful in answering these questions and is illustrated in Table 61.1.[14]

In Step 1 of this decision-making model patients and/or their surrogate are asked to speak first, and care-providers listen carefully and respectfully. This approach helps equalize power and create a safe place for shared understanding. Participants are asked to introduce themselves, explain the conflict as they see it, and indicate what they hope to achieve by the discussion. Thereafter, the care-providers do the same. This step typically takes the most time but is the most important of all the seven steps. It lets off steam, makes the patient/surrogate and allies feel listened to, and optimally leads them to ask for the corrective and supplementary information they need from the care-providers, which (in Step 2) they usually can provide or obtain. (Note the similarity of these early steps to those of the SPIKES protocol for delivering bad news, described by Buckman; see Foley[15].) If successfully carried out, Steps 1 and 2 transform a potential or actual power struggle into a collaborative search for the answers to the next and then the final question listed in Table 61.1.

Table 61.1 Three Questions to Be Addressed When a Clinical Ethics Problem Is Serious and Persistent and the Steps Appropriate for Answering Each Question

1.	What seems to be the problem?	Step 1.	Discover conflicting values of stakeholders
		Step 2.	Discover the relevant information
2.	What can be done?	Step 3.	Identify principles, laws, other values relevant to the decision
		Step 4.	Identify alternative courses of action
3.	What should be done?	Step 5.	Compare alternatives and values: is decision clear?
		Step 6.	If not, assess consequences
		Step 7.	Make decision, collaboratively, if possible

Modified from May WW. *Ethics in the accounting curriculum: cases and readings.* Sarasota, FL: American Accounting Association; 1990:1. With permission of the American Accounting Association and the author.

The conversation of Step 3 may address principles (like respect for persons, beneficence, etc.) but more typically cites relevant laws and rules of the community and/or institution, and/or other values (no unnecessary pain, what the patient would want if able to speak, etc.). Step 4 is usually best carried out using a white board or equivalent to brainstorm and record all the plausible alternative courses of action. In Step 5, the group collaboratively may find a principle, rule, value, or some combination thereof so compelling that the proper alternative is clear. For example, because it is considered unlawful homicide in most locations, large doses of a narcotic primarily intended to stop breathing rather than control pain may be found unacceptable. If the decision is still not clear, Steps 6 and 7 will usually lead to a mutually acceptable decision within boundaries that are acceptable institutionally, legally, and ethically. Rarely, consensus will elude the most sincere adherence to the seven-step process. If further discussion, efforts to transfer care of the patient, and the like fail, an appeal to the courts, or (in at least one state[16]) an appeal to relevant legislation for relief from responsibility for care of the patient, may be necessary.

The Patient Without Decision-Making Capacity, Surrogate, or Advance Directive

In such cases, care-providers typically have no way of knowing or deducing with confidence what the patient's wishes might be in a given set of circumstances. In general, the decision made must seek the best interest of the patient, but the process required may vary. In some jurisdictions, consultation with another physician, the healthcare institution's legal counsel, and/or HEC is mandatory. In others,

a court-appointed conservator might be required. In all such cases (1) the search for a surrogate should be diligent, (2) all relevant medical information must be obtained and reviewed, (3) real or apparent conflicts of interest must be disclosed, (4) the opinions of the healthcare team and of one or more physicians in addition to the responsible attending should be reviewed, (5) the burden versus benefit ratio must be weighed from the patient's point of view, and (6) steps should be taken to ensure the benefit of continued life to a disabled patient is not devalued or underestimated.[17] Some institutions also require that consideration of economic impact on healthcare providers and the healthcare institution be excluded from consideration in such cases. Eventually a surrogate decision-maker is identified, and, hopefully, this is a person who has previously known the patient and his or her values prior to the accident, who has possibly had discussions about extreme end-of-life issues and can speak on the patient's behalf. The surrogate decision-maker must not make the decision based on what he or she would want for the patient. However the surrogate decision-maker must know what that patient would prefer and act as an advocate in this situation since the patient is not able to participate in the decision. They should be expressing the patient's views, not projecting their own views onto the patient.

How Should Organizational Ethics Problems Be Managed?

Currently healthcare decision making affecting burn care occurs at three levels: in the clinic, in the organization, and in society.[8] The disciplines designed to improve ethical decision making at the first and third levels are called *clinical* and *societal ethics*, respectively. They discern facts and values for guiding clinical or societal decisions that affect patient care and have received wide attention in both the media and scholarly journals for years. Recently attention has been called to the need for discernment of facts and values for guiding managerial decisions that affect patient care.[8,18] For example, at times, problems present as difficulties in clinical decision making but have their root causes in areas that require decision making at the managerial level. With dwindling numbers of nurses entering training, increasingly fewer nurses will be available to provide intensive care, and managerial decisions will be required to produce or recruit more nurses and to judge just when it is no longer safe to admit new patients to beds without adequate staffing. Also, when rehabilitation services in a given geographical area have not kept up with the increasing numbers of patients with large burns who survive but require longer and more expert rehabilitation, managerial decisions about the distribution of scarce resources will have to be made if adequate rehabilitation care is to be available. Such decisions are ethical: they involve conflicts of rights, obligations, goods, and/or other values. They tend to be less dramatically immediate and more deferrable, but they usually affect more persons and require more resources and follow-up than clinical ethics decisions.[18] They sometimes appear to be made in the front office, apparently without satisfactory input from care-providers, patients, or other stakeholders and without the availability of extensive literature or assistance from a committee or consultant skilled in ethical analysis and critique applied at the organizational level.

The development of the discipline of "organizational ethics" is just beginning and is overdue in the judgment of JACHO[19] and other authorities.[20] The obligation to be ethical at every level of healthcare decision making will become increasingly obvious and pressing, with continuing changes in the ways health care is delivered. Increasingly institutional leaders are expected to be accountable for their policies, practices, and decisions and to convey their expectations, actions, and results in transparent ways.

Conclusion

Illness, trauma from being burned, and hospitalization can impact a person's sense of wholeness, integrity, autonomy, and sense of identity. In cases involving severe burns, patients are often dependent on others for the most intimate functions of daily life and must rely on the good will, skills, and ethical conduct of others. While it is clear that optimal burn care is infused with technological innovation, clinical sophistication, and the application of evidence-based knowledge, it is also a profoundly moral activity. It requires deliberate sensitivity to the values and needs of others, profound regard for the dignity of each individual, and courage to enter into the world of a vulnerable human being who is in need of help. Providing total care to the burned patient requires an educated heart, an empathic mind, and a humanistic team.

Complete references available online at
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Further Reading

Blakeney P, Herndon D, Desai M, et al. Long-term psychological adjustment following burn injury. *J Burn Care Rehabil*. 1988;9(6):661-665.

Council on Ethical and Judicial Affairs, American Medical Association. Medical futility in end of life care: Report of the council on ethical and judicial affairs. *JAMA*. 1999;281(10):937-941.

Faden RR, Beauchamp TL. *A History and Theory of Informed Consent*. New York: Oxford University Press; 1986:235-381.

Spies M, Herndon D, Rosenblatt J, et al. Prediction of mortality from catastrophic burns in children. *Lancet*. 2003;361(9362):989-994.

Zawacki BE, Imbus S. Enhancing trust and subjective individual dialogue in the burn center. In: Orlowski JP, ed. *Ethics in Critical Care Medicine*. Hagerstown MD: University Publishing Group; 1999:489-512.

References

1. Fulginiti VA. The right issue at the right time. In: Holmes DE, Osterweis M, eds. *Catalysts in Interdisciplinary Education*. Washington DC: Association of Academic Health Centers; 1999:7-24.
2. Carter MA. A synthetic approach to bioethical inquiry. *Theor Med Bioeth*. 2000;21(3):217-234.
3. Ahronheim JC, Moreno J, et al. *Ethics in Clinical Practice*. Boston, MA: Little, Brown & Company; 1994.
4. Gillon R. *Philosophical Medical Ethics*. Chichester: John Wiley & Sons; 1985:2.
5. Boisaubin E, Carter MA. Optimizing ethics services and education in a teaching hospital: rounds vs consultation. *J Clin Ethics*. 1999;10(4):294-299.
6. Maguire DC. *The Moral Choice*. Garden City, NY: Doubleday; 1978:113.
7. Pellegrino E, Thomasma DC. *A Philosophical Basis of Medical Practice*. New York: Oxford University Press; 1981:119-152.
8. Potter RL. On our way to integrated bioethics: clinical/organizational/communal. *J Clin Ethics*. 1999;10:171-177.
9. Zawacki BE. Ethically valid decision making. In: Herndon DN, ed. *Total Burn Care*. 1st ed. London: Saunders; 1996:575-582.
10. Spies M, Herndon D, Rosenblatt J, et al. Prediction of mortality from catastrophic burns in children. *Lancet*. 2003;361(9362):989-994.
11. Zawacki BE, Imbus S. Enhancing trust and subjective individual dialogue in the burn center. In: Orlowski JP, ed. *Ethics in Critical Care Medicine*. Hagerstown MD: University Publishing Group; 1999:489-512.
12. Faden RR, Beauchamp TL. *A History and Theory of Informed Consent*. New York: Oxford University Press; 1986:235-381.
13. Carter MA, Robinson S. A narrative approach to the clinical reasoning process in pediatric intensive care: the story of Matthew. *J Med Humanit*. 2001;22(3):173-194.
14. May WW. *Ethics in the Accounting Curriculum: Cases and Readings*. Sarasota, FL: American Accounting Association; 1990.
15. Foley K. A 44-year-old woman with severe pain at end-of-life. *JAMA*. 1999;281:1937-1945.
16. *Alquist. Health care decisions. (California) Assembly Bill No. 891*, Ch. 4, sections 4730-4736; operative July 1, 2000.
17. Ad hoc drafting committee. *Guidelines for foregoing life-sustaining treatment for adult patients at the LAC+USC Medical Center*. LAC+USC Medical Center, Los Angeles CA, May 5, 1993.
18. Hirsch NJ. All in the family – siblings but not twins: the relationship of clinical and organizational ethics analysis. *J Clin Ethics*. 1999;10:210-215.
19. Joint Commission on Accreditation of Healthcare Organizations. *Ethical Issues and Patient Rights*. Oakbrook Terrace, IL: Joint Commission on Accreditation of Healthcare Organizations; 1998:67-90.
20. Society for Health and Human Values/Society for Bioethics Consultation Task Force on Standards for Bioethics Consultation. *Core Competencies for Health Care Ethics Consultation*. Glenview, IL: American Society for Bioethics and Humanities; 1998:24-26.

62 Intentional Burn Injuries

LISA L. TROPEZ-ARCENEAUX and KWABENA O. SARPONG

PowerPoint Presentation Online

Introduction

Forensic medicine has made tremendous advancements in developing scientific measures to identify child maltreatment and intentional injuries. Despite these advancements, deliberate injury by burning is often unrecognized. According to the U.S. Department of Health and Human Services Administration for Children and Families,[1a] child abuse and neglect are defined as "any recent act or failure to act on the part of a parent or caretaker, which results in death, serious physical or emotional harm, sexual abuse or exploitation, or an act or failure to act which presents an imminent risk of serious harm." In January 2016, The Children's Bureau published the National Child Maltreatment Data from 2014, which reported that 1580 children died as a result of abuse or neglect.[1b] Within the United States alone, 1.5 million children are abused or neglected each year, with 4–39% of these occurrences being reported as intentional burn injuries and less than half ever being substantiated.[2a] In 2015, children aged 0–4 who sustained small burn injuries (total body surface area [TBSA] 0–29%) had a mortality rate of 0.25%, medium burn injuries (30–59.9% TBSA) had a mortality rate of 9.6%, and large burn injuries (≥60% TBSA) had a mortality rate of 29.06%.[2b] These mortality rates are significantly higher than in children over the age of 4, indicating that children younger than 4 years of age are at greatest risk.

It is imperative that all clinicians be aware of the importance of recognizing signs and symptoms of intentional injury presentations because the opportunity for intervention is critical when taking into account that 50%[3] of children experience recurrent abuse and 30% are ultimately fatally injured.[4] Reporting suspicious injuries to child protective services (CPS) is mandated by law for all clinicians working with children.[5] Some treating facilities identify specific treatment team members (i.e., psychologist or social workers) to be responsible for all reporting. In these situations, it may be necessary to follow the protocol of the hospital or treating facility first; however it is important to note that any physician, medical professional, or mental health professional who encounters a suspicious injury must ensure that the injury is reported to the appropriate authorities. At other times, the concern of reporting is more a result of ambiguity or vagueness in the information, which can cause hesitation to report the suspicious injury. In these incidents of doubt, the most salient point to remember is that the clinician is responsible for reporting suspicious injury, not proving or validating abuse. It is always better to report the suspicion than to ignore it. Most state agencies also have hotlines that are available to call 24 hours to ask specific questions regarding reporting suspicious injuries.[6] Although it is overwhelming to imagine that so much abuse occurs, statistics show that it does occur, not only with children but also with adults and our elderly population.

Intentional injuries can occur in the form of neglect, physical abuse, sexual abuse, and emotional abuse. All of these injuries can occur independently, but they often occur simultaneously.[7] Neglect is the most common form of intentional injury. Of the average 5.5 million referrals made to CPS each year, 64.5% of these children are neglected.[8] Physical abuse occurs in 25% of intentional injury cases.[8] More than 15% of victims of abuse suffer more than one type of abuse, and more than one-third of child fatalities are attributed to neglect (Fig. 62.1).[9] Burn injury is frequent in both neglect and physical abuse of children. Severe burns in children are between 10% and 12% of all intentional injuries.[10]

Since the last edition of this book, intentional injuries to adults have increased. It is frequently debated within the literature as to whether the increase is a valid increase or if there is an increase in reporting. Violence specifically against women and young girls has now become a universal phenomenon. The World Health Organization reported that, of the women who were partnered at some point during their lifetime, 15–71% reported experiencing physical or sexual violence by their partner.[11] Within this realm of violence against women and young girls, acid violence is the worst form of violence and violation of human rights.[12] Although steps are being taken to control the widespread free sale of acids to the public,[13] this act of violence is still on the rise and warrants discussion in the burn care literature and sensitivity to this overwhelming problem by all burn care professionals. Another vulnerable population of intentional burn injuries is the elderly. In the past 10 years, burns in the elderly have increased secondary to an increase in size of the aging population.

In this chapter, we have integrated our experience with current literature to classify risk factors in the total population and to propose validated therapeutic interventions to treat the burn wounds and the complex social and psychological familial concerns that both create injury and complicate the recovery and rehabilitation of the patient. It is essential that burn team clinicians understand their role and responsibility in assisting not only burn patients but the perpetrators as well because history and statistics have shown us that the outcome can be fatal if intervention and prevention methods are not implemented with sensitivity to maintain positive relationships with burn patients as well as with perpetrators.

The authors are well versed in clinical experience and research experience of child abuse and pediatric burn injuries; however our experience of intentional burn injuries within the adult population is limited. The literature and our

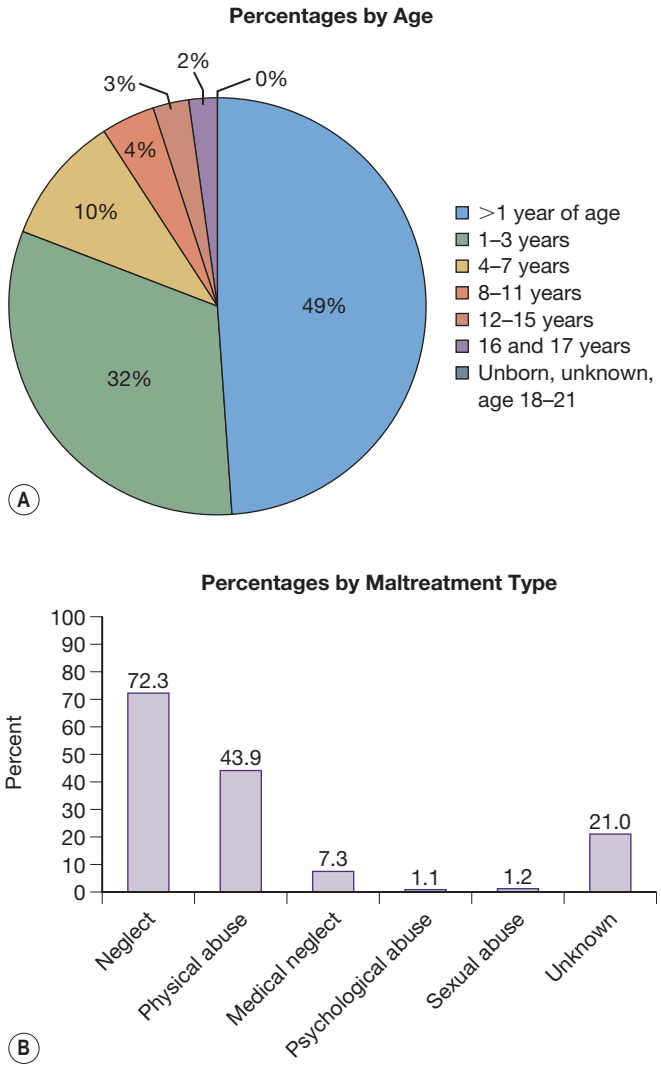

Fig. 62.1 Abuse and neglect fatality statistics. **(A)** Child abuse and neglect fatalities by age, 2006. **(B)** Forms of intentional injury that resulted in fatality. (From Child Welfare Information Gateway. June 2008 numbers and trends, child abuse and neglect fatalities: statistics and interventions. Available at: www.childwelfare.gov/pubs/factsheets/fatality.cfm.)

extensive knowledge of information regarding intentional injuries against children are reflected in this chapter. We have included the most recent literature on adult injuries, but it is not exhaustive. It is important to note that the pediatric population is not the only target for intentional injuries.

Prevalence Rates of Intentional Burn Injuries

Despite the improvement and use of smoke detectors, investment in sprinkler systems, and improvement in building codes in developing countries, burns continue to cause significant intentional and unintentional injuries. Smoking remains the leading cause of death by fire. Cooking is the number one cause of residential fires. Annually fire-related injuries claim more than 300,000 deaths and 10 million disability-adjusted life years worldwide.[13] Middle and low-income countries exceed 95% of fire-related burns.[13–15] Approximately half of these countries are in southern parts of Asia.[15] In the United States, burn injuries result in approximately 1 million emergency department visits and 50,000 hospital admissions, with a 5% mortality rate.[13] Fire and burns represent 1% of the incidence of injuries. Fatal home injury burns and fire deaths rank fifth and third, respectively, in the United States.[16] The incidences of the causes of burns are flame/fire 46%, scalds 32%, hot objects 8%, chemicals 3%, and other forms 6%. Fires/burns occur frequently in the home (43%), on the street/highway (17%), in occupational settings (8%), and in other settings (32%).[17] Burn injuries inflicted in Pakistan occur mostly to adult women: approximately one-third are secondary to stove burns and 13% are acid burns. Husbands inflict more than 52% of these injuries and in-laws one-quarter of the injuries.[18] Victims who are at highest risk of fire-related injuries and deaths are children aged 4 and younger, adults older than 65 years, African-Americans and Native Americans, and the poor or those living in rural areas.[16] A literature review of hospital-based studies of the prevalence of burn injuries in China revealed similar results with the most vulnerable being children younger than 3 years, males more than females, those living in a rural setting, and the incidence occurring between the hours of 17:00 and 20:00.[19]

PREVALENCE OF CHILDHOOD BURNS

Over the past 50 years, child abuse has been documented, especially in the United States. Child abuse characteristics are composed of physical abuse, neglect, sexual abuse, psychological abuse, and other, which include Munchausen by proxy and abandonment. Child abuse may present with multiple characteristics. Major forms of injuries to children include falls, poisonings, car accidents, foreign body, and fires/burns.[20] Ten percent of child abuse is burns, and 20% of burns are child abuse.[21] The child abuse death rate in the United States is approximately 1000 children annually,[18] with burns and scalds as the most frequent cause of death.[10] In China, the mortality rate from abuse ranges from 0.49% to 3.14%. In Hong Kong, it is 2.3%; in Singapore 4.61%, and in Iran 6.4%.[19] The lowest rates are in the United Kingdom and the highest rates are in the United States, where the majority of the studies have been completed.[10] In many cases of burn injuries, it may be difficult to conclude if the burn injury is an incidence of neglect, intentional, or truly an accidental event.[4] More recent studies[10,21–23] have begun to analyze hospital cases of burns to delineate if they are intentional or nonintentional. The characteristics of types of burns include scalding (70%), flame burns (50%), or electrical (3–4%).[19] Bathtub submersions peak at 6–11 months, then again at 12–14 months and remain high until 33–35 months of age.[20] Most studies calculate the mean ages of children with intentional burns at 2–4 years of age.[18] Boys are 2–3 times more afflicted than girls, with the youngest of multiple siblings suffering most often.[21] There is no ethnic predilection. Of children who are victims of physical abuse 10–12% suffer severe burns.[10] In 2007, Hicks and Stolfi[24] concluded that children with burn injuries are at risk for occult fractures at a significant rate. Therefore a skeletal survey should be routine in burn patients presenting to the emergency department, as

recommended by the American Academy of Pediatrics. Males are convicted at a greater rate than females, despite an equal rate as perpetrators.[25]

PREVALENCE IN ELDERLY

Over the past 10 years, prevalence data of burns in elderly have increased secondary to recent emerging studies in this area. As in pediatric burns, geriatric burns are higher in developed countries at a rate of 20%; in the developing world, the rate is 5%.[15] Results of the review of data from the U.S. National Burn Repository demonstrated an increase in the rate of elderly abuse from 1991 to 2005.[15,26] Of those burned, 14% are older than 55 years of age (with 6.2% between 55–64 years, 3.3% between 65–74 years, and 4.4% >75 years of age). There is a male predominance of burns of 1.4:1. However this decreases with age and is thought to be secondary to the decrease in life expectancy of males to females. The most common injuries are flame burns, accounting for 37%, and scalds at 22%. The TBSA was 9.6%, and the majority of injuries were residential.[15,26] In the United Kingdom, residential settings are the leading site for burn injuries to the elderly, at a rate of 18.6%. The occurrences had a 32% higher mortality rate and 33% more TBSA affected than like-sized burns in aged patients from other causes than abuse. Over a 4-year period, Bortolani and Barisoni[27] investigated 53 patients aged 60 and older who were admitted to a local Italian hospital. It was noted that 85% of these burns occurred in the home and 11% in nursing homes. Flame burns were the most common at 55%. The incidences were attributed to preexisting diseases in 85% of patients. These diseases included cardiovascular accidents, neurological problems, and diabetic comas.[27] In addition to illness, lack of adequate supervision is another major etiology for burns in this age group.[18] In the United States, residential care settings accounted for one-fifth of geriatric burns.[28]

With an increase in the aging population, there is concern about an increase in domestic elderly abuse and, proportionately, an increase in burn victims.[29,30] In the United States, elderly physical abuse was underreported, with a rate of 2.8% of total cases of abuse in 1988. However, in 1996, residential institutions estimated only one-fourth to one-fifth of abuse was reported. Another study, from Canada, estimated the prevalence of abuse at 1%.[28] The abuse is usually kept secret owing to guilt, shame, and fear of reprisal, especially if the perpetrator is the victim's adult child (Box 62.1).

The literature reports controversial results on the most likely perpetrator: spouse versus adult children. As in child abuse, disabled adults and those who suffer from dementia are at higher risk for abuse. Drug and alcohol abuse in caretakers also increases the rate of abuse. Other characteristics in caregivers are mental disorder, financial difficulties, and deviant behavior.[28]

Box 62.1 Premorbid Indicators of Intentional Burn Injuries of Adults

- Physical dependence
- Psychological dependence
- Accessibility as a target for abuse, as in institutional living or living with a caretaker
- Caretaker(s) with a history of substance abuse and/or other psychopathology
- Social isolation
- An injury that is not consistent with the story described
- Conflicting reports of the injury
- Scalds with clear-cut immersion lines and no splash marks
- Scalds that involve the anterior or posterior half of an extremity and/or the buttocks and genitals or a flexion pattern
- Other physical signs of abuse/neglect
- History of related incidents

Distinctive Characteristics of Perpetrators and Families

Perpetrators are frequently individuals responsible for the care and supervision of their victims. In 2007, one or both parents were responsible for 69.9% of child abuse or neglect fatalities.[31] More than one-quarter (27.1%) of these fatalities were perpetrated by the mother acting alone.[31] Child fatalities with unknown perpetrators accounted for 16.4% of the total.[31] According to the National Child Abuse and Neglect data system, in 2008, 56.2% of perpetrators were women, 42.6 % were men, and 1.1% were unknown.[32] Of the reported women perpetrators 45.3% were younger than 30 years of age compared to 35.2% of men younger than 30.[32] These percentages have remained consistent for several years in a row. Some 61% of all perpetrators were neglected as children.[1,31,32] Approximately 13.4% of all perpetrators were associated with multiple types of abuse.[1,31–33] Ten percent of perpetrators experienced physical abuse as children, and 6.8% were sexually abused as children.[33] Of the children who are abused, 80% were abused by their parents.[31–33] Other relatives accounted for an additional 6.5%.[31–33] Unmarried partners of parents were 4.4% of perpetrators. Of those parents who were perpetrators, more than 90% were biological parents, 4% were step-parents, and 0.7% were adopted parents.[32,33]

Other characteristics of perpetrators commonly include being adolescent parents, being a single parent, often maintaining inconsistent expectations for a child's development, experiencing a lack of external supports, stressors such as substance abuse, poor education (no high school diploma), unemployment, poor housing, mental illness, and being reliant on children for emotional support (Box 62.2).[34] Most fatalities from physical abuse are caused by fathers or other male caregivers. Mothers are most often held responsible for deaths resulting from child neglect.[35] In some situations, there are two "perpetrators," the actor and the overtly passive observer who does not stop the abuse.[36] Justice and Justice,[37] in their work with families who mistreat children, identified several erroneous belief systems that are commonly held by perpetrators; these are listed in Box 62.3. Since, as most authorities believe, violence is a multigenerational intrafamily pattern, then it is likely that the belief systems attributed to child perpetrators can be extrapolated to perpetrators of adult abuse as well.[36]

Often in homes where abuse occurs, there is little to no emotional support for the perpetrators. They are often dealing with tremendous life stressors and unfortunately

Box 62.2 Risk Factors for Abuse/Neglect by Burning

Forced-Immersion Demarcation

- Symmetrical, mirror-image burn of extremities
- Glove-like (burned in web spaces)
- Circumferential
- Minimal splash marks
- Uniform depth
- Full-thickness
- Clear line of demarcation, crisp margin
- Doughnut-shaped scars on buttocks/perineum (spared area forcibly compressed against container thus decreasing contact with hot liquid if container is not a heated element)
- Flexion burns, "zebra" demarcation to popliteal fossa, anterior hip area, or lower abdominal wall
- Injuries of restraint (e.g., bruises mimicking fingers and hands on upper extremities)[16]

Injury Demarcation, Other

- Incongruent with history of event
- Pattern of household appliance; note whether the burn presents as an even pattern versus a brushed, imperfect mark
- Scald
- Location of injury: palms, soles, buttocks, perineum, genitalia, posterior upper body
- Cigarette burn, if more than one on normally clothed body parts and if impetigo is ruled out

History of Injury

- Evasive, implausible explanation
- Incompatible with child's developmental age
- Changes in story; discovered to be burned
- Rule out dermatologic epidermolysis bullosa (EB), dermatitis herpetiformis, chemical burn due to analgesic cream, phytophotodermatitis,[17] and birth marks, including Mongolian spots[18]
- Undersupervised: inadequate monitoring, impaired person supervising, inordinately young babysitter (<12 years of age)
- Burn is older than history given
- Water outlet temperature greater than 120°F
- Mechanism of burn is incompatible with injury (e.g., exposure time, history of event, and degree of burn are inconsistent)
- Patient's per-event behavior displeasing to caregiver (e.g., inconsolable, failed to meet caregiver's expectations)
- Toileting events related to history of injury[19]
- Burn attributed to:
  - Child or patient, as per caregiver
  - Caregiver who is not present at the healthcare facility
  - Caregiver, as per patient
  - Delay in seeking medical treatment; note estimated time of delay

Developmental Associations

- Preverbal, nonverbal person
- Vulnerable person (e.g., special needs, failure to thrive, elderly)
- Caregiver expectations are inconsistent with patient's development; caregiver overestimates child's developmental skills and safety knowledge; caregiver unaware of patient's developmental capacity
- Patient has symptoms of mental disorder (e.g., ruminating, aggressive)
- Patient displays disturbing behaviors related to attachment (e.g., excessive crying, clinging, apathy/lethargy, excessively withdrawn, listless, unemotional, submissive, polite, fearful, vacant stare)
- Hypersexualized language or behavior as compared to same-age peers

Caregiver–Patient Relations

- History of interrupted caregiver–child bonding
- Adolescent caregiver(s) (e.g., child–child versus adult–child interactions)
- Strained interactions; inappropriate expectations of the patient by the caregiver
- Role reversal (rely on patient for support)
- Inappropriate or lack of caregiver concern:
  - Detached
  - Lack of sympathy
  - Lack of physical contact (e.g., fails to hold or pick up child)
  - Inebriated during visits
  - Infrequent visits

Other Physical Signs of Abuse or Neglect

- Unrelated injuries:
  - Fractures, dislocations; rupture to spleen, liver, or pancreas; point tenderness; impaired range of motion or function
  - Signs of poisoning
  - Ocular insult (edema, scleral hemorrhage, hyphema, bruise, blue sclera)
  - Swelling, bogginess, depressions, cephalohematomas palpable on head or increased intracranial pressure at fontanelle
  - Blood, infection, or foreign body in ear
  - Edema, bleeding, septal deviation of nose; foreign bodies in nose; cerebrospinal fluid rhinorrhea from nose
- Unrelated injuries involving the skin: hematomas, soft tissue swelling, lacerations, fingernail markings, scars, bruises (check behind ear), welts, rope burns, strangulation marks, bites, alopecia; note color, size, shape, and location of each (scalp most visible while shampooing)
- Abdominal tenderness, guarding, rebound tenderness, or bruises
- Cardiac instability, tachycardia, murmurs, flow murmurs secondary to anemia, or palpable rib fractures
- Dehydration or malnutrition; note weight, height, and head circumference
- Previous burns
- Unkempt (e.g., severe diaper rash, dirt under nails or in axillae, odoriferous, dirt on plantar surfaces of feet in cold weather)
- Inadequate or no immunization record
- Inadequate dental care (e.g., caries); trauma to lips, tongue, gums, frenula, palate, pharynx, or teeth
- Inadequate medical care
- Inappropriate dress
- Assess prior to invasive medical procedures
- Genital, urethral, vaginal, or anal bruising, bleeding
- Swollen, red vulva or perineum
- Foreign body in genital area
- Positive cultures for sexually transmitted diseases; if herpes develops, note whether lesions are on unburned body surface area, on genitals of type II
- Pregnant minor
- Recurrent urinary tract infections, streptococcal pharyngitis, abdominal pain

Family

- Caregiver abused or emotionally deprived during childhood
- Limited disciplinary practices (e.g., only uses physical punishment)

Continued

Box 62.2 Risk Factors for Abuse/Neglect by Burning—cont'd

- Lack of external supports; isolation
- Mental illness, substance abuse, criminal history
- Lack of financial self-sufficiency
- Poor employment history
- Dependent caregiver; unable to cope with daily responsibilities; unorganized
- Violent couples; impulsive, easily frustrated
- Previous Department of Protective and Regulatory Services involvement[20]
- Prior accidents to dependents
- Acute family stressors
- No primary caregiver

Box 62.3 Erroneous Beliefs of Abusers

Erroneous belief systems commonly contributing to the family system in which abuse occurs:[37]

- If my child cries, misbehaves, or does not do what I want, he or she does not love me and I am a bad parent
- My child should know what I want and want to do it
- My child should take care of me like I took care of my parents
- My spouse/lover should know what I want and meet all of my needs
- If I have to ask, it does not count
- You cannot trust anyone

resort to immature coping styles to deal with frustrations. Perpetrators resort to abuse as a result of complex behaviors derived from a dysfunctional family history, lack of education, desperation, and, at times, substance abuse. Children and elderly are usually dependent on the perpetrator; ironically, they are a source of stress and therefore become the victim of intentional injuries. Corporal punishment is "the use of physical force with the intention of causing a child to experience pain but not injury for the purpose of correction or control."[38] Some perpetrators will use this explanation as a form of justification for intentional injuries.[36] In young children learning toilet training, a hot bath to clean after a toileting accident is often a form of punishment. Usually the perpetrator's intent is to clean the child well, not to burn; however serious burns often occur. They often fail to seek appropriate and timely medical treatment for an injured child, not only because they fear punishment but also because of their learned helplessness and passivity. They discount the seriousness of the injury, as well as their ability to take care of the injury. "I didn't think it was that bad" is an explanation often given for delay in seeking treatment. By diminishing the significance, they relieve themselves of responsibility to act. When the perpetrator does take the child for help, the perpetrator commonly seeks first a relative or neighbor rather than a physician because perpetrators do not believe in their own ability to decide whether to seek medical treatment. Perpetrators are observed to interact inappropriately with their children because they are preoccupied with having their own needs met. A child who is hurt and demanding is unlikely to reward the perpetrator with feelings of comfort that the perpetrator seeks, and so the perpetrator withdraws from the child. If the child is quiet and compliant, the perpetrator may be observed to ignore the child and sit passively, watching television for long periods until some external force acts as a stimulus to motivate the adult into action.[36]

Indicators of Intentional Injuries

In approaching pediatric burn victims, indicators of possible inflicted burn injuries should be considered (Table 62.1). Patterns of scald burns are highly suggestive of inflicted injuries, and healthcare providers have a general agreement of these indicators (Box 62.2):[22]

a. In scald burns, it is implied that the absence of splash is suggestive of the victim being held down, although some children who jump into a hot tub of water may panic or freeze and not have splash burns. These scald burns have predominantly symmetric, clear upper margins. The burns usually involve lower extremities and the buttocks, without head and neck injuries (Fig. 62.2),[10] although Daria et al. 2004[23] describe six cases of submersion burns that involve the head and neck.
b. If there is uniformity of burn, consider that the patient was held still during the incident.
c. Symmetric bilateral burns (glove and stocking distribution) are highly suggestive of forcible immersion (Fig. 62.3B).
d. In submersion burns, there may be skin sparing secondary to joint flexion or the victim forcibly held against the receptacle. This gives an appearance of a "doughnut" or "halo sign."
e. In an Australian study authored by Heaton in 1989,[39] bilateral burns of extremities are between 2.4 and 4.8 times more common in inflicted burns.[22]
f. Accidental cigarette burns are superficial and ill defined. Yet inflicted wounds are superficial circular or ovoid macular wounds with distinct depigmented lesions and hyperpigmented edges.
g. Heated metal objects cause deeper burns (Fig. 62.3A).
h. Electric shock burns are revealed based on the size of the device and entrance and exit wounds. Areas will vary from full-thickness necrotic areas to superficial wounds that are erythematous. One cannot evaluate these lesions in isolation (Box 62.2). Review of medical records is necessary to assure the presence of a pattern of repeated abuse. Also be aware that perpetrators may frequent a variety of hospitals in the area to decrease suspicion by medical providers. Corroboration of history to physical exam is essential and may suggest indicators of intentional burns.

Table 62.1 Triage Tool for Diagnosis of Intentional Scalds

	Evaluate for Intentional Scald	Intentional Scald Should Be Considered	Intentional Scald Unlikely
Mechanism	Immersion		Spill injury; flowing water injury
Agent	Hot tap water		Non-tap water; other liquids (beverage)
Pattern	Clear upper limits; uniform depth scald symmetry (extremities)	Uniform scald depth; skin fold sparing; central sparing buttocks (doughnut ring pattern)	Irregular margin; irregular depth; lacks stocking distribution
Distribution	Isolated buttock/perineum, ± lower extremities; isolated lower extremities; rarely the face	Glove and stocking; 1 limb glove/stocking	Asymmetric involvement of lower limbs; head, neck, and trunk or face and upper body
Clinical features	Associated unrelated injury (recent or old fractures); history incompatible with examination findings	Previous burn injury; neglect/faltering growth; history inconsistent with assessed development	
Historical/social features	Passive, introverted, fearful child; previous abuse; domestic violence; numerous prior accidental injuries; sibling blamed for injury	Trigger, such as soiling/enuresis/ misbehavior; differing historical accounts; lack of parental concern; unrelated adult presenting child; child known to social services	

Adapted from Maquire S, Moynihan S, Mann M, et al. A systematic review of the features that indicate intentional scalds in children. *Burns* 2008;34(8):1072–1081.

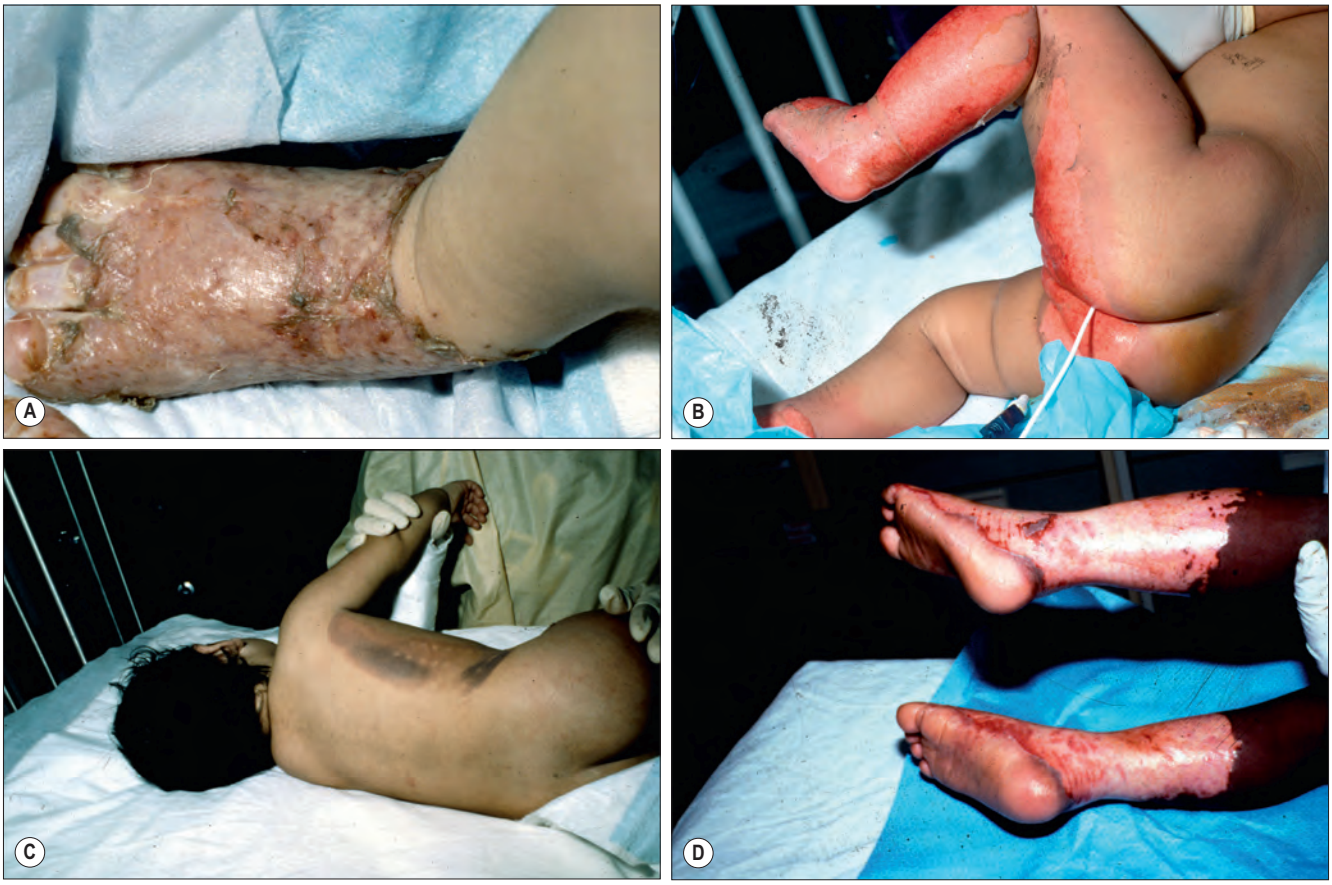

Fig. 62.2 Newborns who were burned in hospitals by improperly trained hospital personnel.

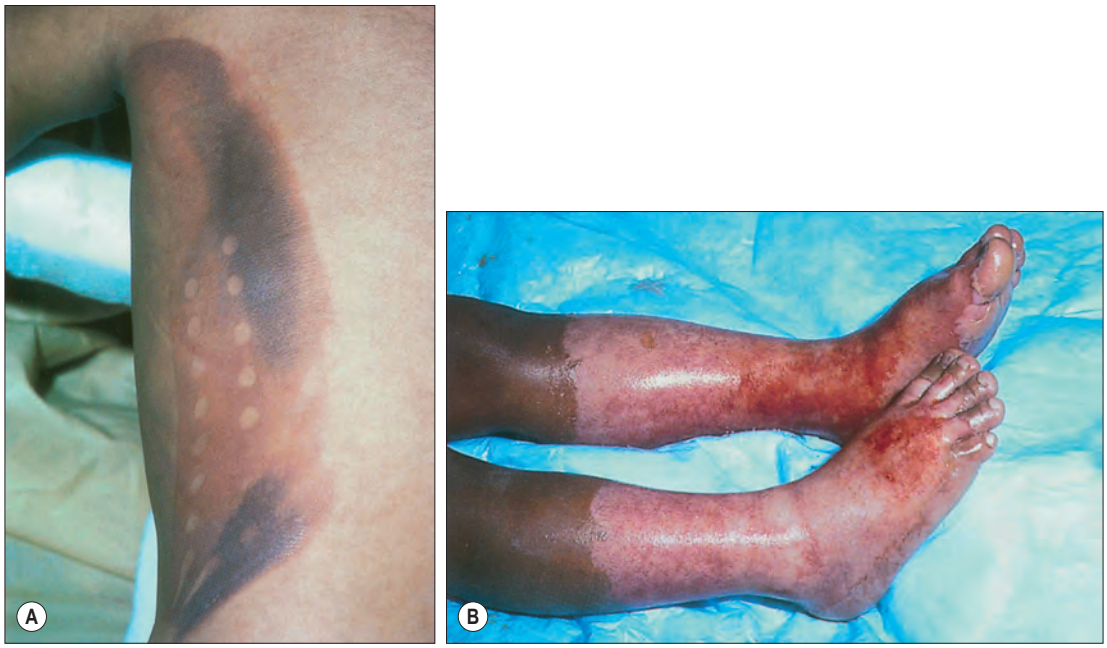

Fig. 62.3 (A) Abuse: contact burn in which the markings of an iron are clearly visible. **(B)** Abuse: classic stocking pattern resulting from feet being immersed in very hot water. The initial history given by the mother of the 21-month-old infant was that an older sibling had turned on the hot water, and the patient herself dipped her feet into the tub.

Self-Inflicted Burn Injuries

One of the most violent means of suicide is self-immolation by burning. Self-immolation can also act as part of a deliberate self-harm syndrome consisting of continual, sudden urges toward self-harm.[21] There has been an increase in the literature on self-immolation, but it is unclear if this emphasis is a result of increased rates of occurrence or increased reporting.[13,41] Historically there is a debate as to whether self-immolations are more acceptable if they are religiously or politically motivated.[21,42–46] Characteristics of females who self-immolate include substance abuse, a lack of social support, younger age, and diagnosed eating disorders.[21] Males who self-immolate are also younger, with severe mental illness,[21] or pathological family dynamics, or possibly an adherence to fundamentalist religious convictions.[13] Regardless of sex, self-inflicted burn patients usually have some previous psychiatric problems, often depression or borderline personality disorder; previous failed suicide attempts with a poor response by others to suicidal ideation; and recent life stressors with feelings of helplessness.[21] One of the highest rates of this behavior is in Iran among young females in whom marital conflict is a significant risk factor. Others risk factors include low literacy, low socioeconomic status, limited access to mental health services, and posttraumatic stress disorder.[13]

Although self-inflicted burn injuries are less frequent in Western culture, studies report a rate of 0.5–2% in adolescents and up to 25% in adults.[21,47,48,46,49–54] In Africa, south Asia, and the Middle East self-inflicted burn injury rates account for up to 28% of all burn injuries.[55] There is an estimated range of self-immolation accounting for 9–32% of all suicides in India, Zimbabwe, and Iran,[21,56–58] with rates for Iranian and Brazilian women being as high as 46% of suicides.[21,59,60] Some studies have found that there are no gender differences in the rates of self-immolation,[61,62] but some have determined that it is most common in females,[63–65] specifically Asian and Latin females,[47,55,66,67] whereas others have found that it is more common in males.[49,68] Other risk factors for self-immolation in Western culture include previous psychiatric treatment, diagnosis of a psychotic disorder,[61,63,69,70] unemployment,[61,69,68] or severe relationship difficulties.[61]

The most common mechanism of self-immolation is flame as a result of fire accelerant such as kerosene, gasoline, or rubbing alcohol.[13,70] In a 2004 Finnish study, 43% of all patients used flame, but 93% of women with self-inflicted burn injuries used flame.[70] The reported mean TBSA among self-inflicted burn injuries is higher (median 42.2%; range, 22–79%) than other burn patients (median 36%; range, 11.8–77%). These burn injuries are usually deeper full-thickness burns with increased risk of inhalation injury, poorer long-term prognosis, and a higher rate of mortality.[21,49,58,59,63,64,66] Self-immolations are 1.5–1.7 times more frequent than reflected in current literature. This is an area where more studies are needed to identify more accurate prevalence rates and prevention interventions.

Clinical Evaluation of Suspicious Injury With Pediatric Patient and Family

The history of the burned child is of particular importance in assessing whether the burn is likely to be intentional or accidental. Evaluating for intentional burn injuries requires a multidisciplinary team effort (Box 62.4).

Box 62.4 Documentation for Reporting

In addition to the documentation of first-hand observations, the following tasks should be delegated:

- Examine the patient for other signs of maltreatment, including a skull and long-bone radiological scan. Clearly state that the radiology consultation is for assessment of occult trauma
- Photograph injuries and any possible evidence
- If the patient has been referred from another hospital, access information from the staff at that hospital to determine whether they identified suspicious aspects of the injury and whether the injury was reported to an investigating agency. If so, ascertain the number assigned to the patient's case by the investigating agency. This number is needed for subsequent calls related to the patient
- Interview the patient
- Interview the family members or caretakers individually and together for thorough histories of the event, being sensitive to differences in the story or changes across time
- Obtain a thorough family history, the patient's medical history, and the developmental capacity of the patient
- Gather other available collateral information (e.g., medical records from other places of treatment)

Created by Patricia Blakeney PhD and Rhonda Robert PhD, 2007.

PHYSICIAN ASSESSMENT

The physician–patient relationship is paramount in assessing patient injuries and providing an accurate assessment of an incident to determine if suspicious injuries are intentional or nonintentional. Obtaining a detailed history from the patient and the caretaker is foremost in assessing the creditability or plausibility of history to what is seen on physical exam (Box 62.2). It is essential that providers are familiar with child development in order to incorporate child development into the assessment process. Trust issues may interfere in obtaining a precise history. The assessment always requires an open mind for the possibility of intentional injury, which should be thoroughly investigated when clinical features are present in the history and examination. Features of the physical exam consist of identifying the pattern of burn injury, with the distribution and associated features being the more important aspects to distinguish. The reported method of injury must be clearly associated with the observed pattern of injury, burn depth, and appearance on physical examination (Box 62.2).[71] Children who are burned are also in a high-risk group of being subjected to other forms of abuse. Although a few studies have indicated that pediatric burn patients are at a lower risk for related fractures from abuse, approximately 18.6% of children in this subgroup had fractures on their skeletal survey.[72,73] Another study found that pediatric burns have a 14% risk of fractures.[24] This rate may be underestimated since all patients did not receive a skeletal survey. These fractures are occult and may not have physical evidence of their existence. Further evidence has also revealed that children with burns are less likely to be evaluated for fractures, reflecting the erroneous belief that they are a lower-risk group. All children 2 years and under should receive a skeletal survey on initial exam to denote concomitant new or old fractures.[72,73] The clinician must also be mindful at this time to assess for signs of abusive head trauma such as intracranial and retinal hemorrhage.[71]

A child who presents with suspected unintentional and intentional burn injury should be evaluated by a child abuse pediatrician or a pediatrician with experience in the evaluation of the causes and mechanism of burn injury. However such an evaluation should be done when the child is medically stable.[74]

The evaluation of burn injury should begin with a thorough history, which should be taken directly from a child who is verbal or developmentally matured enough to give the history and also from parents and caregivers who were present at and around the time of the injury. The history of the injury and the sequence of events should be as detailed and concise as possible.[75]

The developmental ability of the child, as well as home and social environmental factors, should also be taken into account.

The patient's past and current medical histories are also important factors to be considered. Additional specific questions should be asked depending on the type of burn injury. Ask about the temperature of the hot water setting at home in cases of scald burns and the duration of contact in cases of contact and scald burns.

The next step in the medical evaluation will be a complete physical examination. The physical exam should include a good assessment of the general presentation of the child, looking for signs of adequate nourishment, emotional status and general well-being, and hygiene.

If possible, a developmental assessment should be done, although in severe burns it is quite difficult to assess development, and the medical history should be relied on or the developmental assessment done later. All organ systems should be evaluated to look for bruises, fractures, head injury, and other signs of trauma.

The burn injury should then be specifically evaluated, looking at patterns, line of demarcation, distribution, planes of the body involved, size, and symmetry. Every injury should be well-documented, and photo documentation should be done ideally at the time the child is admitted or as soon as the child is stable.

After the child has been assessed other testing may be important. The American Academy of Pediatrics recommends that children younger than 2 years who present with concerns for physical abuse should have a skeletal survey. For children between 2 and 5 years of age, a skeletal survey may be done depending on the history and examination; however a skeletal survey is not indicated after 5 years of age.[76,79]

Skeletal surveys are important to diagnose subtle fractures such as classical metaphyseal lesion fractures and rib fractures that have a high specificity for abuse. Because such fractures can be subtle and may not be obvious in the first skeletal survey, a repeat skeletal survey needs to be done 10–14 days later to look for callus formation.[76,77]

Recent research shows that the incidence of fractures in children with inflicted burns is about 33% compared to those with accidental burns,[80] although some have reported the incidence of fractures in nonaccidental burns to be as high as 53% in children younger than 24 months.[77]

After the history, physical examination, lab and radiological investigations, and sometimes scene investigations have been done, the medical expert should then make an assessment of the injuries to determine if the history explains the mechanism and is consistent with the burn injury. The assessment should be made with no biased principles, and the physician or medical health professional should be focused on his or her role, which is mainly the care and protection of the child. It is not the role of medical personnel to find who may have caused the burn injury or to pass judgment on caregivers or the alleged perpetrators.[81]

Types of Burn

SCALD

Scald burn is the most common form of nonaccidental burn injury. The typical child who has sustained a nonaccidental burn injury has a history of being potty trained at around 2 years of age.[75,84] The burn mechanism is normally an immersion in hot water. These children present with a burn of uniform depth, with well-demarcated borders and an absence of the splash or splatter common with accidental burns. Nonaccidental burns often show bilateral symmetry and in most cases such burns also spare the flexors[83] (Fig. 62.4).

CONTACT

Contact burns are the second most common form of abusive burns.[84] Nonaccidental contact burns normally have very defined distinct borders. They could also assume the pattern of the instrument that may have been used to cause the burn.[86]

In nonaccidental cigarette burns, the burns are normally in clusters with ovoid to circular shape and with a circumference of 5–10 mm.[87] Reported mechanisms of contact burns include curling irons and steam irons.[86] Such burns normally leave the distinct pattern of the object used to cause the burn.

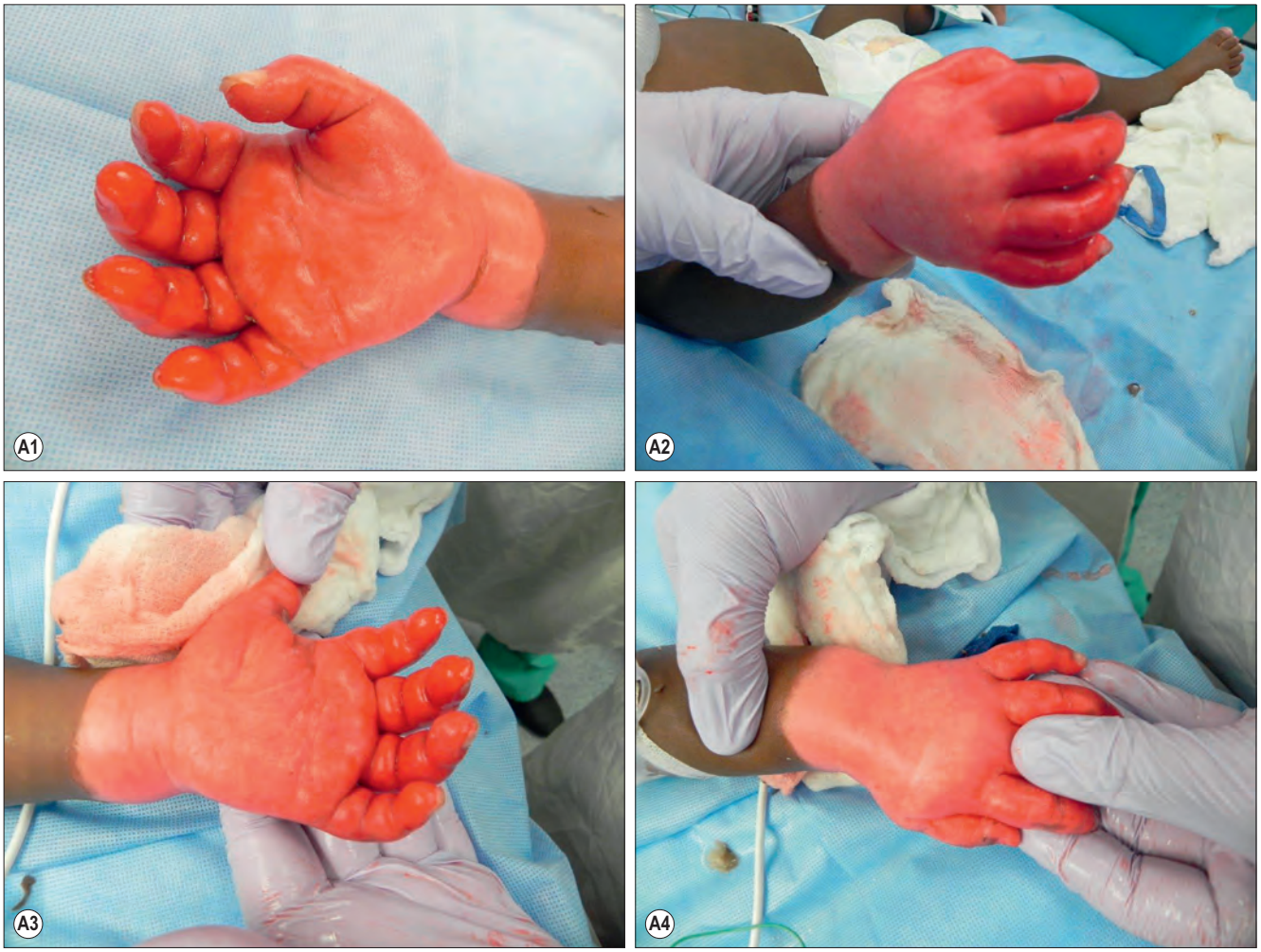

Fig. 62.4 Bilateral symmetry shown in non-accidental burns and in most cases such burns also spare the flexors.

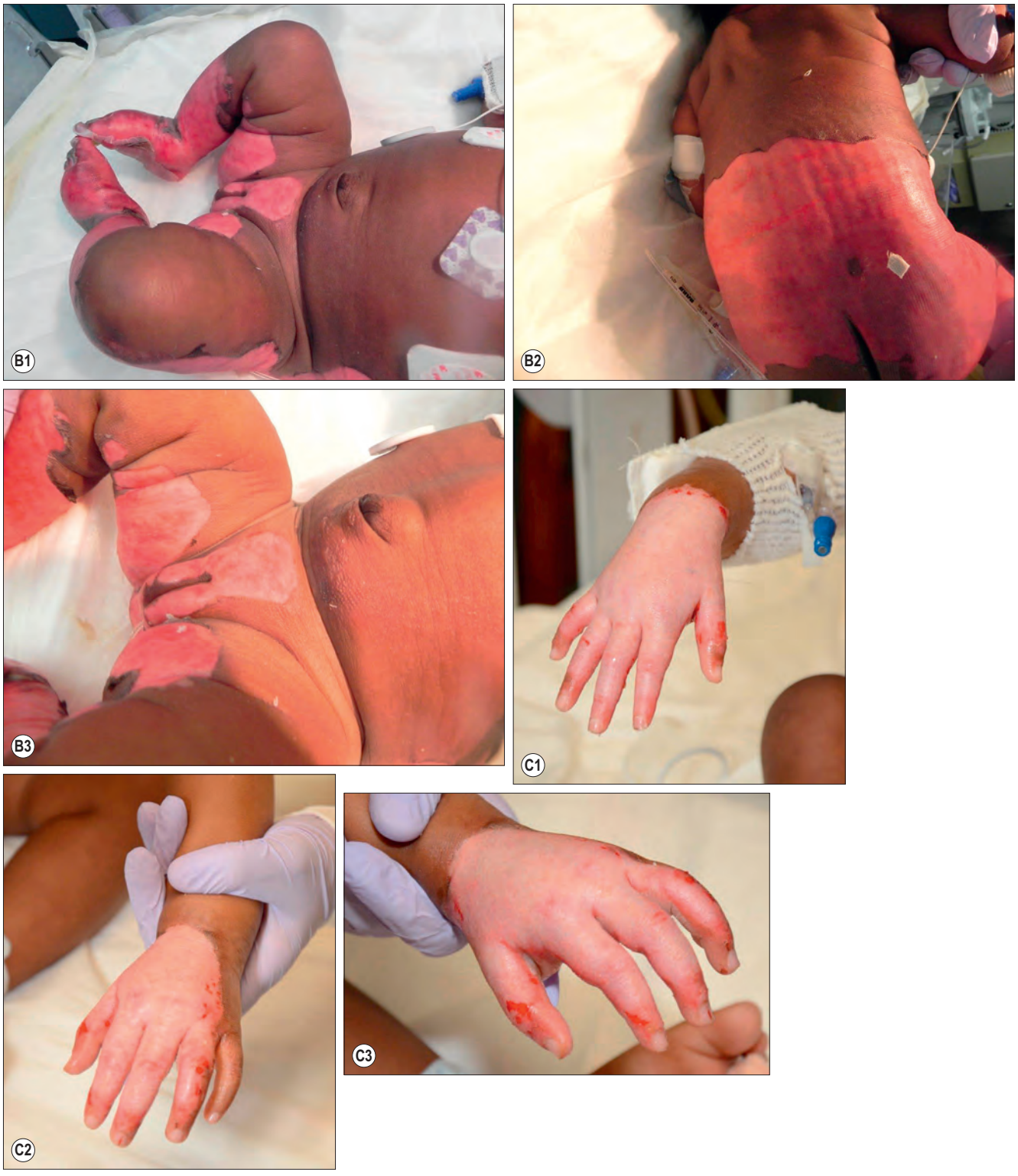

Fig. 62.4, cont'd

CHEMICAL BURNS

These burns can be caused by alkali-based, acid-based, inorganic, and organic agents. It is important to discover the injury-causing agent so as to prevent further damage. Alkali burn injuries may seem innocuous at first but may produce deeper tissue injury and could produce further damage even after removal of the immediate cause of the burn.[85] Alkali burns may not be painful compared to acid burns, which produce painful deep ulcers. Chemical burn injury could be either from supervisory neglect or from an inflicted intentional injury.

Psychosocial Assessment

Multidisciplinary work is essential for appropriate management of children or adult burn/abuse victims. Psychologists are critical in the initial evaluation and to assist in interviewing, and social workers are advocates for referral and follow-up care. Both are skilled at assessing family dynamics and social situations in greater detail and should be your focal point for referral to appropriate government agencies. Psychosocial assessment and interview with the patient separately (when possible) from the caretaker will provide a more accurate picture of the injury events. Inconsistency is a marker of discrepancies in the history, which may alert an examiner to possible abuse. The patient and caretaker must have a detailed interview documented verbatim by the historian. Paraphrasing information increases the likelihood of personal interpretation of history. The presence of witnesses and the exact timing of events must be confirmed, and these persons must be interviewed to assess for correlation in narratives.[74] A thorough event reconstruction soon after admission should be conducted and documented. This limits the room the suspect has to alter the events and timeline related to the burn or the opportunity to collude with witnesses.[3] The pattern of circumstances is extremely important, with suspicions raised when the adult responsible claims not to have seen the incident, attributes the injury to a sibling, or presents late, or when relatives other than the adult supervising at the time of the burn bring the child for assessment.[21] The clinician conducting the interview must be well versed in child development to ascertain normal developmental responses to those that are suspicious of abuse. Observations of interactions and behavior are equally as important as the specific questions that are asked during the interview process.

Abused children often are under the age of 2, making them vulnerable to their caregivers. Other characteristics include inconsolable crying, difficulty in toilet training or associated toilet training accidents, insufficient or strained parent–child attachment, and inappropriate behavior such as apathy or apparent tolerance to invasive procedures. Severely abused children will demonstrate exaggerated responses by either being overly fearful or overly affectionate with the medical team. When requested to provide immunization records parents or caregivers suspicious of abuse will often fail to provide or will avoid providing accurate medical records and records of immunizations (Box 62.4).[3]

The interview with the child is an essential component to determining if the injury was intentional. The rapport that is established through a therapeutic relationship is the key factor to a successful interview. Warm-up questions or nonthreatening questions should be asked first to establish rapport: Ask "when is your birthday?"; ask questions about school or friends, or ask the child to verbalize a story of his or her best day. Once sufficient rapport is established, asking open-ended questions about the injury is most effective (i.e., "What happened? How did you get hurt?").[36] The child should be encouraged to tell the story freely. Specific questions for clarification should be asked only after the child has told the story. If the child seems unwilling to talk about what happened, the interviewer can suggest the child raise a hand or wiggle a finger to signal that they know something but do not yet want to talk about it. When interviewing younger children, short sessions with breaks will allow rapport-building and trust to develop so that child feels safe sharing his or her story.[36]

The suspicious injury assessment should be discussed confidentially with family members, including the suspected perpetrator.[36] Perpetrators should be allowed time to process their concerns in a nonjudgmental and therapeutic manner. The family should remain informed of the process and potential CPS interventions. It is important to share with families an understanding that often CPS is seen as a punitive agency but essentially the main goal is the safety and protection of all children. Sharing information will initiate a therapeutic relationship. Most perpetrators are reluctant to trust medical teams, especially when they feel as if they are being judged. Being honest about the process and the information shared with CPS minimizes mistrust. As stated previously, perpetrators often have limited emotional support. When an intentional burn injury occurs, psychologists are an essential component to providing the initial support and addressing the fears, sadness, and helplessness those perpetrators may feel. Regular psychotherapy sessions are critical to making a positive change in family dynamics.

Reporting Suspected Intentional Burn Injury

In 1967, state legislatures in every state had laws mandating that any reasonable suspicion of intentional injury be reported to the appropriate authorities.[36] In 1974, the Federal Child Abuse Prevention and Treatment Act was passed. These laws require professionals to report suspected intentional injuries to a child when there is sufficient information that would lead a "competent professional to believe maltreatment is reasonably likely."[36] It is important to be knowledgeable of not only state laws but also of local governing agencies' policies on reporting suspicious injuries. Most hospitals have risk management or legal teams that are well versed in the federal and state laws as well as in the policies, rules, and regulations of the hospital. Methods of communications regarding intentional injuries should be clearly outlined and reviewed prior to sharing any information regarding intentional injuries.

Providers who suspect abuse should report to the appropriate agency as designated by the state in which they

practice. As you interview, note the interaction between caregiver and patient. Providers should document inappropriate concerns, lack of sympathy, detachment, delay in seeking care, or use of drugs or alcohol (Box 62.2). If you suspect that inconsistency exists, without being confrontational, alert the caregiver and give him or her the opportunity to give a more truthful history. Detailed documentation of history and physical exam may be used in litigation charges and should be clear, concise, and accurate. It is imperative for clinicians responsible for reporting suspected abuse to be as accurate as possible because there are significant consequences for inaccurate assessment and diagnosis of suspected abuse. Some 50% of children who sustain intentional injuries have recurrent injuries that are eventually fatal.[3]

Ultimately it is not the hospital or any of the medical staff's obligation to prove that a suspicious injury was intentional. It is important to report the suspicion, ensure continuity of care, and cooperate with the legal process.[3] While the child is receiving medical treatment, it is imperative to keep accurate records and document all treatment and interactions among family members. The prosecuting attorney is responsible for proving intentional injuries; however medical records are often a key element. Physician reporting and cooperation are invaluable to legal prosecution. The physician's opinion on likelihood of intentional injury strongly influences CPS workers and prosecutors.[3] Salient to remember with intentional injury cases is that most attorneys have limited to no experience with burn injuries, and the expertise of medical investigators, burn psychologists, and social workers is the foundation for proving allegations and protecting the child from future injuries.

There are no federal programs to specifically address the reporting of suspected abuse in adults. All states have individual laws, reporting guidelines, and penalties for adult abuse. It is best practice to be aware of your state laws if you work with adults, but, if unsure, following the same guidelines as for children until the exact information can be obtained is acceptable. Most states have a statewide intake office that can be located online, and most states have online reporting. The National Center on Elder Abuse provides information and assistance on elder abuse, including a listing of state elder abuse hotlines. Child Help USA is a private charity that established and maintains the National Child Abuse Hotline (800)-4-A-CHILD (800-422-4453) and provides a listing of statewide reporting numbers at their website (http://www.childhelpusa.org/report). Telecommunications Device for the Deaf number is (800)-2-A-CHILD. The U.S. Department of Health and Human Services Administration for Children and Families provides a listing of statewide reporting phone numbers at their website (http://nccanch.acf.hhs.gov/topics/reporting/report.Cfm).

Clinical Interviewing With Other Vulnerable Populations

When interviewing vulnerable patients, it is important to provide a safe and confidential environment that is nonconfrontational and nonjudgmental. Developing rapport and trust is an essential component of the interview process. The older adult is likely to be dependent on the abuser in matters of daily living. Often the perpetrator is a family member or loved one. Whether the patient is able to express his emotions or not, he will likely experience fear, worry, shame, and a desire to protect the perpetrator. The therapeutic relationship developed will allow the patient to trust that the medical team will work in his best interest as well as the best interest of the perpetrator.

Maintaining Professional Relationships With Patient and Family

When approaching a child/adult who is an abuse victim, the provider must maintain professionalism and self-control and remain nonaccusatory. Clinicians within the healthcare profession are natural protectors of children with the desire to automatically align with the child. Addressing one's own feelings is vital to providing the best care for the patient. Establishing a therapeutic relationship with the family may be difficult, but it is imperative because many of these children are reunited with their family at discharge or at some point during outpatient burn care.

Future Burn Prevention and Child Safety

Burns and scalds are a significant cause of morbidity and mortality in children. Some studies have shown successful countermeasures to prevent burn- and scald-related injuries.[75] To prevent accidental burns, the American Burn Association Scald Injury Prevention Educator's Guide has published steps by which physicians can instruct their patients to assist in burn and scald prevention. Hot food and beverage scalds are the most common causes of scald injuries in both children and adults. Providing a safe cooking area and a supervised environment is foremost in prevention. Suggested examples are: do not carry hot liquids when carrying your child; place children in a playpen or high chair away from the stove; do not use child walkers; cook on back burners and remember to turn the pot handles to the inside; keep appliance cords coiled and out of reach from the counter; when removing lids, do not forget that steam can burn the face or arms; wear tight-fitting clothing or short sleeves when cooking; and, for those with mobility impairment, use a sturdy, large lap tray to carry hot liquids. Microwave scald burns have risen significantly since the 1980s.[16] Proper placement of the appliance, where the face is higher than the door of the microwave, is recommended. Children under 7 years of age should never operate this appliance. Never heat baby formula in the microwave due to unevenness of heating. Always allow microwave-cooked items to sit for 1 minute prior to opening. Prevent tap water scalds by setting hot water heaters below 120°F (Table 62.2). The American Burn Association reminds us that "Adequate and constant supervision is the single most important factor in preventing tap water scalds." Other tips

Table 62.2 Exposure Time to Receive a Severe Burn in Hot Water; Time and Temperature Relationship

Water Temperature		Time for a Third-Degree Burn to Occur
155°F	68°C	1 s
148°F	64°C	2 s
140°F	60°C	5 s
133°F	56°C	15 s
127°F	52°C	1 min
124°F	51°C	3 min
120°F	48°C	5 min
100°F	37°C	Safe temperature for bathing

Note: Downward adjustments to time needed for young children.
Data from Moritz AR, Henriques FC. Studies of thermal injury: II. The relative importance of time and surface temperature in the causation of cutaneous burns. *Am J Pathol.* 1947;23(5):695–720. See also American Burn Association. Scald Injury Prevention Educator's Guide. Available at http://www.ameriburn.org/Preven/ScaldInjuryEducator'sGuide.pdf.

include placing a single-faucet handle always in the cold water position and avoiding sudden fluctuations in water temperature (e.g., flushing the toilet while showering). The CDC has free material that can be downloaded from the web (/safechild/FactSheets/Burns-Fact-Sheet-a.pdf).

Prevention of nonaccidental burn injuries is more difficult. Further research and education of physicians and maltreatment teams are imperative. Since the establishment of the National Burn Repository (NBR) by the American Burn Association, a Burn Registry was established to create a national database. Physicians need to recognize suspicious burns and document exam and history in detail. Further research will assist in identifying clearer indications and patterns to determine intentional injuries.

Complete references available online at www.expertconsult.inkling.com

Further Reading

Definitions of child abuse and neglect: summary of state laws as of 2009. Available at: http://www.childwelfare.gov/systemwide/laws_policies/statutes/defineall.pdf [(PDF 1.2MB] (/safechild/FactSheets/Burns-Fact-Sheet-a.pdf.

Kolko D. *Juvenile firesetter intervention clinical training*. Pittsburgh, PA: Department of Psychiatry, University of Pittsburgh School of Medicine; 2000.

National Center on Elder Abuse. Website: www.elderabusecenter.org and phone number: (202)-898-2586.

National Clearinghouse on Child Abuse and Neglect Information. What is child abuse and neglect? US Department of Health and Human Services Administration for Children and Families; 2004. Available at: http://nccanch.acf.hhs.gov/pubs/factsheets/whatiscan.cfm.

References

1a. US Department of Health and Human Services. Administration for children and families; 2009.
1b. CDC Children's Bureau Child Maltreatment from National Data on Child Abuse and Neglect known to Child Protective Agencies in the U.S. during federal fiscal year 2014. Published January 25, 2016.
2a. Ojo P, Palmer J, Garvey R, et al. Pattern of burns in child abuse. *Am Surg*. 2007;73(3):253-255.
2b. Hodgman EI, Saeman MR, Subramanian M, et al. The effect of burn center volume on mortality in a pediatric population: an analysis of the National Burn Repository. *J Burn Care Res*. 2016;37(1):32-37. Available at: http://doi.org/10.1097/BCR.0000000000000274.
3. Peck MD, Priolo-Kapel D. Child abuse by burning: a review of the literature and an algorithm for medical investigations. *J Trauma*. 2002;53(5):1013-1022.
4. Hettiaratchy S, Dziewulski P. ABC of burns: pathophysiology and types of burns. *BMJ*. 2004;328(7453):1427-1429.
5. Reed JL, Pomerantz WJ. Emergency management of pediatric burns. *Pediatr Emerg Care*. 2005;21(2):118-129.
6. D'Souza AL, Nelson NG, McKenzie LB. Pediatric burn injuries treated in US emergency departments between 1990 and 2006. *Pediatrics*. 2009;124(5):1424-1430.
7. Child Welfare Information Gateway. Recognizing child abuse and neglect: signs and symptoms; June 2007.
8. National Child Abuse and Neglect Data System (NCANDS); 2004.
9. Nasrullah M, Haqqi S, Cummings K. The epidemiological patterns of honour killing of women in Pakistan. *Eur J Public Health*. 2009;19(2):193-197.
10. Maquire S, Moynihan M, Mann M, et al. A systematic review of the features that indicate intentional scalds in children. *Burns*. 2008;34:1072-1081.
11. World Health Organization. *WHO multi-country study on women's health and domestic violence against women: summary report of initial results on prevalence, health outcomes and women's responses*. Geneva: World Health Organization; 2005.
12. Begum AA. Acid violence: a burning issue of Bangladesh – its medicolegal aspects. *Am J Forensic Med Pathol*. 2004;25(4):321-323.
13. McKibben J, Ekselius L, Girasek D, et al. Epidemiology of burns injuries II: psychiatric and behavioural perspectives. *Int Rev Psychiatry*. 2009;21(6):512-521.
14. Mock C, Peden M, Hyder A, et al. Child injuries and violence: the new challenge for child health. *Bull World Health Organ*. 2008;86(6):420.
15. Dissanaike S, Rahimi M. Epidemiology of burn injuries: highlighting cultural and socio-demographic aspects. *Int Rev Psychiatry*. 2009;21(6):505-511.
16. Centers for Disease Control and Prevention. Injury prevention and control: home and recreational safety: fire deaths and injuries: fact sheet; n.d. Available at: http://www.cdc.gov/homeandrecreationalsafety/fire-prevention/fires-factsheet.html.
17. American Burn Association. National burn repository: fact sheet; 2005.
18. Nasrullah M, Muzzam S. Newspaper reports: a source of surveillance for burns among women in Pakistan. *J Public Health (Oxf)*. 2010;32(2):245-249.
19. Kai-Yang L, Zhao-Fan X, Luo-Man Z, et al. Epidemiology of pediatric burns requiring hospitalization in China: a literature review of retrospective studies. *Pediatrics*. 2008;122(1):132-142.
20. Agran PF, Anderson C, Winn D, et al. Rates of pediatric injuries by 3-month intervals for children 0 to 3 years of age. *Pediatrics*. 2003;111(6):83-92.
21. Greenbaum A, Donne J, Wilson D, et al. Intentional burn injury: an evidence-based, clinical and forensic review. *Burns*. 2004;30:628-642.
22. Greenbaum AR, Horton JB, Williams CJ, et al. Burn injuries inflicted on children or the elderly: a framework for clinical and forensic assessment. *Plast Reconstr Surg*. 2006;118:46e-58e.
23. Daria S, Sugar NF, Feldman KW, et al. Into hot water head first; distribution of intentional and unintentional immersion burns. *Pediatr Emerg Care*. 2004;20(5):302-310.
24. Hicks RA, Stolfi A. Skeletal surveys in children with burns caused by child abuse. *Pediatr Emerg Care*. 2007;23(5):308-313.
25. Ruth GD, Smith S, Bronson M, et al. Outcomes related to burn-related child abuse: a case series. *J Burn Care Rehabil*. 2003;24(5):318-321.
26. Pham TN, Kramer CB, Wang J, et al. Epidemiology and outcomes of older adults with burn injury: an analysis of the National Burn Repository. *J Burn Care Res*. 2009;30:30-36.
27. Bortolani A, Barisoni D. Burns in the elderly, epidemiology and mortality: analysis of 53 cases. *Ann Burns Fire Disasters*. 1997;10(4). Available at: www.medbc.com/annals/review/vol_10/num_/text/vol10n4p197.htm.
28. Keck M, Lumenta DB, Andel H, et al. Burn treatment in the elderly. *Burns*. 2009;35:1071-1079.
29. Wasiak J, Spinks A, Ashby K, et al. Epidemiology of burn injuries in an Australian setting, 2000–2006. *Burns*. 2009;35:1124-1132.
30. Hansen JC, Barnhill LR. *Clinical approaches to family violence*. Rockville, MD: Aspen; 1982:157.
31. National Child Abuse and Neglect Data System (NCANDS); 2007.
32. National Child Abuse and Neglect Data System (NCANDS); 2008.
33. US Department of Health and Human Services Administration for Children and Families. Child maltreatment, 2008. Available at: http://www.acf.hhs.gov/programs/cb/stats_research/index.htm.
34. Schwartz JP, Hage SM, Bush I, et al. Unhealthy parenting and potential mediators as contributing factors to future intimate violence: a review of the literature. *Trauma Violence Abuse*. 2006;7(3):206-221.
35. US Advisory Board on Child Abuse and Neglect; 1995.
36. Robert R, Blakeney P, Herndon DN. Maltreatment by burning. In: Herndon DN, ed. *Total burn care*. Edinburgh, Scotland: Elsevier Saunders; 2007:771-780.
37. Justice R, Justice B. Crisis intervention with abusing families: short-term cognitive coercive group therapy using goal attainment scaling. In: Roberts AR, ed. *Crisis intervention handbook*. Belmont, CA: Wadsworth; 1990:153-172.
38. Straus MA, Kantor GK. Corporal punishment by parents: a risk factor in the epidemiology of depression, suicide, alcohol abuse, child abuse, and wife beating. *Adolescence*. 1994;29(115):543-561.
39. Heaton PA. The pattern of burn injuries in childhood. *N Z Med J*. 1989;102(879):584-586.
40. Reference removed while revising.
41. Laloe V. Patterns of deliberate self-burning in various parts of the world. A review. *Burns*. 2004;30(3):207-215.
42. Grossoehme DH, Springer LS. Images of God used by self-injurious burn patients. *Burns*. 1999;25(5):443-448.
43. Bostic RA. Self-immolation: a survey of the last decade. *Life Threat Behav*. 1973;3:66-73.
44. Adityanjee DR. Jauhar: mass suicide by self-immolation in Waco, Texas. *J Nerv Ment Dis*. 1994;182(12):727-728.
45. Kumar V. Burnt wives – a study of suicides. *Burns*. 2003;29(1):31-35.
46. Stoddard FJ, Pahlavan K, Cahners SS. Suicide attempted by self-immolation during adolescence. Literature Review, case reports, and personality precursors. *Adolesc Psychiatry*. 1985;12:251-265.
47. Andreasen NC, Noyes R Jr. Suicide attempted by self-immolation. *Am J Psychiatry*. 1975;132(5):554-556.
48. Cameron DR, Pegg SP, Muller M. Self-inflicted burns. *Burns*. 1997;23(96):519-521.
49. Daniels SM, Fenley JD, Powers PS, et al. Self-inflicted burns: a ten-year retrospective study. *J Burn Care Rehabil*. 1991;12(2):144-147.
50. Persley GV, Pegg SP. Burn injuries related to suicide. *Med J Aust*. 1981;1(3):134.
51. Scully JH, Hutcherson R. Suicide by burning. *Am J Psychiatry*. 1983;140(7):905-906.
52. Antonowicz JL, Taylor LH, Showalter PE, et al. Profiles and treatment of attempted suicide by self-immolation. *Gen Hosp Psychiatry*. 1997;19(1):51-55.
53. Wallace KL, Pegg SP. Self-inflicted burn injuries: an 11 year retrospective study. *J Burn Care Rehabil*. 1999;20(2):191-194.
54. Forhuoh SN. The mechanism, intensity of treatment and outcomes of hospitalized burns; issues for prevention. *J Burn Care Rehabil*. 1998;19(5):456-460.
55. Ahmadi A. Suicide by self-immolation: comprehensive overview, experiences and suggestions. *J Burn Care Res*. 2007;28(1):30-41.
56. Rastegar Lari A, Alagehehbandan R. Epidemiological study of self-inflicted burns in Tehran, Iran. *J Burn Care Rehabil*. 2003;24(1):15-20.
57. Adityanjee DR. Suicide attempts and suicides in India: cross-cultural aspects. *Int J Soc Psychiatry*. 1986;32(2):64-73.
58. Mzezewa S, Jonsson K, Aberg M, et al. Prospective study on the epidemiology of burns in patients admitted to the Harare burn units. *Burns*. 1999;25(6):499-504.
59. Panjeshahin MR, Lari AR, Talei A, et al. Epidemiology and mortality of burns in South West of Iran. *Burns*. 2001;27(3):219-226.
60. DeSouzza DA, Marchesan WG, Greene LJ. Epidemiological data and mortality rate of patients hospitalized with burns in Brazil. *Burns*. 1998;24(5):433-438.

61. Davidson TI, Brown LC. Self-inflicted burns: a 5 year retrospective study. *Burns Incl Therm Inj*. 1985;11(3):157-160.
62. Layton TR, Copeland CE. Burn suicide. *J Burn Care Rehabil*. 1983;4:445-446.
63. Scully JH, Hutcherson R. Suicide by burning. *Am J Psychiatry*. 1983;140(7):905-906.
64. Swenson JR, Dimsdale JE. Substance abuse and attempts at suicide by burning. *Am J Psychiatry*. 1990;147(6):811.
65. Hammond JS, Ward CG, Perira E. Self-inflicted burns. *J Burn Care Rehabil*. 1988;9(2):178-179.
66. Laloe V. Epidemiology and mortality of burns in general hospital of Eastern Sri Lanka. *Burns*. 2002;28(8):778-781.
67. Mabrouk AR, Mahmos Omar AN, Massoud K, et al. Suicide by burns: a tragic end. *Burns*. 1999;25(4):337-339.
68. Thombs BD, Bresnick MG, Magyar-Russell G. Who attempts suicide by burning? An analysis of age patterns of mortality by self-inflicted burning in the United States. *Gen Hosp Psychiatry*. 2007;29(3):244-250.
69. Palmu R, Isometsa E, Suominen K, et al. Self-inflicted burns; An eight year retrospective study in Finland. *Burns*. 2004;30(5):443-447.
70. Pham TN, King JR, Plamieri TL, et al. Predisposing factors for self-inflicted burns. *J Burn Care Rehabil*. 2003;24(4):223-227.
71. Purdue G, Hunt J, Prescott P. Child abuse by burning – an index of suspicion. *J Trauma*. 1988;28(2):221-224.
72. Degraw M, Hicks RA, Lindberg D. Incidence of fractures among children with burns with concern regarding abuse. *Pediatrics*. 2010;125(2):e295-e299.
73. Hudson M, Kaplan R. Clinical response to child abuse. *Pediatr Clin North Am*. 2006;53(1):27-39.
74. Christien C. The evaluation of suspected child physical abuse. *Pediatrics*. 2015;135(5):e1337-e1354.
75. Greenbaum AR, et al. Review Intentional burn injury: an evidence-based, clinical and forensic review. *Burns*. 2004;30:628-642.
76. Section on Radiology; American Academy of Pediatrics. Diagnostic imaging of child abuse. *Pediatrics*. 2009;123(5):1430-1435.
77. Kellogg ND. Evaluation of suspected child physical abuse. *Pediatrics*. 2007;119(6):1232-1241.
78. Reference removed while revising.
79. Kleinman PK, Nimkin K, Spevak MR, et al. Follow-up skeletal surveys in suspected child abuse. *AJR Am J Roentgenol*. 1996;167(4):893-896.
80. Fagen KE, Shalaby-Rana E, Jackson AM. Frequency of skeletal injuries in children with inflicted burns. *Pediatr Radiol*. 2015;45:396.
81. Peck MD, Priolo-Kapel D. Child abuse by burning: a review of the literature and a logarithm for medical investigations. *J Trauma*. 2002;53:1013-1022.
82. Reference removed while revising.
83. Maguirea S, Moynihana S, Mannb M, et al. A systematic review of the features that indicate intentional scalds in Children. *Burns*. 2008;34(8):1072-1081.
84. Toon MH, et al. Children with burn injuries-assessment of trauma, neglect, violence and abuse. *J Inj Violence Res*. 2011;3(2):98-110.
85. Hettiaratchy S, Dziewulski P. Pathophysiology and types of burns. *BMJ*. 2004;328(7453):1427-1429.
86. Kemp AM, Maguire SA, Lumb RC. Contact, cigarette and flame burns in physical abuse: a systematic review. *Child Abuse Rev*. 2014;23:35-47.
87. Faller-Marquardt M, et al. Cigarette burns in forensic medicine. *Forensic Sci Int*. 2008;176(2-3):200-208.
88. Reference removed while revising.
89. Reference removed while revising.

63 Functional Sequelae and Disability Assessment

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Introduction

Advances in acute burn care during the past 25 years in terms of decreased mortality and decreased length of hospital stay have been truly remarkable. Current and historical perspectives on burn mortality can be found in preceding chapters. In almost every burn unit in the United States, the length of stay has decreased from nearly 3 days/% burn to less than 1 day/% burn. The success can be stated simply: patients with larger, more severe burns are surviving.

But if patients with larger and more severe burns are surviving, this has created new problems for patients' quality of life. Although the problems are magnified in massively burned patients, they exist also in smaller burns. These problems are demonstrated in a pediatric burn patient with a 95% total body surface area (TBSA) burn (Fig. 63.1). Cultured keratinocytes were utilized to achieve wound coverage. The child survived; however, when we examined the patient's current and future reconstructive needs, they totaled 33 potential reconstructive procedures. Thus the reconstructive problems are monumental in a child with very few donor sites. With regard to survival, the results of this patient are impressive; however, we must ask the question: "Has the medical expertise in terms of survival progressed past the ability to reconstruct and rehabilitate patients?" Unfortunately the answer is clearly "yes." Are we returning our patients to a society that is not ready financially, psychologically, or socially to accept them? Again, unfortunately, the answer is clearly "yes."[1]

Under Titles II and XVI of the Social Security Act, adult disability is defined as "the inability to engage in any substantial gainful activity, by reason of any medically determinable physical or mental impairment(s) which can be expected to result in death or which has or can be expected to last for a continuous period of not less than 12 months." For children, the definition differs slightly, "a child under the age of 18 will be considered disabled if she or he has a medically determinable physical, mental, or combination of impairments that causes marked and severe functional limitations and that can be expected to cause death or last for a continuous period of not less than 12 months." These guiding principles of functional assessment require a further definition. "Medically determinable impairment" means that the impairment(s) can be demonstrated, witnessed, or otherwise known and described by some third-party means.[2] These may include laboratory tests, physical examination demonstrating signs of the underlying disease process, and disease-specific historical information elicited during the interview. When impairment results from two or more systems, the ratings should be combined according to a combined values chart or its underlying formula. Using the American Medical Association (AMA) formula, the first diagnosis-based impairment is subtracted from a 100% whole person, and each subsequent impairment is subtracted as a percentage of the remaining, or fractional, unimpaired person.[3] Disability ratings can only be performed after a patient has reached maximal medical improvement. This concept is unfortunately both subjective and undefined but retains its utility when applied with equal measures of common sense and medical judgment.

Postburn System-Based Disability Assessment

Description of an alleged impairment should begin before physician introduction. Careful observation of general appearance: how an individual is groomed, enters the building, comports himself while waiting, interacts with clinical staff during check-in, and completes initial paperwork all provide useful, global insight into how his life has been impacted by burn injury and how he has adapted to it. A whole person's impairment depends on disruption of organ system function. For each system, impairment is categorized into five classes: 0 (no impairment), 1 (minimal), 2 (moderate), 3 (severe), and 4 (very severe). Generally, these correspond to function and symptoms, where 0 is no symptoms despite strenuous activity, 1 is symptoms only with strenuous activity, 2 is symptoms with normal activity, 3 is symptoms with minimal activity, and 4 is unabated symptoms. In cases where an objective measure is widely accepted to correlate with experiential symptoms, this objective measure becomes the key factor (e.g., see the section on respiratory function, which uses the results of pulmonary function tests as a key factor).

This classification allows assignment from no impairment to complete impairment of the system being evaluated, which can be expressed as a percentage of whole-person impairment. Within each diagnosis-based impairment class, impairment can be modified up or down based on additional clinical information or supplementary diagnostic tests. These vary somewhat for each condition (for full details please refer to the individual chapters in the most recent edition of the AMA's *Guides to the Evaluation of Permanent Impairment*). The assessment of typical postburn sequelae is described in the following sections.

CONSTITUTIONAL

Body mass, composition, and growth curves in children provide important objective data regarding the overall magnitude of the postburn systemic insult. The weight trend,

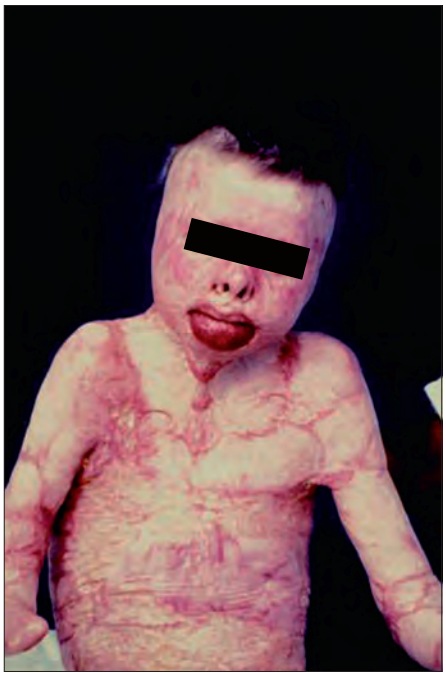

Fig. 63.1 A pediatric burn patient with a 95% total body surface area burn.

particularly compared with a preinjury weight, is helpful in estimating the loss of lean body mass, although confounding by body compositional changes does occur. In general, loss of 10–30% of body mass correlates with increasingly severe manifestations of malnutrition and catabolism, namely impaired wound healing, pressure sores, and pneumonia. Losses approaching 40% of preinjury body mass (in survivors seen for disability assessment) indicate a near-fatal systemic insult of malnutrition combined with postinjury hypermetabolism.

While the gold standard of body compositional analysis is potassium-40 scintillation counting coupled with deuterium oxide dilution measurement of total body water,[4] whole-body dual energy X-ray absorptiometry (DEXA) provides a useful and more readily available surrogate. Whole-body DEXA scans provide bone density measurements of the axial and appendicular skeleton, as well as assessment of peripheral and visceral fat mass, bone mass, and extremity/central lean mass.[5] Bone metabolism[6–10] is markedly disturbed after severe burn injury; accordingly growth arrest is seen in growing (prepubertal) children.[11] This is attributable to stalled endochondral bone formation. Patients are also prone to fracture from trivial trauma such as ground-level falls, and fracture healing is slowed.

SKIN/INTEGUMENT

As the organ most visibly affected by burn injury, photodocumentation of affected areas can provide efficient insight into the magnitude of the injury and the status of the healing process. Scars from healed burn wounds or skin grafts and donor site morbidity are described by TBSA and location. It is also important to note associated venous congestion, tissue edema, chronic wounds, pain, itch, tissue disfigurement, and distortion of adjacent unburned mobile structures (nipple, umbilicus, and/or genitalia) by burn scar contraction. Large burns (>20% TBSA) can result in homeostatic impairment of the skin. Manifestations may include subjective heat intolerance, impaired thermoregulation, and loss of sweat function in the scars, or cold intolerance owing to loss of adipose tissue insulation. The latter is of particular concern after deep or infected burns with fascial excision or other significant adipose tissue débridement in the course of burn care. While a goal of burn care is rapid, durable wound closure, chronic wounds still occur after burn injury. If present, these should be described including size, depth, location, exudate/odor, and status of the healing process/granulation tissue. Previously applied wound therapies should be described. If a wound has been present beyond 3 months, a more detailed assessment of the reasons for failure of healing is warranted (including malnutrition, pressure, infection/colonization, osteomyelitis, loss of sensation, tension, and lack of blood flow). This assessment may include a search for neoplasia (Marjolin's ulcer) and related examination of the draining lymph nodes because nonbasal cell skin cancer (not in remission) is assigned 58% whole-person impairment.[12] The claimant's history is the key factor in classifying nonfacial skin/scar-related impairment, focusing on the impact of the skin-related conditions on an individual's ability to perform activities of daily living. Whole-person impairment resulting from nonface skin disorders can range from 0% to 58%.[12]

FACIAL INJURIES, SCARS, AND EAR/NOSE/THROAT PROBLEMS

Burn scars involving the face can be a significant cause of impairment. Beyond aesthetics, these may include cicatricial microstomia (causing weight loss and malnutrition), loss of facial expression, and nasal deformity/tissue loss with associated airway dysfunction and loss of humidification. Air passage deficits, including nasal injuries and vocal cord paralysis, are rated from 0% to 58% whole-person impairment based on the key factor of degree of dyspnea and interference with daily or work activities.[13] Voice and speech impairment is rated at 0–35% of the whole person, based on the key factors of speech audibility, intelligibility, and functional efficiency of speech in everyday communication.[13] Ear loss, in addition to the aesthetic deficit, can compromise sound localization/lateralization and make it difficult to wear glasses or similar headgear that rests on the ears. Auditory function may be compromised in several ways following burn injury. Significant blast injuries are associated with tympanic membrane (TM) rupture. Middle ear infection, often with TM perforation, may complicate convalescence from severe burns; multidrug-resistant organisms are usually observed, and clearance can require prolonged treatment. Resulting TM scarring may reduce auditory acuity. Several ototoxic medications (especially aminoglycosides and furosemide) are routinely used during critical care of the severely burned patient. The key factor for hearing evaluation is decibel threshold sum audiometry using 500, 1000, 2000, and 3000 Hertz sounds. Whole-person impairment from binaural hearing loss ranges from 0% to 35%, with the latter value reflecting complete hearing

loss.[13] Facial disfigurement is rated separately from overall skin assessment, and the key factor determining classification is the degree of facial anatomical distortion, loss of expression/facial features, and the degree of difficulty experienced by the patient in social settings due to facial disfigurement. Whole-person impairment resulting from facial scars/disfigurement can range from 0% to 45%.

MUSCULOSKELETAL

Burn-related amputations are not infrequent, especially in the setting of electrical injury. If an amputation is present, the requisite description is straightforward, including the level of the amputation, the condition of the stump (note if chronic wound present), any prosthetic used, how well it works for the patient, and specific (work and home) activities that are difficult or require adaptation due to the amputation.

The main cause of musculoskeletal impairment after burn injury is scar contracture across joints. In the acutely injured state, patients typically assume a "position of comfort." Contraction of the burned joint may reduce the area of the wound to heal but at the cost of losing range of motion with scar formation. The use of splinting, exercise, and release with tissue interposition have all been shown to mitigate this problem, but rarely is function completely restored to the preburn state. In describing scar contractures, particularly involving joints, one may note that the resting position is often abnormal. Range of motion, strength, associated chronic wounds or ulcers, and pain/tightness at the scar also provide helpful medical evidence of impairment. The description of specific daily living or work activities that the patient finds difficult due to specific scars/contractures is needed to communicate the experiential severity of impairment.

Prolonged immobilization and excessive use of static splints may also lead to joint fibrosis and impaired range of motion. Heterotopic ossification, generally occurring in patients with burns greater than 30% TBSA, can cause near complete loss of joint mobility.[14] When it occurs, the joint becomes immobilized in the position in which it was maintained. It causes significant pain, and the lost range of motion is generally refractory to surgical intervention and rehabilitation. For example, at the elbow, the ulnar nerve at the cubital tunnel can be affected.

Muscular conditions of systemic import may accompany burn convalescence. Sarcopenia is increasingly diagnosed after critical illness, sepsis, and prolonged immobilization.[15] Rhabdomyolysis and compartment syndromes may lead to the rapid loss of mass of involved muscles. Especially common after electrical injury, these may exacerbate the muscle wasting and skeletal muscle protein catabolism due to the burn injury proper. Loss of lean muscle mass leads to decreased strength and endurance and can contribute to metabolic derangements including altered glucose homeostasis and decreased insulin sensitivity. Muscle bulk can be assessed by the examiner and extremity circumference measurements reported if they appear grossly abnormal. Ultrasound is increasingly utilized to quantitate the degree of sarcopenia (e.g., midfemur vastus lateralis thickness), but its role in routine disability assessment is not yet widely established.[16–19] The key factor for musculoskeletal impairment classification is the diagnosis itself, supplemented with the "functional history," and comprises the extent to which the diagnosis-defined problem interferes with vigorous activity, work, daily living, and basic functioning. It also considers the extent to which another person is required to accomplish these tasks. Because of the complexity in rating nonamputation impairments of the extremities, the reader is advised to obtain and refer to the most recent edition of the *Guides to the Evaluation of Permanent Impairment.*[20]

HAND FUNCTION

Hand function is both uniquely important to daily and work activities and frequently impaired by burn injury and scars. Loss or deformity of digits leads to a variety of deficits. Complete loss (amputation) results in the following impairment ratings:

- Ring/small finger: 10% of hand, 9% of upper extremity, and 5% whole-person impairment
- Index/middle finger: 20% of hand, 18% of upper extremity, and 11% whole-person impairment
- Thumb: 40% of hand, 36% of upper extremity, and 22% whole-person impairment
- Hand: 90% of upper extremity and 54% whole-person impairment
- Entire upper extremity: 60% whole-person impairment.[20]

Flexion contracture or boutonniere deformity digit(s) leads to impairment in dexterous movements, and extension contracture compromises grip strength and carrying tasks. Scoring is more complex for partial losses and functional impairments but may not exceed the impairment rating for amputation.[20] Due to the hand's complex tissues and their response to splinting, immobilization, and vasoactive medications it is not uncommon for muscle, tendon, and bone/joint involvement to be demonstrable in addition to the obvious skin/soft tissue cicatrization.

In the lower extremity, amputation results in the following impairment ratings:

- Lesser toe: 3% of foot/ankle, 2% of lower extremity, and 1% whole-person impairment
- Great toe: 17% of foot/ankle, 12% of lower extremity, and 5% whole-person impairment
- Foot/ankle: 70% of lower extremity, and 28% whole-person impairment
- Entire lower extremity: 40% whole-person impairment.

For nonamputation impairment at the upper and lower extremities, if none of the diagnosis-based grids reflects the patient's impairment (as is often the case with significant musculoskeletal compromise after burn injury), then impairment can be rated according to range of motion testing. A comprehensive description of this process is beyond the scope of this chapter, but can be found in Rondinelli et al.[21]

An assessment of gait and balance (i.e., heel/toe, tandem gait, and Romberg tests) provides insight into the coordinated function of the nervous and musculoskeletal systems. Impairment of the ability to respond quickly to changing conditions (general weakness, loss of balance, or

unsteadiness) can impair the ability to safely function in physically demanding occupations. Exertional tolerance, although subjectively reported, can be assessed by asking how far the patient can walk without resting or how many flights of stairs can be climbed without stopping. The reason for exertion limitation (e.g., shortness of breath, musculoskeletal cramps, general weakness, joint pain, chest pain, back discomfort, or other) often provides important insight into the dominant underlying disease state.

NEUROLOGICAL

Both focal and global nervous system problems are possible after burn injuries. Traumatic brain or spinal injury may be seen in high-energy automobile crashes, blast injuries, and escape-related injuries. Burns sustained in closed-space fires are frequently accompanied by the inhalation of a cocktail of toxins and combustion byproducts. These cause inhalation injury (discussed later) but carbon monoxide, cyanide, and other metabolic poisons may also cause global hypoxic insults (classically the hippocampi are most vulnerable to hypoxia, with impairment in learning and memory). Cerebral edema often accompanies carbon monoxide poisoning or hypoxic insult, and herniation syndromes may lead to neurological devastation. Cardiac arrest may also accompany severe burn injury (usually hypovolemic) with hallmark cerebral watershed infarcts between the distributions of the anterior, middle, and posterior cerebral arteries. Hypoxic and ischemic insults may lead to alterations in consciousness and awareness. Impairment is rated 0–100% of the whole person, with continuous impairments (e.g., nonepilepsy) rated higher, from 31% to 100% of the whole person.[22] Alternatively, if consciousness and awareness remain intact, alterations in mental status, cognition, and highest integrative function may be present after traumatic injury or severe central nervous system (CNS) insult. Resulting impairment is rated from 0% to 50% of the whole person, based on mental status exam and interference with activities of daily living, occasionally supplemented with neuropsychiatric testing. Individuals who have suffered an electrical injury may develop a condition characterized by progressive degeneration of fine and gross motor coordination. Resultant complications can range from inability to perform work-related tasks safely to an inability to perform the routine activities of daily living. It is a disease process that takes place over a significant period of time and may worsen after an individual has returned to work. It can be particularly vexing to differentiate this entity from the malingerer, and the objective neurological exam findings must be cataloged in each case. A polyneuropathy of critical illness is also described and should be considered when prolonged ICU care was needed for recovery. A prolonged systemic inflammatory response syndrome, hyperglycemia, corticosteroids (which are endogenously elevated for >12 months after burn injuries), and the use of neuromuscular blocking agents (paralytics) have variously been implicated in its pathogenesis.

Focal peripheral nerve lesions are also possible owing to postburn compartment syndromes. In the upper extremity the ulnar nerve is particularly vulnerable within Guyon's canal and at the cubital tunnel, while the median nerve is vulnerable at the carpal tunnel. If a compartment syndrome is present for 4–6 h without adequate release, irreversible nerve damage may occur anywhere within the affected compartment(s). Fortunately the dire sequelae of contracture and complete defunctionalization of the upper extremity described by Volkman are infrequently encountered owing to rapid escharotomy and fasciotomy of impending compartment syndromes as a routine part of burn center care.[23] The rating of impairment owing to peripheral nerve lesions is based grossly on sensory and motor findings, and the reader is advised to refer to the latest edition of the *Guides to the Evaluation of Permanent Impairment* for both the upper and lower extremities.[20,24]

Characterization of gait, station, balance, sudomotor function, strength, deep tendon reflexes, and sensation (including as needed pain/temperature, light touch/two-point discrimination, and vibratory/joint position sense) deficits should be done; a detailed neuro exam may be supplemented with electromyography or nerve conduction studies if needed.

CARDIOVASCULAR/METABOLIC

Postburn hypermetabolism has been well described in multiple preceding chapters. Impairment may result from decreased exercise capacity (VO_2 peak), in turn related to increased basal energy expenditure. Tachycardia and elevated resting energy expenditure frequently persist for more than 12 months after major burn injury. Although pharmacologic treatment may ameliorate aspects of postburn hypermetabolism, restoration of preinjury metabolism occurs slowly and often incompletely. The stress of major burn injury (and frequently sepsis) may also cause cardiac dysfunction.[25] Significantly elevated catecholamine levels and a chronic high-output state contribute to myocardial remodeling; a depressed ejection fraction, myocardial fibrosis, and diastolic dysfunction are increasingly appreciated via echo in survivors of major burn injuries. Objective evidence of the magnitude of a burn survivor's cardiovascular and metabolic derangement are given by pulse, resting respiratory rate (and depth of respiration), blood pressure, jugular venous pressure/waveform as assessed vertically from the sternal angle, presence of hepatojugular reflux, and precordial palpation. Resulting impairment is classified using the New York Heart Association (NYHA) Functional Classification of Cardiac Disease. Whole-person impairments range from 0% to 65%, and objective testing, such as echo (ejection fraction and diastolic dysfunction based on left atrial E-A waves) and exercise testing (VO_2 max or METS), are used as the key factors. The exercise test results are categorized corresponding to NYHA functional classes, which provide an objective measure of functional status.[26]

RESPIRATORY

Burns that occur in an enclosed space, such as a building structure, often result in some form of inhalation injury to the respiratory system. Impairment may be limited to a temporary need for ventilator support or extend to permanent respiratory disease. Chronic and recurrent respiratory infections and pulmonary insufficiency may limit an individual's ability to perform his or her previous work,

especially when toxic chemicals or dust are present in the workplace. Exposure to irritating gases can also worsen preexisting asthma or result in irritant-induced asthma. Although this form of reactive airway disease usually resolves with time, some individuals may have persistent respiratory impairment that may also require a change in vocation in order to avoid continued exposure to irritants and exacerbation of symptoms.

Furthermore, patients with severe inhalation injuries may require a tracheostomy long after the burn has healed. Closure of the stoma is often delayed due to chronic airway complications or need for future reconstructive surgeries. Tracheal stenosis is not an infrequent complication of tracheostomy and causes increased work of breathing that is exacerbated with exertion and accompanied by stridor. Burns/scars of the trunk and chest wall, especially if circumferential, can impair chest wall mobility resulting in dyspnea and related symptoms. An assessment of chest wall motion, breath sounds,[27] adventitious sounds,[28] stridor, inspiratory/expiratory time and flow,[29] clubbing/cyanosis, and pulse oximetry provide noninvasive medical evidence of pulmonary function. However, the classification of impairment related to pulmonary problems is primarily through pulmonary function tests. These include spirometry, arterial blood gas analysis, carbon monoxide diffusion limit,[30] and exercise testing maximal oxygen uptake (VO_2 max). These tests provide objective descriptions of a patient's respiratory problem(s) if correctly performed and are the key factors determining impairment class.[31] Pulmonary impairment ranges from 0% to 65% whole-person impairment.

EYES/VISION

Chapter 43 covers burn-related eye pathology in detail. The principal visual problems seen after burn are corneal ulcer/scar (after ocular surface infection/exposure), cataract (after electrical injury), and anterior ischemic optic neuropathy (due to orbital compartment syndrome). The key factors in determining visual impairment are distance visual acuity and visual fields. While diagnostic eye care is more concerned with the vision of each individual eye, binocular vision is more important for functional status. The distance visual acuity of each eye and binocular vision is converted into a visual acuity score. The functional acuity score is three times the binocular visual acuity score, plus the right and left visual acuity scores divided by 5. Thus the score is weighted 60% binocular, and 20% for each individual eye. A similar adjustment is made for visual field defects if present. These scores are used to calculate visual system impairment, which can be converted into whole-person impairment ranging from 0% to 85%.[32]

RENAL/GENITOURINARY

Renal failure and genital/perineal burns constitute a major burn-related impairment. Whole-person impairment resulting from kidney disease ranges from 0% to 75% based on frequency/severity of symptoms and need for dialysis. Penile, scrotal, and testicular impairments are each rated separately, although each can comprise 0–15% whole-person impairment. The key factors are sexual function for penile impairment and physical exam findings for testes and scrotum (separately). Physical findings are the key factor for vulvar and vaginal impairment, which ranges from 0% to 20% of the whole person.[33] Unique to burn convalescence, severe scarring of the perineum, buttocks, or gluteal cleft may impair sitting, voiding of urine and stool, and hygiene.

GASTROINTESTINAL

The digestive system is not usually a problem except in those individuals who have had superior mesenteric artery syndrome, cholecystitis, pancreatitis, or peptic ulcer disease during the acute admission. The postdischarge clinical course of these individuals is unpredictable. Upper GI impairment (including esophageal problems, peptic ulcer, and pancreatitis) ranges from 0% to 60% of the whole person, considering frequency and severity of symptoms and need/frequency of treatment. Weight loss below ideal body weight is an important consideration in more severe impairments.[34]

ENDOCRINE

Burn convalescence is complicated by a hyperadrenergic state characterized by elevated catecholamine levels and cortisol. The pathophysiology is described in Chapter 23, along with numerous references. Whole-person impairment from adrenal cortex disorders ranges from 0% to 20% based on signs, symptoms, biochemical abnormalities, and burden of treatment. Although no therapies are currently standard for postburn hypercortisolism (best assessed by 24-hour urinary cortisol), the physical stigmata of moon facies, peripheral muscle wasting, central obesity, and lipodystrophy are familiar to the burn surgeon. Adrenal medullary excess is assessed separately from the adrenal cortex. The postburn alterations in adrenal medulla function and resulting catecholamine excess are also covered in Chapter 23, and numerous references documenting the extent/duration of catecholamine excess postburn are also given. Whole-person impairment resulting from adrenal medulla hypersecretion ranges from 0% to 60%, with the key factor being the presence of symptoms and efficacy of blocking agents. After burn injury, the nonselective β-blocker propranolol is usually able to reduce tachycardia, although supranormal doses (up to 4 mg/kg per dose) may be necessary. Symptoms of catecholamine excess after major burn injury tend to be moderate to severe and may last for several years postburn injury. Stress-induced diabetes is seen after severe burn injury, although the observed elevations in glycosylated hemoglobin are usually mild to moderate. Biochemical evidence includes fasting glucose, insulin levels, and glucose tolerance testing. Impairment from diabetes ranges from 0% to 28% of the whole person, and the rating uses severity and complexity of the required treatment as the key factor. Central hypogonadism has also been described in burned men,[35] and the role of androgen deficiency/replacement during burn recovery is an area of active investigation. Impairment resulting from states of gonadal hormone deficiency or excess is classified according to the key factors of biochemical evidence, physical symptoms, and impact on fertility. Whole-person impairment from gonadal disorders ranges from 0% to 15%.

HEMATOLOGICAL AND LYMPHATIC

Anemia frequently accompanies burn injuries and is of multifactorial etiology. The reader is referred to Chapter 22 for further descriptions of the related pathophysiology. Impairment resulting from anemia is classified according to exertional symptoms experienced by the patient and frequency of need for transfusions or other therapies. Anemia can cause whole-person impairment ranging from 0% to 75%, although the problems typical of burn convalescence are generally in the 0–15% range.[36] Postburn immunosuppression is also discussed in the above-referenced chapter. Although the magnitude of immune suppression is an important determinant of survival,[37] it tends to be self-limiting, with resolution occurring concurrently with wound closure. Significant blood-borne infections (hepatitis, human immunodeficiency virus, cytomegalovirus, and others) do occasionally complicate burn convalescence owing to significant transfusion and allograft needs in major burns. Trauma/burns are a risk factor for venous thrombosis. Whole-person impairment resulting from thrombotic problems ranges from 0% to 40% and is classed using the frequency and timing of thrombotic events as the key factor.[36] Full-thickness burns, particularly of the lower extremities, will also cause damage to the lymphatic system. Such injured individuals often demonstrate a lack of normal lymphatic drainage, resulting in chronic edema and the development of stasis ulcers. There can be little or no improvement expected posthealing. External support in the form of elastic garments is necessary to help replace the normal activity of the lymphatic system in reabsorption of fluid. These individuals frequently have difficulty in standing for long periods of time or working in a hot and humid environment.

PSYCHOLOGICAL

The psychological impact of burn injury is discussed in Chapter 65. Impairment may result from mental problems predating (and occasionally causing) the burn injury or be related to the injury and treatment. Substance abuse, suicidal ideation, and mood disorders are all common comorbidities in burn patients. They may predispose the patient to risk-prone behaviors, impair the ability to escape injury, or even prompt self-harm such as self-immolation. If present, an understanding of the patient's impairment requires documentation of symptoms and signs, including previous suicide attempts, psychiatric hospitalization, and self-injuries. The time course, frequency, and severity of suicidal ideation, previous traumatic injuries, and substance use should be detailed. Flat or expansive affect, flight-of-ideas, loosened associations, and level of psychomotor activity all comprise signs (medical evidence) that help assess impairment. After burn injury and acute hospitalization, both acute and posttraumatic stress disorders are frequent. An abnormally high level of anxiety is also present, perhaps owing to the prolonged sympathetic hyperactivation that accompanies burn injury. A description of the content, frequency, and intrusiveness of flashbacks and sensation of anxiety is helpful in gauging the patient's burden and level of impairment. Impairment is calculated as the median value of scores obtained from the global assessment of function, brief psychological rating scale, and the psychiatric impairment rating scale. Whole-person impairment from mental and behavioral disorders ranges from 0% to 50%.[38]

OVERALL QUALITY OF LIFE

Survey instruments have been constructed in an attempt to measure quality of life and subjective disability.[39] Of these, the World Health Disability Assessment Scale II measures generic function and is useful for comparison across disease states. The Burn-Specific Health Scale-Brief is, as the name suggests, constructed to capture the specific difficulties experienced by burn survivors and is useful in comparing within a population of burn survivors. In a cohort of 50 large pediatric burns, greater TBSA, male sex, increasing age at burn, burn after school entry, and survivors transitioning to adulthood were all associated with lower quality of life using both of these scales.[40] From 1994 to 2014, the Burn Model System Database (established by the National Institute on Disability, Independent Living, and Rehabilitation Research) has enrolled more than 2000 children and almost 3500 adults. More than 33 survey instruments have been administered within this population to better understand and quantitate the experience of the burn survivor. In 2016, publications resulting from this endeavor were comprehensively reviewed.[41] While these demonstrate progress toward quantitation and understanding of postburn quality of life, as suggested at the start of this chapter, these measurements have not been optimized and accepted as routine standards in clinical burn follow-up. As the use of these scales is mainstreamed, it may be instructive to compare experiential patient quality of life with whole-person impairment ratings.

Complete references available online at
www.expertconsult.inkling.com

References

1. Warden GD. Burn patients: coming of age? The 1993 Presidential Address to the American Burn Association. *J Burn Care Rehabil*. 1993;14(6):581-588.
2. Administration SS Consultative examinations: a guide for health professionals. US Government; 2014.
3. Rondinelli RD, Katz RT, Mayer TG, et al. *Guides to the Evaluation of Permanent Impairment*. 6th ed. Chicago: American Medical Association; 2008:604-606.
4. Moore FD. *Metabolic Care of the Surgical Patient*. Philadelphia: Saunders; 1959.
5. Branski LK, Norbury WB, Herndon DN, et al. Measurement of body composition in burned children: is there a gold standard? *JPEN J Parenter Enteral Nutr*. 2010;34(1):55-63.
6. Przkora R, Herndon DN, Sherrard DJ, Chinkes DL, Klein GL. Pamidronate preserves bone mass for at least 2 years following acute administration for pediatric burn injury. *Bone*. 2007;41(2):297-302.
7. Klein GL, Herndon DN, Rutan TC, et al. Bone disease in burn patients. *J Bone Miner Res*. 1993;8(3):337-345.
8. Klein GL, Herndon DN, Goodman WG, et al. Histomorphometric and biochemical characterization of bone following acute severe burns in children. *Bone*. 1995;17(5):455-460.
9. Klein GL, Herndon DN, Langman CB, et al. Long-term reduction in bone mass after severe burn injury in children. *J Pediatr*. 1995;126(2):252-256.
10. Klein GL, Wolf SE, Goodman WG, Phillips WA, Herndon DN. The management of acute bone loss in severe catabolism due to burn injury. *Horm Res*. 1997;48(suppl 5):83-87.
11. Herndon DN, Voigt CD, Capek KD, et al. Reversal of growth arrest with the combined administration of oxandrolone and propranolol in severely burned children. *Ann Surg*. 2016;264(3):421-428.
12. Rondinelli RD, Katz RT, Mayer TG, et al. *Guides to the Evaluation of Permanent Impairment*. 6th ed. Chicago: American Medical Association; 2008:159-182.
13. Rondinelli RD, Katz RT, Mayer TG, et al. *Guides to the Evaluation of Permanent Impairment*. 6th ed. Chicago: American Medical Association; 2008:247-279.
14. Levi B, Jayakumar P, Giladi A, et al. Risk factors for the development of heterotopic ossification in seriously burned adults: a National Institute on Disability, Independent Living and Rehabilitation Research burn model system database analysis. *J Trauma Acute Care Surg*. 2015;79(5):870-876.
15. Mueller N, Murthy S, Tainter CR, et al. Can sarcopenia quantified by ultrasound of the rectus femoris muscle predict adverse outcome of surgical intensive care unit patients as well as frailty? A prospective, observational cohort study. *Ann Surg*. 2016;264(6):1116-1124.
16. Heckmatt JZ, Pier N, Dubowitz V. Measurement of quadriceps muscle thickness and subcutaneous tissue thickness in normal children by real-time ultrasound imaging. *J Clin Ultrasound*. 1988;16(3):171-176.
17. Paris MT, Mourtzakis M, Day A, et al. Validation of bedside ultrasound of muscle layer thickness of the quadriceps in the critically ill patient (VALIDUM Study): a prospective multicenter study. *JPEN J Parenter Enteral Nutr*. 2016;41(2):171-180.
18. Takai Y, Ohta M, Akagi R, et al. Applicability of ultrasound muscle thickness measurements for predicting fat-free mass in elderly population. *J Nutr Health Aging*. 2014;18(6):579-585.
19. Abe T, Loenneke JP, Thiebaud RS. Morphological and functional relationships with ultrasound measured muscle thickness of the lower extremity: a brief review. *Ultrasound*. 2015;23(3):166-173.
20. Rondinelli RD, Katz RT, Mayer TG, et al. *Guides to the Evaluation of Permanent Impairment*. 6th ed. Chicago: American Medical Association; 2008:408-492.
21. Rondinelli RD, Katz RT, Mayer TG, et al. *Guides to the Evaluation of Permanent Impairment*. 6th ed. Chicago: American Medical Association; 2008.
22. Rondinelli RD, Katz RT, Mayer TG, et al. *Guides to the Evaluation of Permanent Impairment*. 6th ed. Chicago: American Medical Association; 2008:346-371.
23. Chandraprakasam T, Kumar RA. Acute compartment syndrome of forearm and hand. *Indian J Plast Surg*. 2011;44(2):212-218.
24. Rondinelli RD, Katz RT, Mayer TG, et al. *Guides to the Evaluation of Permanent Impairment*. 6th ed. Chicago: American Medical Association; 2008:493-556.
25. Guillory AN, Clayton RP, Herndon DN, Finnerty CC. Cardiovascular dysfunction following burn injury: what we have learned from rat and mouse models. *Int J Mol Sci*. 2016;17(1).
26. Rondinelli RD, Katz RT, Mayer TG, et al. *Guides to the Evaluation of Permanent Impairment*. 6th ed. Chicago: American Medical Association; 2008:72-101.
27. Forgacs P, Nathoo AR, Richardson HD. Breath sounds. *Thorax*. 1971;26(3):288-295.
28. Forgacs P. The functional basis of pulmonary sounds. *Chest*. 1978;73(3):399-405.
29. Forgacs P. Lung sounds. *Br J Dis Chest*. 1969;63(1):1-12.
30. Hughes JM, Bates DV. Historical review: the carbon monoxide diffusing capacity (DLCO) and its membrane (DM) and red cell (Theta.Vc) components. *Respir Physiol Neurobiol*. 2003;138(2-3):115-142.
31. Rondinelli RD, Katz RT, Mayer TG, et al. *Guides to the Evaluation of Permanent Impairment*. 6th ed. Chicago: American Medical Association; 2008:77-99.
32. Rondinelli RD, Katz RT, Mayer TG, et al. *Guides to the Evaluation of Permanent Impairment*. 6th ed. Chicago: American Medical Association; 2008:281-319.
33. Rondinelli RD, Katz RT, Mayer TG, et al. *Guides to the Evaluation of Permanent Impairment*. 6th ed. Chicago: American Medical Association; 2008:129-158.
34. Rondinelli RD, Katz RT, Mayer TG, et al. *Guides to the Evaluation of Permanent Impairment*. 6th ed. Chicago: American Medical Association; 2008:101-128.
35. Plymate SR, Vaughan GM, Mason AD, Pruitt BA. Central hypogonadism in burned men. *Horm Res*. 1987;27(3):152-158.
36. Rondinelli RD, Katz RT, Mayer TG, et al. *Guides to the Evaluation of Permanent Impairment*. 6th ed. Chicago: American Medical Association; 2008:183-212.
37. Warden GD, Mason AD Jr, Pruitt BA Jr. Evaluation of leukocyte chemotaxis in vitro in thermally injured patients. *J Clin Invest*. 1974;54(4):1001-1004.
38. Rondinelli RD, Katz RT, Mayer TG, et al. *Guides to the Evaluation of Permanent Impairment*. 6th ed. Chicago: American Medical Association; 2008:372-382.
39. Klein MB, Lezotte DL, Fauerbach JA, et al. The National Institute on Disability and Rehabilitation Research burn model system database: a tool for the multicenter study of the outcome of burn injury. *J Burn Care Res*. 2007;28(1):84-96.
40. Murphy ME, Holzer CE 3rd, Richardson LM, et al. Quality of life of young adult survivors of pediatric burns using World Health Organization Disability Assessment Scale II and Burn Specific Health Scale-Brief: a comparison. *J Burn Care Res*. 2015;36(5):521-533.
41. Goverman J, Mathews K, Holavanahalli RK, et al. The National Institute on Disability, Independent Living, and Rehabilitation Research Burn Model System: twenty years of contributions to clinical service and research. *J Burn Care Res*. 2017;38(1):e240-e253.

64 Management of Pain and Other Discomforts in Burned Patients

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Introduction

The words "burn injury" trigger, for almost anyone, immediate and vivid images of excruciating pain and suffering. Children are conditioned from early childhood that burn injuries are painful and can cause great harm. At the time of the first edition of this book there was still debate about the importance of pain management in the burn survivor. Many practitioners believed that the treatment of burn injury pain, especially in children, was more dangerous than leaving it untreated. The past 20 years has shown that children's pain can be effectively and safely managed with significant benefits in recovery and long-term outcomes.[1,2] There are now data showing that even premature babies have significant pain that needs to be addressed.[3]

A series of therapeutic approaches have been developed to approach both pain and its associated anxiety. There is justified concern about opiate and benzodiazepine dependence and abuse, but this is offset by the importance of treating pain aggressively. In addition to pain and anxiety, practitioners are now focused on pruritus as well. Scales have been developed to measure pain, anxiety, and itch separately.

Pathology of a Burn Injury Pain and Pain-Generating Mechanisms

Pain is the most frequent complaint of burn-injured patients.[4] Injury-induced nociceptive responses can be described as hyperalgesia and allodynia. Hyperalgesia is increased nociceptive response to painful stimulus (e.g., pinprick). Allodynia is exaggerated pain to nonpainful stimuli (e.g., touch). All burn injuries are painful. Even first-degree burns can produce at least mild pain and discomfort, especially when something such as clothing rubs against the burned area (allodynia). Even the slightest change in air currents moving past the injured/exposed skin can cause a patient to experience excruciating pain. The loss of protective covering of the epidermis and the associated inflammation leads to sensitization of the nerve endings. Studies of humans and monkeys confirm that burn injuries not only make the injured area but also the surrounding tissue more painful.[5–7] Second-degree, moderate to deep partial-thickness burns result in variable amounts of pain depending on the amount of destruction to the dermis. In addition, as the inflammatory response progresses, the release of cytokines and chemokines increases the pain not only in the burned area but also in the surrounding tissues by the activated peripheral circulating macrophages and the central nervous system microglia.[5]

Areas of deeper partial-thickness and full-thickness burns may display a confusing pattern of pain over the first few days. These areas may show little or no response to sharp stimuli such as a pinprick initially, yet a patient may complain of deep, severe pain related to the inflammatory response. In a full-thickness burn, the dermis is completely destroyed along with its rich network of nerve endings. This leads to an initial response of a completely anesthetic wound when a sharp stimulus (e.g., pin prick) is present on the dead skin. Over time, patients begin to complain of a dull or intense pain during manipulation of these areas (e.g., dressing changes). Once the devitalized tissue (i.e., eschar) sloughs and is replaced by granulation tissue, the patient again experiences the sensation of sharp pain to noxious stimuli. Thus it appears that, in all types of burn injury pain, there is an inflammatory and neuropathic component both resulting from injury to tissues and to sensory nerves endings. As to which of these (inflammatory vs. neuropathic) components contributes more to the nociceptive responses is still not understood.

Additional Factors Contributing to Pain Generation

Ptacek et al.[8] found that although there was a general trend for pain to decrease over time in patients with small or superficial burns, there was also considerable variability in the course of pain among adult survivors after major burns. Persons with large burns showed a higher affective (suffering) component to the pain, but there was no reliable correlation between the pain scores and burn size. Quite in contrast to that report, studies in children have shown that the intensity of pain increased as the burn size increased.[9] Whether this is related to the increased anxiety of children is unclear. Other reports confirm that pain intensity at rest was correlated with psycho-affective responses such as anxiety, depression, anorexia, fatigue, and helplessness.[10] Choinière et al.[11] also noted that pain at rest was significantly and positively related to levels of anxiety or depression (i.e., with elevated anxiety or depression, pain scores at rest increased). Depression also plays a similar role in the enhancement of pain.[12] Pain leads to depression, and depression increases the perception of pain.[13,14] Confusion therefore can occur concerning the amount of pain expressed by burn patients on the role played by psychiatric disorders that are concomitantly present in any form of

injury versus injury-induced biochemical changes at the local and central nervous system level. Treatment of anxiety with benzodiazepines may have either beneficial or paradoxical effects on anxiety and pain.[15] Clinical observation and rodent studies indicate that although benzodiazepines acutely potentiate the analgesic effects of other opiates, the prolonged administration of benzodiazepines together with opiates can induce tolerance or even hyperalgesia.

Another factor that contributes to pain is procedures. Baseline pain (pain at rest) is invariably present in most burn patients. This baseline increased nociception can be aggravated by procedural pain (hyperalgesia) induced by dressings changes, physical therapy, and other procedures. Procedural pain is the most intense burn injury pain that is undertreated.[16,17] Thus the anticipation of pain related to procedures (e.g., wound care) that occurs at least once daily can increase a patient's perception of pain, which in turn can lead to greater anxiety. This reaction may explain some findings that suggest that pain increases over time in burned patients.[18–20] There could also be another component—namely, tolerance to analgesics and/or opiate-induced hyperalgesia (see later discussion)—that explains the increase in pain over time.[7] Finally, exaggerated adrenergic stimulation with release of catecholamines is part of the pain and stress response. Stress of any form has paradoxical effects on pain, initially causing stress-induced analgesia and then later exacerbation of pain, a feature known as "stress-induced hyperalgesia.[21–23] Thus the stress of burn injury, with its concomitant release of catecholamines and adrenoceptor stimulation, leads to exaggeration of pain.[21–23]

Pain as a Function of the Healing Process

As deep dermal or full-thickness burn wounds heal, either by primary intention from excision and grafting or by secondary intention through granulation tissue and scar formation, the injured neural tissue is reorganized.[17] Reflex neural function returns to grafted burn skin approximately 5–6 weeks after the burn has been covered by autografted skin.[20] Active vasodilatation, vasoconstriction, and pain sensation all return at this time.[24] These functions also return to the burn wound that heals through scar formation but may take up to 6 months for complete neural reorganization. This could be an additional basis of neuropathic pain at the burn wound site and in surrounding tissue. Despite the healing of tissues, the memory of any form of trauma-induced pain lasts for a prolonged period. In other words, subsequent (e.g., reconstructive) surgery on this area leads to exaggerated nociceptive responses sooner and longer lasting than that seen at initial injury.[32] This memory seems to be maintained by innate immune cells (macrophages and microglia), which seem to be already primed because of previous injury and become activated sooner with release of inflammatory cytokines and chemokines.[26]

Although rare, causalgia, dysesthesia, and phantom pain syndrome can sometimes develop in healing skin. Phantom limb sensation and pain are more common following amputation, which is often associated with large burn injury or electrical injury.[267] The incidence of these chronic pain syndromes seems to be related to the healing process. Burns that have been excised and grafted on a clean and uniform vascular bed rarely develop one of these chronic pain syndromes. Wounds that heal by granulation and scar formation seem to be more apt to develop a chronic pain problem because of the continued stimulation of nerve fibers in the area with enhancement of the hyperalgesia. Skin biopsies of granulation tissue have clearly shown neuronal tissue entrapment.[20] Pain in scar tissue subsides over time as the scar tissue matures.

Tolerance to Opiates and Opiate-Induced Hyperalgesia

Opioids are highly effective analgesics and are the mainstay for treatment of moderate to severe burn pain.[24] Continued use of opiates can lead to burned patients developing tolerance to their analgesic effects. There is a pharmacokinetic component to the tolerance to opiates: the clearance and the volume of distribution of many drugs are increased over time, resulting in lower therapeutic concentrations.[27] The protein binding of opiates is also increased in burned patients, resulting in a lower free fraction available to act on target μ-opioid receptor. The most important reason for the tolerance is indeed related to μ-opioid receptor changes induced by the opiates.

Opiates signal their beneficial analgesic effects by intercellular coupling to G-proteins. Just like any other G-protein coupled receptor (e.g., adrenoceptor), the repetitive administration of an agonist (e.g., epinephrine or opiate to adrenoceptor or opiate, respectively) leads to desensitization of the receptor in which the receptor responses are attenuated with each subsequent administration.[28] The attenuated response is related to phosphorylation and not to down-regulation of receptor. The continued administration of opiates will, with time, result in down-regulation of the opiate receptor number.

Both the desensitization (phosphorylation) and down-regulation of opiate receptors lead to tolerance to opiates. Recent studies indicate that continued administration of opiates also induces increased nociceptive behaviors (hyperalgesia and allodynia: a.k.a. opiate-induced hyperalgesia [OIH]).[17] Tolerance can be overcome by increasing the doses of the opiates, but OIH is made worse by increasing opioid administration. Studies in burn patients confirm OIH when pre- and intraoperative use of opiates resulted in worse postoperative pain.[28] Opiates, similar to bacterial peptides, lead to activation of innate immune responses (activation of macrophages and microglia) with release of inflammatory cytokines and chemokines. Attenuation of microglial activation has been shown to decrease OIH, with improved control of pain.[26]

Measurement of Pain in Burned Patients

Although pain cannot be measured directly, it can be quantified by using one of the standardized tools described here. Using reliable and valid tools allows us to gauge the effectiveness of our treatment for any one patient. Assessing pain on a scheduled basis and using the same tool for each

assessment gives us information about how pain is experienced by a single patient throughout burn treatment; we can note patterns that emerge and schedule medications accordingly. Furthermore standardized tools allow us to compare the pain management of one patient with another, as well as of one burn unit pain management regime with that of other burn units in order to determine the effectiveness of protocols for pain management. Another important reason for assessing pain regularly and in a standardized way is that it communicates to the patient that we believe he or she has pain and that we are trying to do something about it. This communication reassures the patient, thereby reducing the likelihood that the patient will escalate pain, anxiety, and other related behaviors.

Gracely[3] reviewed a number of objective modalities for the measurement of experimental pain. He notes that "pain arises from and is modulated by, a number of mechanisms. These mechanisms are not static but change over time and involve all levels of the central nervous system. In an attempt to understand these mechanisms, several experimental tools have been employed to further elucidate the exact pathways involved in pain transmission and to better understand the therapies used to relieve pain."

Some of these tools are cortical evoked potentials, functional brain imaging (positive emission tomography [PET]), functional magnetic resonance imaging (fMRI), source analysis of evoked activity, and electrophysiological recording from the human brain. As noted by Gracely, comparing these measures with verbal judgments of pain magnitude validates these physiologic measures: "This implicitly elevates subjective judgment to the level of a validation standard."[3] Clinical measurements of pain must continue to rely on standard subjective measures. A tool to use in the clinical setting must be quick and easy to use and useful for frequently repeated assessments.

A major concern in the clinical setting is the use of a consistent pain measurement tool before and 1–2 hours after the administration of a pain-relieving medication. For procedural pain management, the same tool should be used to measure pain at the beginning of a procedure, during the procedure, and post-procedure in order to measure the effectiveness of the pain management regimen used for procedural pain.

PAIN MEASUREMENT TECHNIQUES FOR ADULT BURNED PATIENTS

A variety of pain measurement techniques have been used with adult burned patients. The more common measures include adjective scales (Table 64.1), numeric scales (i.e., rating pain on a scale of 0–5, 0–10, or 0–100), and visual analog scales (Fig. 64.1). Each of these scales measures the sensory component of a patient's pain. Adjective scales and numeric scales are quick and easy to administer because they do not require a visual representation of the scale. The visual analog scale requires a visual representation of the scale to be presented to a patient. Patients must mark or point to the place on the scale that represents their level of pain. This presents a problem for a patient whose hands are burned, so some investigators have used a technique of sliding a line or color strip along the scale with instructions to a patient to direct the movement of the slide, stopping at the point representative of the patient's pain. The visual analog scale has been used in a number of studies with a variety of patient samples and has been shown to be a valid method of measuring the sensory component of a patient's pain. The demonstrated validity of the scale allows for comparisons of visual analog pain assessments between studies with different patient samples. However the visual analog scale is not interchangeable with the graphic numeric rating scale.[29]

Table 64.1 Adjective Scales in English and Spanish.

0	No pain	0	Nada de color
1	Slight pain	1	Dolor leve (ligero)
2	Moderate pain	2	Dolor moderado
3	Severe pain	3	Dolor severo

Fig. 64.1 Visual analog scale (VAS) for children to rate their levels of pain. (From the Varno/Thompson Pediatric Pain Questionnaire. With permission from the American Society for Clinical Pharmacology and Therapeutics.)

Motivational-affective and cognitive-evaluative components of pain are most frequently measured using the McGill Pain Questionnaire (MPQ).[30] The MPQ consists of 20 sets of adjectives that describe all three components of pain: sensory, affective, and evaluative. Qualitative profiles and quantitative scores for each dimension as well as a total pain score can be derived from the selected adjectives. The MPQ has been translated into several languages and has been shown to be a reliable and valid measurement tool. Since it takes 10–20 minutes to administer, it may not be as useful for frequent, repeated measurements. Many studies have employed this measurement on a daily basis to measure either overall or resting pain. Gordon et al.[31] in a prospective multicenter study, asked 40 adult burned patients to rate their pain on four scales. These scales were a visual analog scale, an analog chromatic scale,[32] an adjective scale, and a faces scale.[33] At the end of the study patients were asked to choose their preferred scale. Patients preferred the faces and analog chromatic scales. Although further research is needed to validate these findings, the preference of patients is another variable to be considered.

PAIN MEASUREMENT TECHNIQUES FOR PEDIATRIC BURNED PATIENTS

The measurement of children's pain is much more complex than it is for adults, especially for preverbal children. The American Academy of Pediatrics and the American Pain Society issued a joint statement in 2001 that included the recommendation that, in a hospital setting, "ongoing assessment of the presence and severity of pain and the child's response to treatment is essential."[34] The assessment of pain in children has included physiologic measurements, behavioral assessment, and patient reports of pain. The physiologic indicators that have been evaluated are heart rate,[34]

respiratory rate,[35] blood pressure,[35] endocrine changes,[35,36] and changes in Po_2.[37] None of these shows promise as an indicator for measuring pain in sick children because all are affected by a variety of stressors, metabolic changes related to a burn, and medications in addition to pain.

Behavior scales have been devised to measure pain by providing standardized instructions and guidelines for observing behaviors thought to be specific to pain. A number of investigators[38–43] have looked at infants' cries as measurable behaviors that can be observed in order to evaluate pain. Although these studies demonstrate that length of cry, pitch, intensity, and other characteristics of crying may be used to evaluate pain in infants, the analyses of crying are very time-consuming and require elaborate audio equipment. Izard et al.,[44] Craig et al.,[45] and Granau and Craig[42] have attempted to code facial expressions as measures of pain in infants. Their system characterizes nine facial actions involved in the expression of pain, but its use requires videotaping and detailed analyses of an infant's facial movements. Although this method offers excellent research applications, it, like the detailed analyses of crying, is too cumbersome and not appropriate for the clinical setting. On the other hand, the studies do provide clinicians with information about various facial reactions, as categorized by Granau and Craig, which may be helpful in the clinical identification of pain in infants. Other investigators have devised multidimensional scales that include length of cry, facial expressions, and behavioral states in order to measure pain in infants.[46–48] These scales are easier to use and allow an observer to assess pain as either present or absent without further quantification.

Examples of observational scales that allow for quantification and may be used with toddlers and preverbal children are the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)[49] and The Observer Scale.[50] The CHEOPS is a scale of six behaviors, each scored on a numeric range; it yields a total numeric score for pain. This scale has been shown to be valid and to have good interrater reliability. The Observer Scale is another standardized instrument that categorizes overall pain or comfort behaviors on a scale of 1–5. The five categories are laughing, euphoric; happy, contented, playful; calm or asleep; mild-moderate pain—crying, grimacing, restlessness, but can be distracted with toy, food, or parent; and severe pain—crying, screaming, and inconsolable.

Pain during procedures is especially important to assess. In 1997, the FLACC scale was developed for postoperative pain.[51] This has now been applied for pain related to dressing changes on burn wounds. This scale is now documented to reflect patient pain intensity as well as nurse clinical experience.[52]

A burn-specific observational tool was developed by Barone et al. at Shriners Hospitals for Children-Cincinnati.[53] The Observational Pain Assessment Scale (OPAS) is useful in children 0–3 years of age. The scale is depicted in Table 64.2.

Research suggests that simple self-report scales can be used with preschool children. Examples of such scales include the Oucher Scale (photographs of children with various facial expressions).[54–56] Drawings of faces[19,57] have also been used with preschool-aged children[58] and school-aged children (8 years).[59] Preschool children have also used the Poker Chip Tool,[60] color scales,[61,62] and a thermometer[62] to report the degree of pain or hurt. These simple tools allow a preschooler to report pain and are easy to use. One caution with the face scales is that a practitioner must help a child differentiate between physical pain and sadness unrelated to pain. Since there is no evidence that any one of these is more valid than another, it is recommended to pick one and use it consistently. When self-report scales are used in conjunction with observational scales, a practitioner gets a better picture of a child's response to pain and pain therapies.

A school-aged child's cognitive development allows for more abstract thinking. In addition to the Faces Pain Rating Scales, which they enjoy,[19] they can use simple numeric scales 0–5 in the early school years (ages 7–8)[63] and more complex scales 0–10 or 0–100 in the later years (age 9–12). Visual analog scales anchored with happy and sad faces[62] and simple adjective scales[62,64] also can be used with this age group. In addition to self-reports of pain, observational scales such as the CHEOPS[40] or the Procedure Behavior Check List[65] can be used with a school-aged child. Again, the important issue is to use one selected scale consistently since no one has been shown to be more valid than others.

Adolescents can think abstractly and can quantify and qualify phenomena and so can use the same scales as adults. One concern with adolescents is that when they are ill they tend to regress and thus may require the use of a simpler scale during such times.[66]

Table 64.2 Observational Pain Assessment Scale (OPAS)[44]

Assess each of the areas identified in the "Observed Behavior" column rating each behavior using the 0, 1, or 2 rating. Add the ratings together for each observed behavior. Document your total score.

Observed Behavior	0	1	2
Restlessness	Calm, cooperative	Slightly restless, consolable	Very restless agitated, inconsolable
Muscle, Tension	Relaxed	Slight tenseness	Extreme tenseness
Facial Expression	No frowning or grimacing, composed	Slight frowning or grimacing	Constant frowning or grimacing
Vocalization	Normal tone, no sound	Groans, moans, cries out in pain	Cries out, sobs
Wound Guarding	No negative response to wound	Reaching/gently touching wound	Grabbing vigorously at wound

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Intubated and sedated children provide more challenges in the assessment of pain. The more disabilities that a child has and the more medications that are being given to the patient create challenges to the clinician. A 2-year-old child who is blind, with only one extremity that is functioning and on numerous medications presents a huge assessment challenge to the clinician. Table 64.3 presents a list of clinically useful tools according to patient age.

"Pain is what the child says it is."[67] What about the case where the nurse documents a lower number than the child says because the nurse believes the child is over-rating the score? Reiman et al.[68] surveyed nurses' knowledge and attitudes regarding pain and their ability to manage pain. The modified Pediatric Nurses' Knowledge and Attitude Survey Regarding Pain tool (PNKAS – Shriners Version 2002) needs further validation but demonstrates the need to consider the healthcare provider's attitude and knowledge of pain.

Measurement of Anxiety

Anxiety is measured in a variety of ways. In 2000, Robert et al. surveyed 64 burn treatment centers to determine how they evaluated and treated anxiety, especially in children.[69] They found that most centers did not use standardized measures of anxiety. Based on that survey and other information, the Shriners Hospital for Children in Galveston has been using the Fear Thermometer adapted by Silverman and Kurtines[70] from the Walk's Fear Thermometer[71] (Fig. 64.2).

Taal and Faber introduced a tool to measure burn-specific pain anxiety (BSPAS).[72] It uses a five-item scale used to measure anxiety associated with anticipated procedural pain in adult patients.[73] Initial reliability, validity, and utility studies have been completed.[73,74] A similar tool is needed for children.

Table 64.3 Recommended Pain Measurement Tools for Burned Patients

INFANTS AND TODDLERS
CHEOPS[42]
The Observer Pain Scale[43]
PRESCHOOLER
Faces Pain Rating Scale[26,48]
Oucher[45-47]
Pediatric Pain Questionnaire[52]
CHEOPS[42]
SCHOOL-AGED CHILD
Faces Pain Rating Scale[26,54]
Visual analog
Numeric scale
Pediatric Pain Questionnaire[52]
Procedure Behavior Checklist[56]
ADOLESCENTS AND ADULTS
Visual analog
Numeric scales
Adjective scales
McGill Questionnare[23]

Measurement of Itching

Itching is very common in burn survivors. Even in small burns, the prevalence is 35% with moderate pruritus and 14% with severe, and, in many cases, the pruritus impacts daily living.[75–77] Another series of 510 burns reported a prevalence of 87%.[78] The severe itching of burn scars and wounds has not been discussed much in the literature, but clinicians can testify that this phenomenon is a very serious problem. Patients who experience such itching often excoriate new grafts or recently healed skin, thus enhancing their susceptibility to infections. The measurement of itching has been part of a number of scales that focus on all the problems that the patient has, such as the Patient and Observer Scar Assessment Scale (POSAS)[79] and the Assessment of Health Outcomes in Children with Burn Injury.[80] When pruritus is severe, patients can focus on nothing else. Until very recently there have not been any tools focused on measuring itch. Now, Field et al.[81] reported using a visual analog scale of 1–10 to assess itching. Pat Blakeney and Janet Marvin at the Shriners Hospital for Children in Galveston developed an instrument to measure itch called "itch man" (Fig. 64.3). This instrument was based on a patient's drawing of his experience in the hospital.[82] Children seem to be able to relate to "itch man," and validation has been completed.[83] Several scales have been developed for adults to use. One from Belgium has been translated and validated in English and seeks to measure all the aspects of itching and how it relates to other types of variables.[84] Another coming from the dermatologic literature measuring itching in five dimensions is named the 5-D itch Scale.[85]

In summary, symptom assessment and management are very important in burn care. The experience of pain may affect the perceptions of other symptoms, including anxiety, fear, or itch. Each symptom should be assessed within the context of other symptom assessments. There are many measurement tools for pain, anxiety, and itch assessment across the life span that can be useful to the clinician and the researcher. Further studies need to be completed in all these areas.

Treatment Considerations

Once pain has been assessed and quantified, treatment can be considered. Three modalities of treatment are effective

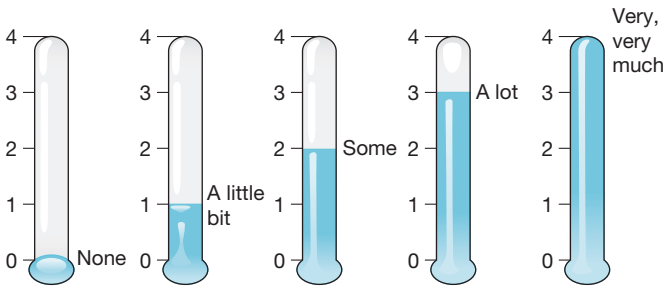

Fig. 64.2 Fear thermometer to rate anxiety level. (From Silverman and Kurtines W. *Anxiety and phobic disorders: a pragmatic approach*. New York: Plenum; 1996; Springer Science and Business Media.)

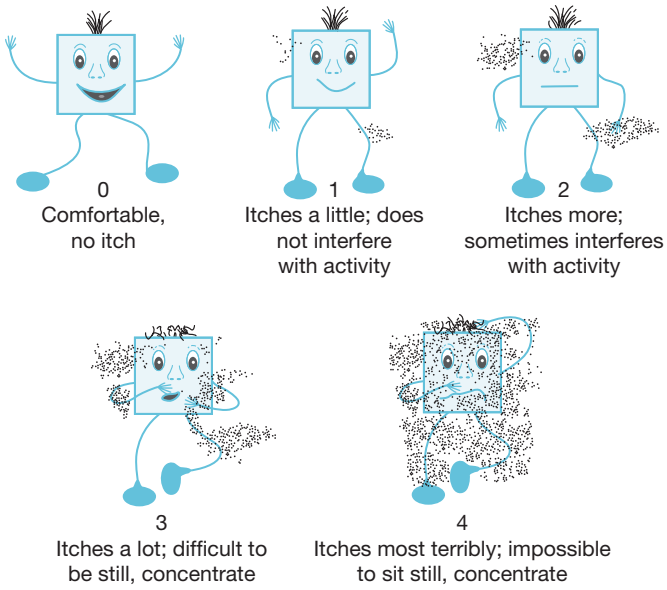

Fig. 64.3 Itch Man Scale to rate itching intensity in children, designed by Blakeney and Marvin, 2000, at Shriners Hospital for Children. (Reprinted with permission of Shriners Hospital for Children.)

with pain secondary to burn injury: surgical, pharmacological, and behavioral.

SURGICAL TREATMENT OF PAIN

In burn patients, pain is predominately related to the open wound. Once the wound is closed, the pain subsides. The use of resection and grafting of open burn wounds significantly reduces burn pain. Open wounds should be grafted as soon as they are clean enough to do so. Even temporary coverage with cadaver skin or pigskin reduces pain in the area of the burn. In the case of second-degree wounds, the use of Biobrane, Opsite, Tegaderm, Dressilk, Polymem, Copoymer, Acticoat, Mepilex AG, Duoerm, or other wound-covering dressings almost immediately eliminates pain at the burn wound site.[86–95] Biobrane has also been used for toxic epidermal necrolysis and was found to reduce pain significantly; Duoderm is a similar but cheaper product than Biobrane and has the same beneficial effect on pain. Cultured allogeneic keratinocyte sheets accelerated healing and thereby reduced pain and suffering compared to Opsite treatment. The cultured keratinocyte sheets cut healing time in half. Pain assessment as early as day 3 revealed lower pain scores in those sites treated with keratinocyte sheets. Less costly dressings include honey because it provides the synergistic interactions of a moist environment, antibacterial activity, and antiinflammatory action and thereby promotes healing.[96–98]

Negative-pressure wound dressing therapy is a relatively new approach to the closure of wounds. As a byproduct of that treatment, Fischer et al. claim less pain but give no data.[99] Other new techniques include laser treatment of scars. The CO_2 fractional photothermolysis treatment of scars does reduce scars and pain. On the other hand, it reduces neuropathic pain by 54% and pruritus by 49%.[100]

The newest approach to reducing the pain of a scar is the use of fat grafting. It was initially developed in animals and more recently used clinically in humans.[101] The fat decreases local neuroinflammation.

TOPICAL AGENTS

Aloe vera has been used as a home remedy for burns for many generations, and several recent studies have examined its efficacy more thoroughly. Maenthaisong et al. conducted a systematic review and meta-analysis and concluded from the published studies of first- and second-degree burns that aloe vera was more effective than Vaseline gauze alone.[102] In that study, aloe use was associated with a shorter healing time by 8.79 days. A more recent randomized controlled study in 2009 by Khorasani et al. confirmed the greater efficacy of aloe over silver sulfadiazine.[103]

In contrast, topical morphine was not very effective in reducing the pain of partial-thickness burns.[104] The final word on the effectiveness of topical heparin is still out.[105]

Physical coverage of the burn wound decreases pain. For example, blisters left intact lead to less pain,[106] but this practice is questionable because of possible infection associated with the blisters. One additional issue concerning procedures is the amount of pain created by removing a dressing from the burned area. These removals are usually facilitated by soaking the dressings off, but the soaks are sometimes painful. Some newer dressings are easy and painless to remove, and moist, exposed-burn ointment dressings[107] are being developed to further reduce pain.

Acticoat was found to be much less painful than silver sulfadiazine in the treatment of partial-thickness burns by Varas et al.[108] Several new lipido-colloid dressings seems to show promise for reducing pain.[109, 110] Cellulose dressings also reduce pain.[111] Several new products are adherent to dry skin but not moist skin and therefore much less pain than has been reported to be associated with silver sulfadiazine.[112,113] Suprathel is a reabsorbable skin substitute that goes even further to reduce the pain of dressing by eliminating the need for dressing changes.[114]

A more novel technique of painlessly cleaning the burn wound is to use an ultrasound mist, and there are two short reports advocating this.[115,116]

PHARMACOLOGICAL TREATMENT OF BURN PAIN

Optimal pain management for burn patients requires a multidisciplinary approach and individualized therapy. However pharmacologic management of burn pain is the mainstay of therapy. General rules are helpful in governing the use of pain medication. The first tenet is that if the patient says he or she is having pain, he or she is suffering. The second tenet is that analgesics are most effective when given on a regularly scheduled basis (not "as needed" or PRN). The third tenet is that, when avoidable, pain medication should not be given as an intramuscular injection since injections themselves cause pain and anxiety. In addition, initial physiological changes associated with large burns make uptake from injection sites erratic and unpredictable. Last, dose and type of medication should be reevaluated frequently during the hospital course to make sure pain is

continuously controlled and that the patient is experiencing no serious side effects.

Dramatic physiological changes associated with large burns produce significant pharmacokinetic and pharmacodynamic alterations that affect drug selection and dosing considerations.[117] Two metabolic and hemodynamic phases are recognized following major burn injury. An initial burn shock (ebb) phase with decreased circulating blood volume, decreased cardiac output, and increased systemic vascular resistance is followed after approximately 48 hours by a hyperdynamic/hypermetabolic (flow) phase with increased cardiac output and decreased systemic resistance, increased oxygen consumption, and intense catabolism. These changes in cardiac output and organ perfusion also affect hepatic and renal drug clearance in a biphasic fashion. For example, during the ebb phase, hepatic and renal blood flow may be reduced enough to impair drug metabolism and excretion. Conversely, during the flow phase, increased hepatic blood flow enhances clearance of drugs such as fentanyl and propofol that are efficiently extracted by the liver.[118] Likewise renal excretion of some drugs may be increased enough to require alteration of the dose. Furthermore loss of plasma proteins through open wounds and extensive edema due to massive fluid resuscitation profoundly alter drug distribution and binding to plasma proteins. Sympathetic tone and drug exposure during the hospital course alter the up- and downregulation of various drug receptors. Perception of pain is enhanced by anxiety. Devastating burn injuries produce intense anxiety that can be exaggerated or reduced by the effectiveness of pain control. All these factors ultimately affect responses to analgesic (and other) drugs in ways that are often unpredictable. Patient response should be closely monitored and drug selection and dosing adjusted carefully to avoid undertreatment or complications of overdose.

OPIOIDS

Opioid analgesics have been the mainstay of burn pain drug therapy.[119] Burn pain is not a single entity but is experienced in several distinct ways: background, breakthrough, procedural, and postoperative pain. Drug selection and dosing are very different for each of these clinical situations. There are several opiate drugs with widely different pharmacokinetic profiles. This allows selection of an agent with speed of onset and duration of action appropriate to specific clinical needs. For background pain, slower onset and long duration of action are suitable. For patient-controlled analgesia (PCA), a rapid onset is desirable. For procedural pain, it is best that the drug effect (and adverse effects) not last much longer than the procedure. A variety of routes of administration are also possible with this large group of drugs. In most cases, it is better to give a sufficient dose to control pain over its recommended length of action rather than smaller doses more frequently. This problem occurs frequently when physicians are reluctant to prescribe the recommended dose for pain.

The use of opiate analgesics is often limited by their adverse effects. Continuous use may be limited by pruritus or constipation. Higher doses needed for intense pain associated with procedures may cause unsafe depression of respiration. Use of adjuvant drugs and a multimodal approach to pain control can increase the quality of pain control in part by reducing the dose and thus the adverse effects of opiates needed.

Morphine

Morphine has been described as the gold standard for treating burn pain and remains the first choice in many burn units. Time to peak effect and duration of action for morphine are appropriate for treating background and breakthrough pain most of the time. Although morphine is often used with PCA, some clinicians prefer drugs with quicker on–off kinetics, especially for painful procedures. The active morphine-6-glucuronide metabolite of morphine is excreted in urine and can accumulate in patients with renal failure.[120]

Chronic treatment with opiates will result in tolerance and increasing dosage requirements to control pain. Opiate tolerance is accompanied by an increased sensitivity to pain. The central mechanism of this hyperalgesia appears to involve glutamate transmission mediated by N-methyl-D-aspartate (NMDA) receptors. In addition to tolerance to narcotic analgesics, some patients experience a phenomenon referred to as OIH. OIH differs from tolerance in that, where patients tolerant to morphine respond to larger doses, with OIH, increasing doses of morphine are associated with increased pain.

OIH associated with burns has been reviewed by Holtman and Jellish.[121] Although it may at times be difficult to distinguish opiate tolerance from OIH, deteriorating pain control despite large increases in morphine dosage is suggestive of OIH. One benefit of a multimodal approach to pain control is that it allows lower doses of opiates, which also reduces the risk of OIH. When OIH is suspected, the dose of morphine must be reduced, and additional changes in drug therapy are needed to compensate for the reduced effect of morphine. All patients with OIH will not respond in the same manner to pharmacological interventions. A switch to methadone has been reported effective in patients poorly controlled by morphine. This benefit has been explained by NMDA receptor antagonism by methadone. α-2 Adrenergic agonists, as well as low-dose ketamine have also been found effective. Additional agents included in multimodal strategies to reduce narcotic analgesics are benzodiazepines, acetaminophen, gabapentin, and pregabalin.

Fentanyl

Fentanyl is a potent synthetic opiate with a relatively rapid onset of action and a shorter duration of effect than morphine. The relatively rapid onset and shorter duration of action with bolus doses make fentanyl a suitable choice for analgesia during painful procedures and with PCA. An oral transmucosal dosage form is also available and has been found effective in pediatric patients during procedures.[122] With continued infusion, however, the drug accumulates, and, due to its long context-sensitive half-time, prolonged infusions can delay extubation of ventilated patients. This can be prevented by the daily wake-up protocols practiced in many ICUs. Discontinuing sedation in ventilated patients can also be associated with significant morbidity, such as unplanned extubations. A benefit similar to daily wake-up protocols but without associated morbidity is also possible with a protocol of daily assessment of sedation and dosage adjustment.[123]

Remifentanil

Remifentanil is an ultra-short-acting opioid with a rapid time to peak activity (90 s). Elimination is very rapid by nonspecific esterases in blood and tissue, which give it a context-sensitive half-time of approximately 4 min without regard to duration of infusion.[124] The pharmacokinetic properties of remifentanil make it appropriate when rapid emergence is desired. The abrupt recovery from remifentanil analgesia has been associated with hyperalgesia. This can be prevented by concomitant doses of α-2 adrenergic agonists, ketamine, or a longer-acting opiate prior to termination of infusion.[125]

Alfentanil

Alfentanil has a short time to peak effect similar to remifentanil (90 s) and shorter duration than fentanyl. With a Vd of less than one-fourth that of fentanyl, alfentanil also has a faster clearance and shorter half-life.[126] These properties make it suitable to provide analgesia for brief procedures and to infuse for longer procedures and yet provide relatively rapid recovery. The pharmacokinetics of alfentanil are especially suited for PCA. Sim and others[127] used alfentanil alone with PCA for burn dressing and wound care with excellent satisfaction of patients and nurses.

Methadone

Methadone is a synthetic opiate that combines μ receptor agonist, NMDA antagonist, and amine uptake inhibition properties.[128] Preclinical studies have shown that through its NMDA receptor antagonist action, methadone inhibits morphine tolerance and hyperalgesia.[129] These properties make it theoretically suited for treating burn pain by reducing the risks of central sensitization of pain and OIH. In clinical studies there appears to be a lack of cross-tolerance with morphine. There are multiple reports of improved pain control in patients switched from morphine to methadone.[130,131] The mean bioavailability is about 80% after enteral administration. Its onset of action is more rapid than morphine after intravenous injection due to its higher lipid solubility. Its elimination is quite variable but significantly longer ($t_{1/2}$ 7–65 hours) than that of morphine ($t_{1/2}$ 1.7–3.3 hours).[128]

BENZODIAZEPINES

Significant burn injuries are associated with considerable anxiety and psychological stress. Pain sensation is enhanced by anxiety and, in some cases, pediatric patients for example, even complete elimination of pain does not make procedures stress-free. Reducing anxiety can reduce narcotic requirements for pain control. Benzodiazepines are the most commonly used anxiolytic agents used in burn centers. Pharmacokinetic considerations influence the choice of benzodiazepines in burn patients. Martyn et al. evaluated the clearance of diazepam[132] and lorazepam[133] in burned patients and in nonburned controls. Diazepam is metabolized by P450 oxidases (phase I reaction), and its metabolism and clearance were depressed in burned patients. In contrast, lorazepam is metabolized by conjugation (phase II), and its clearance is slightly enhanced in burned patients. These results suggest that although the clearance of diazepam may be unpredictably slow and accumulation of doses may be possible in burned patients, this is not the case with lorazepam. As a result, treatment of burn patients with lorazepam should be more predictable than with diazepam and therefore more controllable and effective. Diazepam has a relatively long half-life and is biotransformed to active metabolites. Midazolam is a shorter-acting agent suitable for brief procedures or infusion and is the most frequently used sedative in U.S.-based burn centers.[134] Midazolam undergoes extensive first-pass metabolism by intestinal and hepatic tissues after oral administration. However its major hydroxylated metabolite, α-hydroxymidazolam, is at least as potent as midazolam.[135] Lorazepam has a duration intermediate between midazolam and diazepam. Lorazepam is metabolized by glucuronidation to inactive metabolites, and, because of this, it is often preferred for anxiolysis in burn ICUs.

NONOPIATE ANALGESICS

Acetaminophen is a nonantiinflammatory antipyretic analgesic. Although its analgesic action is too weak to adequately control pain of more than minor burns by itself, acetaminophen acts synergistically with more potent analgesics and is an important component of multimodal pain protocols. When used in this manner acetaminophen reduces the dose requirements of opiates. It is effective when given alone for minor burns. Meyer et al. found that 10–15 mg/kg of acetaminophen given orally every 4 hours was effective without producing toxic plasma concentrations.[136]

Nonsteroidal antiinflammatory drugs (NSAIDs) also possess significant analgesic and antipyretic action and are also antiinflammatory agents. They are not used routinely in burn patients due to additional adverse effects. NSAIDs have been found to promote acute kidney injury in hypovolemic patients through inhibition of prostaglandin synthesis, which reduces renal blood flow due to constriction of afferent renal arterioles.[137] Increased bleeding due to an antiplatelet effect is another concern.

ANTICONVULSANTS

Drugs originally intended as anticonvulsants have also proved helpful in pain management protocols. Gabapentin and pregabalin are such drugs that have been found to be effective for the management of neuropathic pain.[138,139] Since neuropathic pain and narcotic-induced hyperalgesia appear to share pathophysiological etiologies, it is likely that drugs effective against neuropathic pain should also facilitate pain control by reducing hyperalgesia associated with narcotic administration. The proposed mechanism is not established, but there is preclinical evidence that these drugs reduce central sensitization through an interaction with spinal voltage-gated calcium channels.[139] Van Elstraete and colleagues found that although gabapentin did not affect the initial analgesic effect of fentanyl in rats, it did prevent, in a dose-dependent manner, the delayed hyperalgesia associated with fentanyl administration.[140] In a clinical study Rimaz et al.[141] reported that a single preoperative dose of gabapentin given prior to burn surgery decreased

the postoperative PCA morphine consumption. These drugs are often used as part of a multimodal pain control protocol.

KETAMINE

Ketamine is a potent analgesic with many characteristics that make it suitable for treating burn patients. It has been used extensively alone and in combination with other drugs primarily for controlling pain during procedures related to burn care, but also low-dose infusions can improve pain control in some patients tolerant to morphine. It has been administered orally, intramuscularly, and intravenously. Ketamine causes pain when administered intramuscularly or through a peripheral intravenous catheter. It also causes tachycardia and hypertension, which may be poorly tolerated by older patients with hypertension or coronary artery disease. These side effects can be reduced by concomitant administration of an α_2 adrenergic agonist. Ketamine has been avoided in patients with increased intracranial pressure because it has been reported to cause increased cerebral blood flow that might further increase intracranial pressure. More recent evidence contradicts this warning. Clinical and experimental data suggest that, especially for patients who are mechanically ventilated, ketamine may offer neurological protection, decreased intracranial pressure, and improved cerebral perfusion.[142]

In doses above 1–2 mg/kg intravenously ketamine produces a dissociative state that renders the patient insensible. At the same time, respiratory drive, airway patency, and airway reflexes are preserved.

Ketamine has an extensive record of safety in pediatric emergency departments even when given without regard to prandial state.[143] This combination of features is especially beneficial in pediatric patients who can experience intense psychological stress and may be combative even if all pain is prevented. A more bothersome problem is delirium during emergence. Midazolam is often described as a remedy, but dexmedetomidine may be more effective.[144] It is best that midazolam be co-administered with ketamine to avoid this complication. Ketamine sedation can be associated with increased salivation that can make laryngospasm more likely but, in contrast to laryngospasm caused by inhalation agents, laryngospasm with ketamine is largely self-limiting.

α_2 AGONISTS

The use of α_2 adrenergic agonists has increased dramatically for perioperative and ICU applications.[145] These drugs are used for both sedative and analgesic properties. For these applications α_2 agonists' predominant effect is mediated by central inhibition of norepinephrine release. This action results in sedation and reduction of sympathetic tone. Peripheral release of norepinephrine is also inhibited. If blood pressure is maintained by increased sympathetic tone, as with decreased circulating blood volume, administration of clonidine or dexmedetomidine can cause hypotension.

Clonidine is available for oral or intravenous use. When administered by mouth or nasogastric tube, clonidine has an approximately 85% bioavailability. Dexmedetomidine is available as a solution for injection and can also be administered as an intranasal mist.[146] Clonidine is the more inexpensive of the two agents.

The analgesic action of dexmedetomidine and clonidine is weak, and these drugs are most effective as adjuvants. They reduce dose requirements for narcotics and counteract opiate-induced hyperalgesia. Compared to clonidine, dexmedetomidine is a more selective adrenergic agonist and has a higher affinity for the α_2 receptor. The elimination half-life for dexmedetomidine is much shorter than clonidine's (2 hours vs. >12 hours).[147] Intravenous infusion of dexmedetomidine allows more precise titration of sedation to the patient's needs but is more expensive.

Among the advantages of α_2 adrenergic agonists are the lack of effect on airway patency, respiratory drive, and airway reflexes. Dexmedetomidine is especially effective in combination with ketamine. Dexmedetomidine limits the hypertension and tachycardia associated with ketamine, which can be problematic in older patients. In addition, dexmedetomidine also potentiates the analgesic effect of ketamine and in this way reduces the dose of ketamine needed.

PROPOFOL

Propofol is a nonbarbiturate intravenous anesthetic without analgesic activity.[148] Advantages include rapid onset of action and a rapid emergence with little cumulative effect after prolonged infusion.[149] A disadvantage is pain when administered through a peripheral vein. It is most commonly used for induction and/or maintenance of general anesthesia. Propofol has also been used in sub-anesthetic doses along with an analgesic drug for sedation during stressful procedures.

Under certain conditions and with limited duration propofol is given by intravenous infusion for sedation of intubated patients requiring mechanical ventilation in the ICU. Ronan and others found sedation of intubated patients to be superior with propofol than with midazolam infusion in terms of speed of wake-up and quality of sedation.[149] The rate and duration of propofol infusion should be limited, and patients receiving propofol should be closely observed for signs and symptoms of propofol infusion syndrome (PRIS). This is a rare but serious and often fatal complication of propofol. PRIS has a variable clinical presentation but includes combinations of metabolic acidosis, arrhythmias, rhabdomyolysis, renal failure, and other disorders. The total cumulative dose is the main risk factor for PRIS, and the U.S. Food and Drug Administration (FDA) recommends a maximum dose rate of 4 mg/kg per hour, but case reports have included dose rates lower than this.[150] Some intensivists limit propofol to provide sedation during weaning of longer-acting agents or for relatively short-term infusions of 24–48 hours.

In doses that result in loss of consciousness (general anesthesia) propofol causes loss of pharyngeal tone, which may cause airway occlusion.[151] It also causes reduction of respiratory drive and loss of airway reflexes, making patients vulnerable to hypoventilation or apnea, aspiration, and laryngospasm. Hypotension is also associated with these doses. As a result, propofol in these higher doses should only be administered by personnel with formal anesthesia

training or by credentialed personnel who are part of a care team designed to provide sedation for procedures.

NITROUS OXIDE

Nitrous oxide is the only nonhalogenated anesthetic gas still in clinical use. Its low potency requires 50–70% inhaled concentrations to provide significant analgesia. Filkin and Marvin have reported effective analgesia during burn wound care with self-administered nitrous oxide.[152] More recently, Ozil et al. used 50% nitrous oxide in combination with morphine premedication to provide analgesia for 33 children with small (<10% TBSA) burns.[153] In these cases pain scores and patient/parent satisfaction were favorable.[205] Do Vale et al. found that the use of fentanyl was not reduced by using nitrous oxide.[154] A brief intermittent exposure to nitrous oxide and chronic exposure to trace amounts appear safe, but repeated exposure to higher concentrations can result in significant hematopoietic and neurological toxicity. This results from oxidation by nitrous oxide of the cobalt in vitamin B_{12}, which impairs its coenzyme function. Synthesis of methionine and tetrahydrofolate needed for DNA synthesis and metabolic reactions involving methylations is inhibited by nitrous oxide inactivation of vitamin B_{12}. Clinical presentation mimics pernicious anemia, with megaloblastic anemia and subacute combined degeneration of the spinal cord. Hayden and colleagues reported a case of myeloneuropathy in a burn patient chronically exposed to high concentrations when he was given 50% nitrous oxide in oxygen to self-administer ad lib over approximately 4 months.[155,206] Chronic exposure also is possible for workers chronically exposed to nitrous oxide. Sweeny et al. found bone marrow changes consistent with nitrous oxide toxicity in three of 21 dentists who used nitrous oxide for sedation and analgesia for their patients during long procedures.[156,207] Ambient nitrous oxide concentration were as high as 4,600 ppm in their work areas. With modern scavenging systems, operating room personnel are not considered at risk. If nitrous oxide is used for analgesia for burn patients, adequate consideration must be given to chronic exposure of personnel.

Initial Injury

Although areas of full thickness burn injury are initially insensate, Singer and colleagues[157] reported that only 25% of patients presenting with isolated full-thickness burns had pain scores of 0; that is, were painless. Of all other patients with partial or partial plus full-thickness burns, 18% were also painless. The differences in the frequency of painless wounds between these two groups were not statistically significant. These observations suggest that most patients with full-thickness burns have significant pain.

If possible, intramuscular injections should be avoided. Not only is the injection painful, but, during the early stages of major burns, absorption from tissue sites is highly variable and unpredictable. With decreased intravascular volume and cardiac output, tissue perfusion may be low and absorption poor. Later, with fluid resuscitation, drug may enter the circulation as tissue perfusion is restored. This can combine with any sedative or analgesic drugs given later and lead to oversedation and respiratory depression.

In the case of second-degree wounds, the use of wound-covering dressings almost immediately eliminates pain in the burn wound site. As an example, Schwarze and colleagues compared the clinical efficacy of two synthetic burn wound dressings, Suprathel and Omiderm. Both were highly effective in reducing pain. Omiderm was more cost effective, but Suprathel was slightly more effective in reducing pain (10-day average visual analog score [VAS] pain score was 1.0 for Suprathel, 1.59 in the Omiderm group).[158]

Although the most widely followed burn shock formula, the Parkland formula, recommends 4 mL/kg per percentage of TBSA burned, Engrav and colleagues reported in 2000 that many burn centers were administering considerably more fluid than this and that patients were experiencing serious morbidity from overresuscitation.[159] This trend of administering increasing amounts of resuscitation fluids has been termed "fluid creep" by Pruitt and is associated with significant morbidity due to fluid overload. The mechanism of this phenomenon has not been established, but Sullivan and colleagues found an association of increased fluid volumes administered with increased doses and variety of narcotics given to burn patients.[160] They suggested that higher doses of narcotics could contribute to hypotension and increase the fluid needs of these patients. Saffle examined factors associated with "fluid creep" and reasoned that it is unlikely that narcotics contribute significantly to the practice of administering larger volumes of fluid to burn patients.[161]

Background and Breakthrough Pain

Pain perception and analgesic requirements for burn injuries vary widely. Adequate pain control requires that each patient be continuously assessed for pain and anxiety. For a variety of reasons the simplest effective treatment plan is optimal. Often morphine in combination with a benzodiazepine is adequate. However the advantages of a multimodal approach to pain control are generally accepted, especially for patients with moderate and severe pain. The use of multiple drugs with different mechanisms of action provides synergistic effects that improve pain control and allows the use of lower doses of opiates. For this reason the addition of scheduled doses of acetaminophen and gabapentin may reduce OIH and neuropathic pain. Cuignet et al. reported that if 2400 mg of gabapentin is given to adult burn survivors per day, the amount of morphine needed is less and the pain control better.[138] An unexpected finding was that improved pain scores and reduced morphine requirements persisted after treatment with gabapentin was stopped.

During the acute phase of recovery from burn injuries patients with good pain control often experience transient periods of sudden intense increase in their pain. This is referred to as *breakthrough pain*. A pain management plan must include orders for as-needed or p.r.n. doses of an analgesic. The intensity of breakthrough pain is usually so great that an opiate is required.

One technique that can accommodate both background and breakthrough pain is PCA. PCA requires patient

cooperation, which means that the patient is able to understand and perform tasks necessary to self-administer the medication. When hands are burned and the PCA pump cannot be activated manually by the patient, a foot pedal can be used. When neither of these options is possible, protocols have allowed a nurse to activate the pump at the patient's request. To avoid overdose when PCA is used to cover postoperative pain or background pain in the burn ICU, it is important that family members or other visitors do not activate the PCA for the patient. Nilsson and colleagues evaluated the use of PCA with morphine to control burn-related background pain and pain associated with mobilization.[162] Background pain was adequately controlled, but even a double PCA dose given in anticipation of mobilization was not sufficient to control the associated increased pain. Although subcutaneous administration is generally to be discouraged in burn patients, Shipton and others reported safe and effective control of background pain with PCA morphine administered subcutaneously.[163]

Fear related to a traumatic injury and apprehension associated with pain enhance the perception of pain and make it more difficult to control. Pain is most effectively treated if aggressive measures to control pain are accompanied by consideration for the patient's anxiety. Complaints of pain should not be attributed solely to anxiety, however.

Patterson et al.[164] reported that in a double-blind placebo-controlled study of 79 patients, 1 mg lorazepam significantly reduced procedural pain ratings in those patients with high baseline pain, but did not reduce baseline trait anxiety. In a survey of the use of antianxiety drugs in burned children, 72% received lorazepam at a dose of 0.03–0.05 mg/kg or higher every 4 hours for much of their initial hospitalization.[165] Lorazepam provided aid in anxiety control with essentially no side effects.

Occasionally the quality of pain control will deteriorate to the point that changes in drug dose or selection must be changed to maintain adequate analgesia. A variety of mechanisms can account for difficulty or deterioration of pain control by standard protocol (Table 64.4). Also, intubated patients requiring mechanical ventilation present an additional challenge for managing pain control.

Burn patients poorly controlled with increasing doses of morphine have benefited from substitution of methadone.[130] As discussed earlier, in addition to μ opiate receptor agonist activity, methadone is an NMDA antagonist and inhibits amine uptake similar to tricyclic amines.[166] These properties reduce central sensitization and hyperalgesia that are not sensitive to morphine. Methadone reduces a neuropathic component of pain that often develops with healing of burn wounds.

Table 64.4 Factors Complicating Quality of Pain Control

- Repeated pain of daily wound care
- Intubation for mechanical ventilation
- Physical therapy range of motion and exercise therapy
- Postoperative pain
- Wound infection
- Tolerance to narcotics
- OIH
- Development of neuropathic pain
- Exaggerated anxiety
- Post-traumatic stress disorder

α_2 Adrenergic agonists represent another class of drugs that may dramatically improve pain control in patients no longer controlled with morphine. Clonidine has been found effective specifically in burn patients poorly controlled by large doses of morphine.[167] Clonidine is inexpensive, and bioavailability is very good when given via nasogastric tube. Fagin and colleagues compared sedation of burned pediatric patients with midazolam or dexmedetomidine infusions. Patients receiving dexmedetomidine were treated for an average of just over 3 weeks. They found sedation more effective with dexmedetomidine and with less hypotension.[168] Caution is necessary when giving α_2 adrenergic agonists to acute burn patients, however. If the patient is hypovolemic and blood pressure is maintained by increased sympathetic tone, administration of clonidine or dexmedetomidine can result in hypotension. In pediatric patients this may be treated by volume administration, but adults, especially those with coexisting disease, may need prompter treatment with vasoactive drugs while hypovolemia is corrected. Dexmedetomidine can also be helpful when increased doses of morphine are ineffective. It is more expensive than clonidine but sedation can be more easily titrated with alterations of rate of intravenous infusion.

Not all patients respond in the same manner to analgesics, and it is necessary to have alternative choices when pain control is especially challenging. Ketamine is an effective NMDA receptor antagonist, and, as a result, it can reduce central sensitization and improve analgesia for patients with neuropathic pain or who are experiencing OIH. Subanesthetic doses (0.1–0.3 mg/kg as bolus or 0.1–0.3 mg/kg per hour infusion) have been found to improve pain scores and reduce perioperative narcotic requirement.[169] We have found low-dose ketamine infusion helpful in patients with poorly controlled pain and inadequate response to methadone and α_2 adrenergic agonists (unpublished observation).

Analgesia for Procedures

Burn patients require frequent painful procedures to facilitate healing of their wounds. Among others, these include initial wound débridement, daily dressing changes, range of motion and exercise therapy, wound staple removal, and placement of intravascular catheters. Providing safe and effective sedation and analgesia for these procedures can be challenging for a number of reasons (Table 64.5).

Poorly controlled pain can make it difficult to accomplish a procedure effectively or safely and increases anticipatory anxiety, which can impair patient compliance and may contribute to behavioral morbidity such as post-traumatic stress syndrome.[170] Effective pain control in adults can often be sufficient to reduce anxiety. In pediatric patients, however, anxiolysis is also needed. For especially stressful procedures, most pediatric patients must be rendered insensible. For this reason, the popular term "conscious sedation" is inaccurate and misleading when treating pediatric patients. A very young patient who is aware of the procedure will resist enough to make the procedure difficult or less safe, and the anxiety associated with this experience makes future

Table 64.5 Challenges of Sedation and Analgesia for Burn Procedures

- Intense but brief pain requiring rapid onset and short duration of drug effects to avoid overdose or delayed recovery
- Lack of intravenous access, especially for outpatient care
- Nutritional requirements for large burns preclude frequent fasting periods for deep sedation
- Exaggerated anxiety states
- Staffing resources may limit availability of personnel credentialed to provide deep sedation

Table 64.6 Risks of Deep Sedation for Burn Procedures

- Decreased respiratory drive (hypoventilation or apnea)
- Upper airway obstruction
- Difficult airway (difficult intubation and/or difficult mask ventilation)
- Decreased airway reflexes
- Aspiration after emesis
- Cardiovascular depression

procedures more difficult. The level of sedation and analgesia required in this situation cannot accurately be described as "conscious sedation." A more accurate descriptive term is "moderate or deep sedation for procedures." The depth of sedation must be individualized depending on the intensity of the pain associated with the procedure and the patient's maturity, level of anxiety, and pain tolerance.

Clinical needs of patients presenting for burn procedures vary widely from outpatient care of small superficial burns to inpatients with extensive burns who require intensely painful dressing changes and wound care. Additionally, availability of staff credentialed to provide deep sedation varies from hospital to hospital. In Europe and elsewhere many burn centers are staffed by anesthesiologists who can provide general anesthesia at the bedside. In the United States burn centers are staffed by surgeons, and, with some exceptions, anesthesiologists may not always be available for these procedures outside of the operating suite. It is not possible to describe a protocol that is appropriate for all centers. Each institution must recognize the challenges faced in controlling pain during burn procedures and plan care to address these challenges with the resources available.

Minor injuries treated with outpatient procedures may need very little medication for preparation. Children may benefit from low doses of benzodiazepines and/or opiates. More extensive outpatient procedures become progressively more problematic as the intensity of pain and associated anxiety increase. Several effective protocols for delivery of moderate sedation for procedures have been published involving a variety of drugs and routes of administration.[122,127] The ideal pharmacological treatment would be easily administered in a palatable form, produce intense analgesia with a rapid onset, have a relatively short duration of action, and produce minimal side effects. Most drugs in current use will produce prolonged sedation when given in doses that prevent most of the intense pain during wound care. On a daily basis, this prolonged period of sedation can interfere with nutritional support and other therapies. In the outpatient setting without an intravenous catheter, the most common technique is to give a preprocedural fixed dose of an analgesic with or without an anxiolytic by the oral, transmucosal, or intranasal route. Fentanyl citrate is available as a flavored Oralet to administer by the oral transmucosal route. The oral transmucosal route has the advantage of direct absorption into the systemic circulation, which bypasses the first-pass hepatic clearance effect and improves its bioavailability.

Sharar and colleagues have compared oral transmucosal fentanyl citrate with hydroxymorphone[122] and oxycodone[171] and found similar analgesic and sedative efficacies. Humphries et al. found oral ketamine to be effective.[172] In pediatric patients prior to dressing change, Borland and colleagues compared analgesia and sedation with morphine administered orally and fentanyl given intranasally.[173] Although both were effective, intranasal fentanyl was more palatable and had a much more rapid onset. Although these regimens provide significant analgesia, pain control is often not optimal. It is difficult to provide sufficient analgesia with enterally administered drugs to control intense pain without unacceptable risk of adverse effects, especially prolonged sedation. Remifentanil administered intranasally is an attractive alternative. Remifentanil is an ultra-short-acting opioid rapidly metabolized by plasma esterase.[174] In our institution 5–10 μg/kg of intranasal remifentanil enhanced the effectiveness of oral transmucosal fentanyl as judged by pain scores and the subjective evaluations of nurses and patients (unpublished observations) and did not delay recovery. The ultra-short duration of action allows rapid recovery, which reduces risks of sedation and may improve patient satisfaction.

When patients have an intravenous catheter in place there are many more treatment options that allow more profound analgesia, more rapid onset with shorter duration of action, and, depending on which drugs are administered, reversal of drug toxicity with antagonists. Sedative and analgesic drugs can be given as a bolus with supplemental doses given as needed, as an infusion to be titrated or supplemented with bolus doses, and by PCA. Infusion of short-acting opiates such as remifentanil or alfentanil is a logical choice.

Deep sedation can be associated with the risk of serious adverse events, including mortality (Table 64.6). These include airway obstruction, depressed airway reflexes and respiratory drive, and hemodynamic instability. Loss of consciousness with most sedatives causes reduced pharyngeal tone and airway obstruction of varied degree depending largely on the patient's anatomy.[151] If this is not recognized or attempts to open the airway are not successful (operator skill or difficult patient anatomy), hypoxia can result. An airway exam is a critical part of the preprocedure evaluation, and a sedation plan must take into consideration potential difficulties with airway and respiration. Obstruction due to laryngospasm can be very difficult to relieve and, in extreme cases, may require muscle relaxation and intubation. Hypoxia can also result from hypoventilation due to depressed respiratory drive. If airway reflexes are depressed, aspiration of gastric contents may occur when passive reflux or active vomiting occur. In addition, deep sedation can cause loss of sympathetic tone or direct cardiovascular depression. These effects can lead to morbidity due to hemodynamic instability (Table 64.7).

Table 64.7 Organizational Recommendations for Provision of Moderate or Deep Sedation for Procedures

1. Preprocedural evaluation of the patient, including airway exam
2. A documented plan for sedation and monitoring
3. Availability of equipment for continuous monitoring of breathing effort, airway patency, oxygenation, and circulation
4. A designated practitioner with documented airway skills whose primary responsibility is to administer the sedative drugs and monitor the patient during the procedure and during recovery
5. Personnel administering and monitoring sedation cannot be the same individual performing the procedure and can do other tasks only for brief intervals
6. Resuscitation equipment must be immediately available

Ketamine has been widely used as a sedative and analgesic for painful procedures in burn patients. The properties of ketamine described above make it a nearly ideal drug for use during stressful procedures, especially for children. As Ketamine has recently been described as possibly the first choice for anesthesia in burn patients.[175] Several qualities make ketamine an effective drug for stressful procedures. It is a potent analgesic, and its inhibition of NMDA receptors reduces hyperalgesia associated with morphine tolerance.[176] Increased salivation with ketamine can be controlled with glycopyrrolate.

The combination of an opiate with a benzodiazepine is another common choice for sedation and analgesia. Adverse events associated with deep sedation with these agents during endoscopy[177] led the Joint Commission to set guidelines for sedation that included restrictions regarding who can administer deep sedation. A controversy developed since the American Society of Anesthesiologists (ASA) defines general anesthesia as a condition induced by medication that results in the patient's inability to respond purposefully to verbal communication.[178] Since hospital guidelines restrict administration of general anesthesia to anesthetists, this interpretation precludes personnel other than anesthetists from administering deep sedation. Requiring the presence of an anesthesiologist or certified nurse anesthetist during moderate or deep sedation creates problems in that there are not enough anesthetists available to provide coverage for all procedures and the added professional fees significantly increase the costs of these procedures, often, it is argued, without proportional added benefit. Numerous studies have demonstrated that with competency-based credentialing along with appropriate planning and organization, moderate and deep sedation can be administered safely by nonanesthetists.[179,180] Components of a suitable program are listed in Table 64.7. Currently (Joint Commission update from July 10, 2010), Joint Commission standards require that personnel "permitted" to administer sedation must be able to rescue patients from the effects of sedation that intentionally or unintentionally result in a state of general anesthesia. These standards leave it up to each organization to decide how to determine which personnel are permitted to administer moderate or deep sedation. Regional regulations as well as interpretation vary and change over time. To be compliant, each institution must examine current regulations to determine which personnel are permitted to provide sedation and monitor patients during procedures. Departments of anesthesia are a logical and convenient resource for training, organizing, and monitoring sedation programs. In our institution (Shriners Hospital for Children, Galveston), competency-based credentialing for sedation privileges requires knowledge of hospital policy regarding sedation guidelines, current advanced cardiac life support (ACLS) or pediatric advanced life support (PALS) training, passage of a written exam over self-study didactic material, and successfully managing the airway of a minimum of five patients in the operating room under general anesthesia each year. Educational material, supervision of airway training, and oversight of adverse events is provided by personnel from the anesthesiology department. Medication errors and adverse events are monitored, and adverse events are to be reviewed during monthly hospital morbidity and mortality conferences. Owens described the safe and effective implementation of a similar protocol at the Northern California Shriners Hospital (Table 64.8).[180]

PCA is a technique that can effectively avoid many problems associated with titrating sedatives and analgesics during stressful procedures since the patient remains conscious and in control of dosing. Requirements and limitations of PCA were described earlier. During procedures rapid and intense changes in pain level are experienced. Adequate control in these circumstances requires a rapid onset of effect. Narcotics such as remifentanil, alfentanil, and fentanyl are more appropriate. A number of studies have described a variety of PCA protocols for burn procedures. Prakash and others performed a dose-response study with fentanyl with burn patients during dressing change.[181] They found that after a loading dose of 1 μg/kg the optimal demand dose was 30 μg with a 5-minute lockout period. Sim and colleagues gave a 1 mg loading dose of alfentanil followed by an infusion of 200–800 μg/h. Demand doses of from 200 μg to 400 μg with a lockout time of 3 minutes produced comfort and mild sedation during dressing change.[127] Nilsson and others compared analgesia with a mixture of propofol and alfentanil administered either by PCA or titrated by an anesthesiologist.[182] Patients preferred PCA to titration by an anesthesiologist in spite of the fact that PCA doses were lower and bispectral index scores (BIS) higher than when the patients were sedated by an anesthesiologist. Coimbra and others used BIS scores to individualize PCA propofol doses for patients during burn dressing changes.[183]

Itch Medications

Itch is one of the most common sequelae of burn injury.[184] Field et al. reported that pruritus occurs in 87% of patients who have a burn injury.[185] Itching will often last for many years.[186] Although it is thought to be secondary to the injury of the skin, the possibility that morphine is adding to the itch needs to be kept in mind. Itch can definitely influence the quality of life and duration of rehabilitation required. Scratching further injures the skin, leading to graft loss and skin breakdown requiring sometimes further grafting. In addition, it is very common for the patient to have a significant problem exercising or sleeping if the itching is intense. Several classes of medications can be used to treat itch but very few real comparative studies have been done. The approaches to treatment are as varied as the presumed causes of the itching.[187] Pruritus associated with burns is

Table 64.8 Pharmacologic Therapies for Burn Pain and Anxiety Relief

EMERGENT PHASE		
Procedural Analgesics	**Background Analgesics**	**Anxiolytics**
Morphine (IVB, IVCI)	Morphine (IVCI, PCA)	Diazepam (IV) (Valium)
Meperidine (IVB)	Meperidine (PCA)	Lorazepam (IV) (Ativan)
Fentanyl (IVB, IVCI)	Methadone (PO, NPC)	Midazolam (IV, IVCI) (Versed)
Hydromorphone (IVB, PO) (Dilaudid)		
Nalbuphine (IVB) (Nubain)		
Ketamine (IV) (Ketalar)		
Nitrous oxide (IH)		
ACUTE PHASE		
Procedural Analgesics	**Background Analgesics**	**Anxiolytics**
Morphine (IVB, IVCI, PCA) Roxanol (oral morphine)	Morphine (IVCI, PCA)	Diazepam (PO) (Valium)
Meperidine (IVB, IM)	Meperidine (IVCI, PCA)	Lorazepam (PO) (Ativan)
Fentanyl (IVB, IM)	Methadone (PO, NPC)	Alprazolam (PO) (Xanax)
Hydromorphone (PO) (Dilaudid)	Sustained-release morphine (PO, NPC) (MS Contin)	
Nalbuphine (IVB) (Nubain)	Acetaminophen (PO, NPC)	
Ketamine (IV, IM) (Ketalar)	NSAIDs (PO, NPC)	
Oxycodone (PO) (Percocet)	Choline magnesium trisalicylate	
REHABILITATIVE PHASE		
For Severe Pain	**For Mild to Moderate Pain**	**Anxiolytics**
Hydromorphone (PO) (Dilaudid)	Oxycodone (PO) (Percocet) Nonsteroidal antiinflammatory drugs (NSAIDs) with or without narcotics Usually not necessary: Acetaminophen NSAIDs	Diazepam (PO) (Valium) Lorazepam (PO) (Ativan) Alprazolam (PO) (Xanax)

poorly understood, so blocking histamine, kinins, proteases, prostaglandins, substance P, and serotonin (5-HT) release and receptors have all been tried. The first line of defense is a series of moisturizing body shampoos and lotions to alleviate itching due to dry scaly skin. If these measures are inadequate in providing relief, Preparation H, which contains a local anesthetic has been advocated. In contrast topical benzocaine is not effective in treating itching even though it reduces pain.[188] Topical steroids are not usually used until the skin is well healed because of the infection risk. They are effective in controlling the itching. Only a small area of skin should be treated with steroids in order to reduce the risk of systemic adrenal suppression. Antihistamine creams such as Benadryl (diphenyl hydramine) are available. Other topical medications include colloid and oatmeal baths.[189] Newer topicals are tricyclic antidepressants such as doxepin.[190,191] The major side effect of this preparation is that too much is absorbed, with resultant oversedation. Several nonpharmacologic approaches have been used. Massage seems to have a very beneficial effect.[185] In addition Hettrick et al. reported that transcutaneous electrical nerve stimulations (TENS) considerably reduced the perception of itching in nine adult patients compared to controls.[192] The most recent is the use of pulse dye laser[193] and electroacupuncture treatment[194] to reduce pruritus in burn scar. Silicone gel sheeting has been reported to also be effective.[195]

Usually the antihistamines are given orally. Using only one antihistamine results in complete relief for only 10% of patients.[196] Diphenhydramine PO 1.25 mg/kg every 6 hours is often the first oral medicine used because of its sedative effect as well as helping control the itch. A few children respond better to loratadine, which is much longer acting. If itch is not well controlled using only one, then another class of antihistamine can be added, such as hydroxyzine PO 0.5/kg every 6 hours. Last, if the itch is still not well controlled, an antiserotonergic agent, such as cyproheptadine 0.1 mg/kg every 6 hours, can be added, scheduled so that one of the medications is given every 2 hours. This is targeted against the 5-HT_3 receptors. Care must be taken to not use the cyproheptadine with patients who are on serotonergic antidepressants.

Gabapentin (10–35 mg/kg per day in divided doses) is becoming a reliable safe standard for treating severe itching following burn injury.[197] The typical individual dose is 5 mg/kg during the day and 10 mg/kg at bedtime. Comparative studies using gabapentin have demonstrated its efficacy. Goutos et al. demonstrated that it was usually more

effective than antihistamines.[198] In the experience of the Shriners Hospital in Galveston, a daily dose of 30 mg/kg is often needed in three divided doses. Recently a retrospective study was done with pregabalin with promising results. For many of those who fail gabapentin therapy, pregabalin has been found to be effective.[199]

Another new class of medications to be used in chronic itching is naltrexone. First LaSalle et al.[200] reported some improvement in itch with naltrexone. Then Jung et al.[201] reported a significant decrease in itching sensation and scratching from 9 to 5.9 on a 10-point scale after 2 weeks of treatment with 50 mg of naltrexone at night, when it was given with the usual antihistamines. Side effects of headache and nausea were noted in many of the patients.

Development of Protocols for Comfort

Interest in pain management of burned patients has been a high priority in the treatment of burns only in the past 10–15 years. Several institutions have developed pain and anxiety management protocols. In 1995, the *Journal of Burn Care and Rehabilitation* published a special issue devoted to then-current practices of systematic treatment of burn pain. In the first edition of this book in 1996, we reported the initial use of a burn pain protocol at the Shriners Burns Hospital in Galveston; the protocol currently used there is reviewed and updated every few years.[2] In 1997, a Boston group headed by Tompkins published a 3-year history with a similar protocol.[202] They incorporated a distinction in treating ventilated acute patients differently from nonventilated acute patients. Most recently a national consensus on pain management has been reached. Ulmer[203] brought these recommendations to the attention of the burn community in a 1998 article. The most recent version of the Shriners Burns Hospital protocol is shown in Table 64.9 and includes management of the most common discomforts of burned patients. It is extremely important to continue to improve these protocols as more is learned about the treatment of pain in burn injury.

Nonpharmacologic Therapies in Burned Patients

As discussed, there is a strong interaction between psychological and physiological factors contributing to the pain experience. Anxiety in particular is prevalent in patients with burn injuries and is known to exacerbate acute pain. Nonpharmacologic therapies play an important role in addressing the psychological factors that exacerbate pain as well as having a direct impact on the pain itself.[204]

In American Burn Association practice guidelines for the management of burn pain, Faucher and Furukawa in 2006 argued for the use of nonpharmacological techniques as part of the standard of care for burn centers.[205] In understanding how nonpharmacologic approaches can be used with burn pain, it is important to discuss how behavioral principles contribute to the patient's experience.[206] In terms of classical (stimulus–response) conditioning, patients (particularly children) often develop a conditioned anxiety response to stimuli associated with painful burn procedures. One study demonstrated that the simple event of seeing a healthcare worker who is wearing scrubs was enough to elicit a fearful response in burned children.[207] In terms of operant (reinforcement) conditioning, patients can be thought to gain reinforcement by avoiding or escaping painful procedures, perhaps by screaming enough to terminate treatment, or to obtain some sort of reinforcement from the staff by showing pain behaviors. Between the stimulus that precedes pain and the pain response that follows, there is the cognitive processing of pain. Such cognitions can be modified, as can behavior, and can influence how much pain a patient experiences. Classical and operant conditioning principles and modifying internal cognitions have a bearing on how nonpharmacologic approaches are applied to burn pain. A series of articles by Thurber and Martin and colleagues[208,209] provide an extensive discussion of the theory and application of such principles to controlling pain during pediatric wound care.

Classical Conditioning

If the stimuli associated with a painful procedure have been conditioned to evoke anxiety or pain, then a logical goal is to reduce the impact that the stimuli have on the fear/pain response. An obvious environmental intervention is to make the wound care procedure setting as minimally threatening as possible. For children this might involve making the hydrotherapy tank a "bath tub play area" with age-appropriate floating toys and the like. Cheerful or relaxing music, a warm room, and pleasing art on the walls can also lessen the threatening nature of a typical tank room. Providing the patient with choices in music or art gives a greater sense of control over the procedure. Some clever children's hospital staffs have turned their magnetic resonance imaging (MRI) scanner into a "cave in a jungle"; obviously such a setting will be less threatening to a child than the typical scanner. Similar principles can certainly be applied to burn care.[208,209]

There are other implications from classical conditioning, the most important of which is that the best way to prevent a conditioned pain response is to optimize pain control in the first place. By aggressively and proactively treating pain, the contributions of conditioned anxiety will be minimized. Conversely, once a patient undergoes a procedure with inadequate analgesia, concomitant anxiety can be extremely difficult to treat. Since it is rare that a child who requires wound care would not find the setting anxiety-provoking, burn units will often use an anxiolytic at the first dressing change to prevent this anticipatory anxiety.

Any attempts to enhance a patient's control over the situation can minimize anticipatory anxiety. Patients tell us that the hospital environment, unlike any other environment, strips a person of control. A functioning, independent adult prior to an injury is suddenly dependent on others for almost all aspects of care, including when and what they eat, what medications they will be taking, the painful procedures they will undergo, and their daily schedule. In addition, burn care can be quite complicated, and the medical information that patients are required to process can be overwhelming. When an adult or child feels out of control, anxiety increases. We can enhance a patient's sense of control over the hospital environment by allowing them to have input into their care as much as possible. For

Table 64.9 Shriners Hospitals for Children (Galveston): Comfort Protocol for Children

BACKGROUND PAIN

Inpatient

Consciousness should be noted on the vital signs flow sheet.

- IV Morphine dose: 0.03–0.06 mg/kg/dose IV q2–4h (scheduled while awake)
- PO Morphine dose: 0.1–0.3 mg/kg/dose PO q4h (scheduled while awake)

Note: Begin bowel prep program simultaneously with beginning opioids: prune juice, docusate, etc.

- If requires longer-acting pain medicine
- Methadone dose: 0.1 mg/kg/dose PO q6–8h, then reduce frequency to q12h to taper off

Outpatient:

- Oral acetaminophen 15 mg/kg/dose PO q4h
- Tramadol 1–2 mg/kg/dose q 4–6 h
- If inadequate, add hydrocodone 0.2 m/kg usually in combination with acetaminophen
- Ibuprofen PO 10 mg/kg/dose PO q6h
  - The antiplatelet effects of ibuprofen last as long as the drug is still in the body.

Pre-Wound Cleaning:

- Oral transmucosal Fentanyl (Actiq) dose: 10 µg/kg/dose rounded to nearest available dose. Oral transmucosal Fentanyl is available in 200 µg, 400 µg, and 600 µg doses
- IV Morphine dose: 0.03–0.06 mg/kg/dose IV q 2–4 h (scheduled while awake)
- PO Morphine dose: 0.1–0.3 mg/kg/dose PO q4h
- PO hydrocodone 0.2 m/kg usually in combination with acetaminophen 10–20 mg/kg
- Benzodiazepam added: diazepam 0.1 mg/kg or lorazepam 0.05 mg/kg.

Pre-Rehabilitation Therapy:

- At request of therapist, PO hydrocodone 0.2 m/kg usually in combination with acetaminophen 10–20 mg/kg given with diazepam 0.1 mg/kg

Postoperative Pain:

Option A:

- IV Morphine via PCA pump (if >5 years), total dose 10–20 mg/kg per 4 h.

Option B:

- Attendant administered bolus, slow IV push morphine 0.03–0.05 mg/kg per 2 h (hold if level of responsiveness is decreased)

Neuropathic Pain

- Pain which is described as tingling, or burning in nature; like fire ants or ants walking with cleats; due to nerve entrapment, nerve damage, and venous congestion
- Pain often does not respond to opiates
- PO gabapentin (Neurontin) 100 mg, 300 mg, 600 mg
- Gabapentin dose: 5–30 mg/kg/dose q8h
- PO pregabalin (Lyrica) 50 mg, 100 mg
- Not indicated for small children
- Begin with 50 mg tid; then titrate up to 100 mg tid.
- PO amitriptyline 0.5–2 mg/kg. Do not advance to 2 mg/kg without checking blood level. Do not give with fluoxetine or sertraline; check PR interval on EKG

ANXIETY

Inpatient

- Before using anxiolytics address pain management
- PO lorazepam 0.05 mg/kg/dose q4h (scheduled while awake)

Outpatient

- If muscle relaxation is also desired, PO diazepam 0.1 mg/kg/dose q8–12h

ACUTE STRESS DISORDER OR POST-TRAUMATIC STRESS DISORDER SYMPTOMS

- PO Fluoxetine usually administer in the morning

≤20 kg	2.5 mg
≤40 kg	5 mg
>40 kg and <60 kg	10 mg
>60 kg	20 mg

- PO imipramine 1 mg/kg and increase slowly to 3 mg/kg as needed after checking concentration (usually used in young children where duloxetine could not be easily dosed)
- PO sertraline 1 mg/kg. Available as a 25-mg, 50-mg, and 100-mg tablet. Begin with 25 mg once daily; titrate dose as needed
- Approved for children 6 years old and older

Note: watch for serotonin syndrome characterized by agitation, confusion, rapid heart rate, dilated pupils, twitching muscles, muscle rigidity, heavy sweating

MANAGEMENT OF AGITATION AND HALLUCINATIONS NOT ASSOCIATED WITH ASD AND PTSD:

- PO risperidone (Risperdal)
- Children <5 years: Oral initial dose 0.1–0.2 mg once daily at bedtime
- Children ≥5 years and adolescents: Oral initial dose 0.2–0.5 mg once daily at bedtime; may titrate to the lowest effective dose every 1–2 days
- PO quetiapine (Seroquel)
- Children ≤10 years and adolescents ≤17 years: 25 mg twice daily on day 1; increase to 50 mg twice daily on day 2, then increase by 100 mg daily (administered twice daily) each day until 200 mg twice day is reached on day 5. May further increase up to 600 mg daily in increments of ≤100 mg daily. Usual dosage range: 400–600 mg daily; maximum: 600 mg daily

MANAGEMENT OF SLEEP NOT ACCOUNTED FOR AS ASD OR PTSD:

- Instruct in sleep hygiene
- Rule out pain and anxiety and itching
- PO Benadryl 1– 2 mg/kg at bedtime
- PO melatonin 0.01 mg/kg or 3 mg at bedtime
- PO zolpidem (Ambien) 5 or 10 mg with side effect of sleep walking
- PO Trazodone 1.5–2 mg/kg/dose qh

Reference: *Pediatric and Neonatal Dosage Handbook*, 21st Edition, Lexi-Comp

example, adults and adolescents may be able to work with the nurse to determine the day's schedule, to specify techniques that they have found make wound care go more smoothly, to choose to eat in the cafeteria instead of having meals served in their room, and to choose the music played during wound care. Children should be offered "forced choices" as often as possible to create a sense of control. Forced choice is a technique whereby a child is given two reasonable options and allowed to choose the one they prefer. For example, a child might be given a choice of whether to have wound care before lunch or after lunch, or whether he or she prefers to take medicine with apple juice

or milk. The key is to only provide two options and to ensure that the healthcare provider and parent are agreeable to whichever option is chosen. Kavanaugh has described how giving children more control during procedures can reduce the effects of learned helplessness and enhance pain tolerance.[210] He reported that children who were provided with the opportunity to participate in and make decisions about their wound care showed lower depression, anxiety, hostility, and stress scores than did controls.

Finally, psychological preparation can also play an important role in enhancing control and minimizing anticipatory anxiety. Patients can be provided with procedural or sensory preparatory information.[211,212] When providing procedural-based preparatory information, patients are explained the mechanics of their procedure (e.g., "we will unwrap your bandages, wash your wounds and débride necrotic skin, apply silver sulfadiazine cream, and then rewrap your dressings"). When providing sensory information, patients are prepared about what they might feel during a procedure ("You will likely feel a pulling sensation as we remove your dressings and a stinging sensation when we wash your wounds with an antiseptic"). Such information is usually helpful to patients, but it must be emphasized that some patients prefer to have as little information as possible, given their particular coping styles. It is best to follow a patient's lead in determining how much detail to provide when explaining upcoming procedures.[206]

One study found that a multimodal approach that combines procedural preparatory information and distraction was more effective at reducing pain, distress, and length of treatment than distraction alone.[212]

Another approach based on classical conditioning is relaxation training. Patients can be taught deep relaxation and imagery prior to undergoing painful procedures. The rationale is to counteract the anxiety stimulated by preprocedural stimuli with the relaxation response. If anticipatory anxiety is minimized with deep relaxation, the potential for a cyclical interaction between anxiety and acute pain is reduced. Recent topographic electroencephalographic (EEG) mapping during relaxation and imagery has shown changes in EEG activity that are similar to stage 1 sleep. Imagery also appears to activate the hippocampus, which is involved in emotion regulation.[213,214] Clinicians have also reported success with administering massage therapy on nonburned areas immediately prior to wound care.[215] Children who received 15 minutes of massage therapy reported lower pain scores during wound care than did a control group. A number of studies have applied relaxation training and stress inoculation techniques, as well as some of the behavioral techniques discussed later, to reduce burn pain.[216–224] One study even found that the simple technique of jaw relaxation practiced 20 minutes prior to dressing changes can significantly reduce pain and anxiety during and after the procedure.[225]

Operant Conditioning

The consequences that patients receive for showing pain can have implications for pain control. Since almost all burn procedures are extremely aversive, it will be the natural tendency of patients, particularly children, to be motivated to escape such events. Staff members who allow patients to terminate procedures might be reinforcing and potentially exacerbating such escape behaviors. When left unchecked this process can lead to a distressed patient becoming combative rather than tolerant of procedures. While such avoidance behavior should (more importantly) alert the staff that analgesia is inadequate and that the many potential pharmacologic protocols discussed earlier should be invoked, it can also occasionally suggest a need for further limit setting. Rewarding a patient with rest once a stage of wound care is completed, rather than stopping the procedure based on pain behavior, can be a useful means to minimize such escalating behavior. Children can also be given a predetermined number (usually five is adequate) of "timeout cards" that they can present at any time during wound care, each worth a 1-minute timeout or rest period. Once the cards are used up, they no longer have any timeouts. This technique can enhance their sense of control over the environment as well as ensuring that rest periods do not reinforce pain behaviors. Again, however, the goal of a burn team should be to provide enough preparation and analgesia in a preemptive fashion that the need for such escape behaviors does not develop in the first place.

Operant conditioning also has implications for the manner in which patients receive pain medication. When patients are medicated in response to pain behaviors, they are potentially receiving social reinforcement in terms of attention from the staff as well as the euphoric effects that the drugs might cause. This is one reason that, as mentioned earlier, it is far preferable that patients are medicated at regular time intervals rather than in response to their pain; the latter encourages them to complain more often in order to get the reward.[226] A similar application of operant principles is particularly important for the patient who excessively complains about pain out of emotional dependency needs, attention seeking, or in seeking the euphorigenic properties of the pain medications. In such patients, provided that adequate levels of pharmacologic analgesia have indeed been established, it may be important to extinguish pain behavior by ignoring it and simultaneously engaging the patient in distraction unrelated to pain. This is a model more consistent with that used for chronic pain but one that is occasionally useful for burn patients who seem to overreact independent of how aggressively pain is managed.[227]

Another common application of operant principles has to do with "token economies" for children. It can be extremely useful to reward children for successful completion of procedures by using star charts, prize boxes, or reinforcement schedules of this nature. Thus a child, upon completing a procedure, may receive a star in a grid that covers a week of burn care. Older children can use an accumulation of points to purchase a desired reward. Courage beads have also become popular in pediatric hospital settings. Differently colored beads are assigned to various painful or unpleasant procedures (e.g., wound care, physical therapy, X-ray, blood draws, etc.). Each time a child completes one of these unpleasant procedures, he or she receives a corresponding bead and adds it to a necklace. Both boys and girls have responded positively to these necklaces and often wear or display them as a source of pride. It is important that children are rewarded for completing procedures

rather than for "being brave" as the latter can serve as a subtle form of punishment to children; in other words, reinforcement should not be withheld if children act out and have a bad day during wound care as long as wound care is completed.[208,209]

One final application of operant principles that is borrowed from the chronic pain literature is the use of a quota system that rewards activity with rest. This is particularly useful with patients who are overwhelmed by therapies or who appear to have poor motivation. Patients complete predetermined quotas of activity that are within their capacity and then are allowed to rest. A baseline assessment determines what is within their capacity. For example, a patient who is trying to walk with burned legs might be instructed to walk until tired for three therapy sessions. The distance walked is recorded for those three sessions, the average is taken, and 80% of that average becomes the starting point. For example, the patient walks 50, 150, and 100 feet during three sessions. The average is 100 feet, and 80% of that is 80 feet. This (80 feet) becomes the starting point. Patients start at 80 feet and increase that amount by 5% (about 5 feet) each session. If they fail to meet a quota, they return to the last successful one. However they also quit when they reach the goal. They do not keep exercising even when they are having a "good day." This addresses the problem of pacing and overfatigue. Ehde, Patterson, and Fordyce have reported the successful use of the quota system with a number of patients with burn injury, both in terms of increasing therapy performance and reducing depression.[228]

Cognitive Interventions

How patients think about their pain can be regarded as a modifiable behavior and, in turn, can influence the degree of suffering they experience. As such, an important nonpharmacologic approach is to draw out the thoughts patients have about their pain and teach them to modify these thoughts accordingly. A particularly salient example is catastrophizing about pain. Catastrophizing thoughts include those such as "I cannot stand this pain," "I will never get better," or "The pain means I will die." Such catastrophizing thoughts have been associated with greater amounts of pain and less favorable health outcomes in a variety of studies. Patients can be taught to challenge and reinterpret such thoughts. Along the same lines, it can be useful to teach patients to reinterpret the meaning of their pain sensations. For example, the appearance of skin buds and enhanced pain sensation may indicate that a wound is healing and skin grafts may not be necessary.[206]

Under the rubric of cognitive interventions patients may be taught techniques to enhance their ability to cope with pain. Positive self-talk and imagery designed to facilitate coping during periods of pain are examples of this. Thurber and colleagues have described the *two-process model of control* as it relates to controlling pediatric burn pain.[209] In terms of primary control, the patient attempts to modify the objective conditions of the painful procedure, such as negotiating how and when a dressing change will take place. In secondary control, the patient makes adjustments so that he or she can better tolerate the difficult procedures (e.g., positive self-talk vs. catastrophizing). Thurber et al.[209] and Martin-Herz et al.[208] have published a two-part series on a conceptualization of psychological approaches to burn pain, as well as specific examples for treatment. Crucial in choosing an approach is the assessment of a person's coping strategies. Simply, most adult and pediatric patients have coping styles that fall on an approach-avoidant continuum. At one end of the continuum is the avoidant coping style in which patients prefer to turn away or be distracted during painful procedures. Any distraction technique described in this chapter would be appropriate for this group of patients. On the opposite anchor of the continuum are those with an approach coping style who seek information and like to be involved as much as possible in their care. In this group, having them participate in wound care and giving them as much information as they request will help to decrease their anxiety. If they are told to close their eyes, turn away, and distract themselves from the procedure at hand, their anxiety will only increase.

Distraction is another cognitively based approach to pain control. Processing pain requires a certain amount of conscious attention, and distracting such patients' attention can enable them to tolerate pain better. Movies, music therapy, and games have all been used with some success as distraction techniques for burn pain.[221,223,229] Music has the additional benefit of inducing a relaxation response.[220,230] One study found that music therapy significantly reduced pain and anxiety levels and muscle tension before, during, and after dressing changes.[231]

Augmented Reality

Another form of distraction-gaining attention is the use of *augmented reality* or *virtual reality* (VR) technology. Several researchers have reported on the use of immersive VR as a powerful analgesic.[229,232–242]

VR can immerse patients' attention in a computer-generated world and engage them in interaction with that world. These investigators indicate that VR can significantly reduce pain during wound care and physical therapy,[232] even relative to computer game distraction and television.[233,243] Recently Morris et al. conducted a systematic review on the use of VR distraction for reducing both pain and anxiety in acute burn pain.[244] They found nine studies that met their rigorous inclusion criteria. Results showed that VR distraction is most often used for burn wound care and physical therapy and as an adjunct to pharmacotherapy. When compared to pharmacotherapy alone, it appears that VR distraction is superior in reducing pain. Other interactive video-gaming technology that tracks body movements has also been shown to enhance participation and reduce pain and anxiety during physical therapy.[245,246]

Finally, one randomized controlled trial looked at the used of augmented reality in reducing acute procedural pain in burn patients.[247] Augmented reality overlays virtual images onto the physical world, rather than creating a complete immersive virtual world as in traditional virtual reality. They randomized 42 children between the ages of 3 and 14 years into either the experimental or control

condition and found that augmented reality significantly reduced mean pain scores. This technique shows promise as well.

Hypnosis

Hypnosis involves a blend of relaxation, imagery, and cognitive-based approaches. This technique deserves special attention because there are a number of reports on its use with burn pain, and, when it is effective, its impact on burn pain can be quite dramatic. There are more than 100 anecdotal reports in the literature indicating that hypnosis can dramatically reduce pain, and at least a dozen have been done with pain from burn injuries; however such studies lack control groups, standard measures of pain, or information about pain medications.[248] More recently, tightly controlled studies with reliable measures of pain have supported hypnosis as an effective nonpharmacologic approach to burn pain.[249,250] Patterson and Jensen have reported 12 controlled studies on chronic pain and 17 with acute pain indicating pain reduction; indeed, this modality is becoming far more scientifically acceptable.[251]

Patients with burn injuries are ideal candidates for hypnosis for a number of reasons. In a review of such factors, Patterson et al. listed motivation, regression, dissociation, and hypnotizability as factors that promote hypnotic analgesia on the burn unit.[252] Specifically patients who are faced with the excruciating nature of burn pain are motivated to engage in techniques such as hypnosis. The nature of a burn and its resulting care can cause a patient to become emotionally regressed (i.e., more dependent on the burn staff) and dissociated (i.e., removed from their emotions), and both of these factors seem to be associated with hypnotizability. Such factors likely account for the frequent dramatic effects that are seen with hypnosis during burn care. On the other hand, hypnosis clearly will not benefit some burn patients, and the degree to which patients are inherently hypnotizable (or not hypnotizable) almost certainly has some bearing on this issue.[252]

The protocol used by Patterson and colleagues[243–251,253–255] is to provide hypnosis prior to wound care and have nurses provide standard post-hypnotic suggestions during wound care. This approach is efficient for both the hypnotist and the nurses. Patterson et al. have recommended that hypnosis used in this fashion be an adjunct to, rather than replacement for, pain medication.[250] A randomized controlled trial by Wiechman et al. used this protocol for burn wound pain and found that hypnosis significantly reduced the affective component of pain when compared to an attention-only control group.[256] Furthermore Shakibaei et al. conducted a randomized controlled trial of hypnosis for reducing pain and flashbacks in burn patients.[257] They also showed that the hypnotherapy group had significantly lower pain ratings and fewer flashbacks than did the control group.

VIRTUAL REALITY HYPNOSIS

More recently, investigators have combined immersive VR with hypnosis in order to control burn pain. This approach has the advantage of not requiring a trained hypnotist to be present and appears to work as well as "live hypnosis."[255,257] The technology simply requires patients to open their eyes and watch the induction presented to them; minimal cognitive effort or skill is required. Delivering hypnosis in this way addresses several concerns of standard therapist-induced hypnosis. First, this standardized procedure allows for greater use in that it does not require a trained therapist to be present at each session. Second, with the visual images in front of them, it decreases the extent of cognitive effort required. This is important for patients who are taking opiate medications and cannot concentrate as effectively. It also helps those who are lower in visual imagery skills and therefore unable to visually imagine the scenes described by the therapist during traditional hypnosis. One clinical case series of 13 patients used hypnotic analgesia delivered through VR technology for patients with burn injuries. Pre- and postprocedure pain ratings were collected from patients undergoing painful wound care procedures over a 3-day period. There was a decrease in reported pain and anxiety, the need for opioid medication was cut in half, and there were no undesirable side effects. No randomized controlled trials have yet been published.

OTHER APPROACHES

There is some evidence that TENS can be effective with burn pain,[258] but we are aware of only one study of this nature. Massage therapy has been reported to be useful in reducing burn pain.[259] We are unaware of any studies on the efficacy of acupuncture on burn pain although this modality has been useful in controlling pain from a variety of different etiologies. The acute nature and variable distribution of burn pain may make acupuncture a challenging modality to apply to this problem.

For patients in the post-hospital, long-term rehabilitation phase, nonpharmacologic approaches from physical and occupational therapists become critical. Stretching, strengthening, increasing activity, and hot/cold therapy may all become instrumental in enhancing pain control during the rehabilitative stage.

EMPIRICAL SUPPORT

Recently there have been several rigorous systematic reviews of studies that have focused on both pediatric and adult nonpharmacological pain management strategies. In a review of risk factors for anticipatory distress to painful medical procedures, Racine and colleagues found 77 articles that addressed this issue. Their review concluded that the factors most relevant in increasing anticipatory distress in children undergoing painful medical procedures are child psychopathology, difficult child temperament, parental distress, previous painful events, a parent's anticipation of distress, and anxious disposition in parents. Many of these factors are amenable to intervention with the techniques mentioned in this chapter. It appears that parents' presence during painful procedures is neither inherently good nor bad, but is instead entirely dependent on the characteristics of the parents and their ability to provide a calming presence. A focus on training parents in distress-reducing behaviors is warranted.[260] Hanson, Gauld, Wathen, and MacMillan conducted a systematic review of nonpharmacological interventions for acute procedural pain in pediatric patients with

burn injuries.[261] Using a systematic review of methods of the U.S. Preventative Services Task Force, they found 12 articles that met the study criteria and seven of the 12 articles were rated as "fair or good." They categorized these 12 articles into child-mediated interventions, parent-mediated interventions, and healthcare provider-mediated interventions. Of the child-mediated interventions, both VR distraction and stress management showed promising effects. Of the healthcare provider interventions, massage therapy and optimizing patient control during wound care were effective at relieving wound care pain when compared to a control group. Parent-mediated interventions were not found to be effective, and, in fact, one study showed an increase in childrens' distress when parents were present.[262] Although the study designs in these interventions were rated as poor, the findings are consistent with those reported by clinicians, in that parental presence during painful procedures can either help or hurt a child depending on the parents' affect and ability to soothe their child. This is a difficult intervention to study, but one that deserves more attention in this era of family-centered care and the emphasis on increased parental involvement in a child's care. It would be a tremendous benefit to the field if we could determine which variables are necessary to facilitate a positive parental presence and which variables serve as barriers to the success of this practice. Hanson et al.[261] acknowledged that it is very difficult to conduct randomized controlled trials with adequate sample sizes in this population, but we must strive to find empirical support for the techniques that we choose.

De Jong et al. also conducted a systematic review of the literature for nonpharmacological interventions for acute burn pain in adults.[263] They found that hypnosis was the most frequently studied intervention and that the majority of the studies on hypnosis showed a beneficial effect when compared to a control group. They concluded that hypnosis seems to have a strong impact on the affective component of pain. Their review also showed beneficial effects of distraction relaxation and found that any technique that enhances a patient's control over the situation is beneficial.

The authors of these systematic reviews provided directions for future researchers that would advance our knowledge of the effectiveness of nonpharmacological interventions. These suggestions included the need for large sample sizes, documentation regarding study response rates and randomization methods, experimental control for premorbid psychosocial variables, details on instructions given to patients, cost outcomes, and assurance of treatment integrity/adherence.[261,264]

Conclusion

The state of the art in burn pain management would seem to be based more on personal bias and tradition than on a systematic, scientific approach. In addition, the number of pharmacokinetic studies of pain-relieving drugs of any kind in young children is virtually nil. Since approximately 35% of all burn injuries occur in children under 16 years of age, with a great majority of these occurring in children under 2 years of age, we have almost no information on which to base the use of pain-relieving drugs in burned children. It is no wonder that Perry and Heidrick[264] found great disparity in what burn care staff would order or administer to a young child as compared to an adult with burns of similar size and area of distribution on the body. More pharmacokinetic studies in both adults and children with burn injuries must be initiated.

Similar to the lack of conclusive data about the use of the various opioids or anxiolytic agents is the scarcity of scientific data to recommend any of the nonpharmacologic techniques. However significant progress has been made just since the previous edition of this book 5 years ago. Most burn centers recognize anxiety as contributing to patient discomfort and are beginning to treat both anxiety and pain. Standardized protocols such as the guidelines (see Table 64.9)[2] modified for starting doses of medication from the Shriners Burn Hospital in Galveston are being disseminated. Nonpharmacologic techniques are more frequently included in a center's repertoire of tools for managing anxiety and recognized as a definite adjunct to pharmacotherapy. The major problem currently with these techniques is that they are personnel intensive and therefore are often not offered or reimbursed in the current managed care environment in the United States.

How, then, can we provide the "best" pain management for a burned patient? Probably the first answer to that question is vigilance in assessment and flexibility in treatment. Patients show great individual variation in their responses to the variety of agents and modalities presented. A successful approach with a burned patient requires that healthcare personnel understand the pain associated with the different depths of wounds, the phase of the healing process, and the components of the pain response. For the burned patient during the initial 3–7 days, the more superficial areas give rise to moderate or severe pain, while the full-thickness areas contribute less to the overall pain response.[11] Although moderate to severe pain is usually related to procedures or physical therapy, background pain (or pain at rest) is usually described as mild or very mild but may be exacerbated by emotional concerns and anxiety. By the second week post-burn, the moderately deep partial-thickness burn with its multitude of skin buds accounts for the majority of the moderate to severe pain. In many burn centers, deep dermal and full-thickness burns are excised and grafted between the third and tenth days post-burn. Although this often eliminates the severe pain associated with wound débridement during the second and third week, donor sites are often as painful as the areas of more superficial burns were initially. Dressing changes 3–5 days post-grafting also may be accompanied by the removal of sutures or staples, a procedure that is usually described by patients as excruciatingly painful. By the third or fourth week, if the wounds are not mostly healed, anxiety and depression may cause a patient to perceive increased levels of pain. And, within a single phase of recovery and within a single patient, pain frequency and intensity will vary from day to day. A fixed and inflexible approach to treatment is likely to overmedicate on one day and undermedicate the next.

To avoid over- and undermedication in adults, regimens that allow patients to control their own therapy seem most appropriate. This is very important for adults and teenagers, but children also can benefit from having this control. PCA can be used safely by many children and should not be

disregarded as a tool on the basis of age alone. For procedural pain, patient control regimens may include self-administered nitrous oxide, PCA, hypnosis, a variety of behavioral approaches, or a combination of these approaches. For background pain, the best control seems to be the use of slow-release opioids or other pain cocktails given on a nonpain contingent basis (i.e., scheduled every 4–6 hours) with the flexibility to supplement this with p.r.n. or "as-desired" medication. Another approach is to use PCA with or without a continuous low-dose infusion of narcotics. A variety of nonpharmacologic therapies may also help relieve background pain. Again, the most important aspect to remember with all of these regimens is flexibility. The other obvious aspect is to remember that a patient is not only the best person to assess his pain, but he is also the best to evaluate the success of the therapies provided.

As challenging as managing comfort is for the healthcare provider, it is equally important to the burned patient. Recent studies suggest both physiologic and psychological reasons to successfully manage pain. Kavanagh et al.[265] demonstrated that pain in a burned patient adds significantly to the physiologic demands caused by stress. Schreiber and Galai-Gat[266] as well as Ptacek et al.[8] have shown that successful pain management can significantly reduce the occurrence of psychological disorders such as post-traumatic stress syndrome.

Burn care professionals who desire to keep their patients as comfortable as possible can perhaps best prepare themselves by learning to:

- watch and listen to their patients with vigilance;
- use a standardized assessment tool for measuring discomfort on a scheduled basis as well as during moments when the patient is complaining, either verbally or behaviorally, pre- and post-administration of treatment;
- know how discomforts are likely to change as the patient recovers;
- include a variety of pharmacologic and nonpharmacologic methods for managing discomfort and be prepared to change as the patient's needs change;
- feel comfortable with a process that never ends, but which can bring many moments of relief for the patient and satisfaction for the caregivers.

Complete references available online at
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References

1. Stoddard FJ, Sheridan RL, Saxe GN, et al. Treatment of pain in acutely burned children. *J Burn Care Rehabil*. 2002;23:135-156.
2. Ratcliff SL, Brown A, Rosenberg L, et al. The effectiveness of a pain and anxiety protocol to treat the acute pediatric burn patient. *Burns*. 2006;32:554-562.
3. Anand KJS, Hickey PR. Pain and its effects in the human neonate and fetus. *N Engl J Med*. 1987;317:1321-1329.
4. Gracely RH. Pain measurement. *Acta Anaesthesi Scand*. 1999;43:897-908.
5. Tsuda M. Microglical regulation of neuropathic pain. *J Pharmacol Sci*. 2013;121:89-94.
6. Meyer RP, Campbell JN. Myelinated nociceptive afferent account for hyperalgesia that follows a burn to the hand. *Science*. 1981;213:1527-1529.
7. Summer GJ, Dina OA, Levine JD. Enhanced inflammatory hyperalgesia after recovery from burn injury. *Burns*. 2007;33(8):1021-1026.
8. Ptacek J, Patterson D, Doctor J. Describing and predicting the nature of procedural pain after thermal injuries: implications for research. *J Burn Care Rehabil*. 2000;21:318-326.
9. Atchison NE, Osgood PF, Carr DB, Szyfelbein SK. Pain during burn dressing change in children: relationship to burn area, depth and analgesic regimens. *J Pain*. 1991;47(1):41-45.
10. Esfahlan AJ, Lotfi M, Zamanzadeh V, Babapuor J. Burn pain in patients' responses. *Burns*. 2010;36(7):1129-1133.
11. Choinière M, Melzack R, Rondeau J, Girard N, Paguin MJ. The pain of burns: characteristics and correlates. *J Trauma*. 1989;29(11):1531-1539.
12. Ulmer JF. An exploratory study of pain, coping, and depressed mood following burn injury. *J Pain Sympton Manage*. 1997;13:148-157.
13. Saxe G, Stoddard F, Chawla N, et al. Risk factors for acute stress disorder in children with burns. *J Trauma Dissociation*. 2005; 6(2):37-49.
14. Edwards RR, Magyar-Russell G, Thombs B, et al. Acute pain at discharge from hospitalization is a prospective predictor of long-term suicidal ideation after burn injury. *Arch Phys Med Rehabil*. 2007;88(12 suppl 2):S36-S42.
15. Song L, Wang S, Zuo Y, et al. Midazolam exacerbates morphine tolerance and morphine-induced hyperactive behaviors in young rats with burn injury. *Brain Res*. 2014;1564:52-61.
16. Charlton JE, Klein R, Gagliardi G. Factors affecting pain in burned patients: a preliminary report. *Postgrad Med*. 1983;59:604-607.
17. Nilsson A, Kalman S, Sonesson LK, Arvidsson A, Sjöberg F. Difficulties in controlling mobilization pain using standardized patient-controlled analgesia protocol in burns. *J Burn Care Res*. 2011;32(1):166-171.
18. Beales JG. Factors influencing the expectation of pain among patients in a children's burn unit. *Burns*. 1983;9:187-192.
19. Ponten B. Grafted skin: observations on innervation and other qualities. *Acta Clin Scand*. 1960;257(suppl):1-5.
20. Freund PR, Brengelmann GL, Rowell LB, Engrav L, Heimbach DM. Vasomotor control in healed grafted skin in humans. *J Appl Physiol Respir Environ Exerc Physiol*. 1981;51(1):168-171.
21. Richiebe P, Rivat C, Cahana A. Stress-induced hyperalgesia: any clinical relevance for the anesthesiologist? *Anesthesiology*. 2011;114(6):1280-1281.
22. Flood P, Clark JD. Molecular interaction between stress and pain. *Anesthesiology*. 2016;124(5):994-995.
23. Donello JE, Guan Y, Tian M, et al. A peripheral adrenoceptor-mediated sympathetic mechanism can transform stress-induced analgesia into hyperalgesia. *Anesthesiology*. 2011;114(6):1403-1416.
24. Summer GJ, Puntillo KA, Miaskowski C, Green PG, Levine JD. Burn injury pain: the continuing challenge. *J Pain*. 2007;8(7):533-548.
25. Reference deleted at revises.
26. Loram LC, Harrison JA, Chao L, et al. Intrathecal injection of an alpha 7 nicotinic acetylcholine receptor agonist attenuates GP120-induced mechanical allodynia and spinal pro-inflammatory cytokine profiles in rats. *Brain Behav Immun*. 2010;24(6):959-967.
27. Bittner EA, Shank E, Woodson L, Martyn JAJ. Acute and perioperative care of the burn-injured patient. *Am Soc Anesthesiol*. 2015;122(2):448-464.
28. Al-Hasani R, Bruchas MR. Molecular mechanisms of opioid receptor-dependent signaling and behavior. *Anesthesiology*. 2011;115(6): 1363-1381.
29. De Jong AE, Bremer M, Hofland HW, et al. The visual analogue thermometer and the graphic numeric rating scale: a comparison of self-report instruments for pain measurement in adults with burns. *Burns*. 2015;41(2):333-340.
30. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain*. 1975;1:277-299.
31. Gordon M, Greenfield E, Marvin J, Hester C, Lauterbach S. Use of pain assessment tools: is there a preference? *J Burn Care Rehabil*. 1998;19(5):451-454.
32. Grossi E, Broghi C, Cerchiari EL. Analogic Chromatic Continuous Scale (ACCS): a new method for pain assessment. *Clin Rheumatol*. 1983;1:337-340.
33. Wong D, Baker C. Pain in children: comparison of assessment scales. *Pedia Nurs*. 1988;14:9-17.
34. American Academy of Pediatrics and American Pain Society. Joint policy statement on pain in children. *Pediatrics*. 2001;108:793-797.
35. Attia J, Amiel-Tison C, Mayer MN, Shnider SM, Barrier G. Measurement of postoperative pain and narcotics administration in infants using a new clinical scoring system. *Anesthesiology*. 1987;67:A532.
36. Szyfelbein SK, Osgood PF, Carr DB. The assessment of pain and plasma β-endorphin immunoactivity in burned children. *Pain*. 1985;22:173-182.
37. Williamson PS, Williamson ML. Physiologic stress reduction by a local anesthetic during newborn circumcision. *Pediatrics*. 1983;71:36-40.
38. Fuller B. FM signals in infant vocalizations. *Cry*. 1985;6:5-10.
39. Fuller B, Horii Y. Differences in fundamental frequency, jitter and shimmer among four types of infant vocalizations. *J Commun Dis*. 1986;18:111-118.
40. Fuller B, Horii Y. Spectral energy distribution in four types of infant vocalizations. *J Commun Dis*. 1988;20:111-121.
41. Franck LS. A new method to quantitatively describe pain behavior in infants. *Nurse Res*. 1986;35:28-31.
42. Granau RVE, Craig KD. Pain expression in neonates: facial action and cry. *Pain*. 1987;28:395-410.
43. Johnston C, O'Shaughnessy D. Acoustical attributes of infant pain cries: discriminating features. In: Dubner R, Gebhart G, Bond M, eds. *Pain Research Clinical Management*. Vol. 3. Amsterdam: Elsevier; 1988:341-347.
44. Izard CE, Huebner RR, Risser D, McGinnes GC, Douougherty LM. The young infant's ability to produce discrete emotional expressions. *Dev Psychol*. 1980;16:132-140.
45. Craig KD, McMahon RJ, Morison JD, Zaskow C. Developmental changes in infant pain expression during immunization injections. *Soc Sci Med*. 1984;19:1331-1337.
46. Johnston CC, Strada ME. Acute pain response in infants: a multidimensional description. *Pain*. 1986;24:373-382.
47. Katz ER, Kellerman J, Siegel SE. Behavioral distress in children with cancer undergoing medical procedures: developmental considerations. *J Consult Clin Psychol*. 1980;48:356-365.
48. Mills N, Preston A. Acute pain behaviors in infants/toddlers. In: Funk S, Tomquist E, Champagne M, et al, eds. *Key Aspects of Comfort: Management of Pain, Fatigue and Nausea*. New York: Springer; 1989:52-59.
49. McGrath PJ, Johnson G, Goodman JT, et al. *CHEOPS: A Behavioral Scale for Rating Pain Research and Therapy*. New York: Raven Press; 1985:395-402.
50. Tyler DC, Tu A, Douthit J, Chapman CR. Toward validation of pain measurement tools for children: a pilot study. *Pain*. 1993;52:301-309.
51. Merkel SI, Voepel-Lewis T, Shayevitz JR, The Malviya S. FLACC: a behavioral scale for scoring postop weRICW pin in young children. *Pediatr Nurs*. 1997;23:293-297.
52. Shen J, Giles SA, Kurtovic K, et al. Evaluation of nurse accuracy in rating procedural pain among pediatric burn patients using the Face, Legs, Activity, Cry, Consolability (FLACC) scale. *Burns*. 2017;43(1):114-120.
53. Barone M, McCall J, Jenkins M, Warden G The development of a Observational Pain Scale (OPAS) for Pediatric Burns. Abst 230. Presented at the 32nd Annual Meeting of the American Burn Association, Las Vegas, Nevada, March 14–17, 2000.
54. Beyer J, Aradine C. Content validity of an instrument to measure young children's perceptions of the intensity of their pain. *Pedia Nurs*. 1986;1:386-395.
55. Beyer J, Aradine C. Patterns of pediatric pain intensity: a methodological investigation of self-report scale. *Clin J Pain*. 1987;3:130-141.

56. Beyer J, Aradine C. The convergent and discriminant validity of a self report measure of pain intensity for children. *Children's Health Care*. 1981;16:274-282.
57. McGrath PA, de Veber L, Hearn M. Multidimensional pain assessment in children. In: Fields H, Dubner R, Cerrera F, eds. *Advances in Pain Research and Therapy*. New York: Raven Press; 1985:387-393.
58. Maunuksela EL, Ollskola KT, Korpela R. Measurement of pain in children with self-reporting and behavioral assessment. *Clin Pharma Ther*. 1987;42:137-141.
59. Bieri D, Reeve RA, Champion GD, Addicoat L, Ziegler JB. The face pain scale for the self-assessment of the severity of pain experienced by children: development, initial validation, and preliminary investigation of ratio scale properties. *Pain*. 1980;41:139-160.
60. Hester NO. The pre-operational child's reaction to immunization. *Nurse Res*. 1979;28:250-254.
61. Varni JW, Thompson KL, Hanson V. The Varni/Thompson Pediatric Pain Questionnaire in chronic musculoskeletal pain in juvenile arthritis. *Pain*. 1987;28:23-38.
62. Eland J. Minimizing pain associated with pre-kindergartner intra muscular injections. *Issues Compr Pedia Nurs*. 1981;5:361-372.
63. McGrath PJ, Unruh AM. *Pain in Children and Adolescents*. Amsterdam: Elsevier; 1987:351.
64. Sevedra M, Gibbons P, Tesler M, Ward J, Wegner C. How do children describe pain? A tentative assessment. *Pain*. 1982;14(2):95-104.
65. LeBaron S, Zettzer L. Assessment of acute pain and anxiety in children and adolescents by self-report, observer reports, and behavior checklist. *J Consult Clin Psychol*. 1984;52:729-738.
66. Maunuksela EL, Ollskola KT, Korpela R. Measurement of pain in children with self-reporting and behavioral assessment. *Clin Pharma Ther*. 1987;42:137-141.
67. McCaffery M, Beebe KD. *Pain: Clinical Manual for Nursing Practice*. St. Louis: Mosby; 1989.
68. Reiman M, Gordon M, Marvin J. Pediatric nurses' knowledge and attitudes survey regarding pain: a competency tool modification. *Pediatric Nurs*. 2007;33:303-306.
69. Robert R, Blakeney P, Villarreal C, Meyer WJ. Anxiety: current practices in assessment and treatment of anxiety of burn patients. *J Burn Care Rehabil*. 2000;26:549-552.
70. Siverman W, Kurtines W. *Anxiety and Phobic Disorders: A Pragmatic Approach*. New York: Plenum Press; 1996.
71. Walk RD. Self-ratings of fear in a fear invoking situation. *J Abnorm Soc Psychol*. 1956;52:171-178.
72. Taal LA, Faber AW. The burn specific pain anxiety scale: introduction of a reliable and valid measure. *Burns*. 1997;23:147-150.
73. Taal LA, Faber AW, van Loey NEE, Reynders CL, Hofland HW. The abbreviated burn specific pain anxiety scale: a multicenter study. *Burns*. 1999;25(6):493-497.
74. Aaron LA, Patterson DR, Finch CP, Carrougher GJ, Heimbach DM. The utility of a burn specific measure of pain anxiety to prospectively predict pain and function: a comparative analysis. *Burns*. 2001;27(4):329-334.
75. Casaer M, Kums V, Souters PJ, Van den Kerckhove E, Van den Berghe G. Pruritus in patients with small burn injuries. *Burns*. 2008;34:185-191.
76. Carrougher GJ, Martinez EM, McMullen KS, et al. Pruritus in adult burn survivors: postburn prevalence and risk factors associated with increased intensity. *J Burn Care Res*. 2013;34:94-101.
77. Schneider JC, Nadler DL, Herndon DN, et al. Pruritus in pediatric burn survivors: defining the clinical course. *J Burn Care Res*. 2015;36:151-158.
78. Van Loey NE, Bremer M, Faver AW, Middelkiip E, Nieuwenhuis MK. Itching following burns: epidemiology and predictors. *Br J Dermatol*. 2008;158:95-100.
79. McGarry S, Surrows S, Ashoorian T, et al. Mental health and itch in burns patients: potential associations. *Burns*. 2016;42(4):763-768.
80. Kazis L, Lee A, Hinson F, et al. Methods for assessment of health outcomes in children with burn injury: the multi-center benchmarking study. *J Trauma*. 2012;73:S179-S188.
81. Field T, Peck M, Hernandez-Reif M, et al. Postburn itching, pain, and psychological symptoms are reduced with massage therapy. *J Burn Care Rehab*. 2000;21(3):189-193.
82. Blakeney P, Marvin J Itch Man Scale. Shriners Hospitals for Children. Reprinted with the permission of Shriners Hospitals for Children. 2000.
83. Morris VE, Murphy LM, Rosenberg M, et al. Itch Assessment Scale for the pediatric burn survivor. *J Burn Care Res*. 2012;33:419-424.
84. Van Loey NEE, Hofland HW, Hendrickx H, et al. Validation of burns Itch questionnaire. *Burns*. 2016;42(3):526-534.
85. Yosipovitch G. Itch questionnaires as tools for itch evaluation. In: Yosipovitch G, Greaves MW, Fleischer AS, McGlone F, eds. *Itch: Basic Mechanisms and Therapy*. New York: Marcel Dekker; 2004:169-182.
86. Gerding RL, Imbembo AL, Fratianne RB. Biosynthetic skin substitute vs. 1% silver sulfadiazine for treatment of inpatient partial-thickness thermal burns. *J Trauma*. 1988;28:1265-1269.
87. Demling RH. Use of Biobrane in management of scalds. *J Burn Care Rehabil*. 1995;16:329-330.
88. Ou LF, Lee SY, Chen YC, Yang RS, Tang YW. Use of Biobrane in pediatric scald burns – experience in 106 children. *Burns*. 1998;24(1):49-53.
89. Barret JP, Dziewulski P, Ramzy PI, et al. Biobrane versus 1% silver sulfadiazine in second-degree pediatric burns. *Plastic Reconstr Surg*. 2000;105(1):62-65.
90. Schulz A, Depner C, Lefering R, et al. A prospective clinical trial comparing Biobrane®, Dressilk®, and PolyMem® dressings on partial-thickness skin graft donor sites. *Burns*. 2016;42:345-355.
91. Everett M, Massand S, Davis W, Burkey B, Glat PM. Use of a copolymer dressing on superficial and partial-thickness burns I a paediatric population. *J Wound Care*. 2015;24(7):S4-S8.
92. Glat PM, Zhang SH, Burkey BA, Davis WJ. Clinical evaluation of a silver-impregnated foam dressing in paediatric partial-thickness burns. *J Wound Care*. 2015;24(4):S4-S10.
93. Gee Kee EL, Kimble RM, Cuttle L, Khan A, Stockton KA. Randomized controlled trial of three burns dressings for partial thickness burns in children. *Burns*. 2015;41:946-955.
94. Yang B, Wang X, Li Z, Qu Q, Qiu Y. Beneficial effects of silver foam dressing on healing of wounds with ulcers and infection control of burn patients. *Pak J Med Sci*. 2015;31(6):1334-1339.
95. Silva MO, Yañez V, Hidalgo G, Valenzuela F, Saavedra R. 5% Lidocaine medicated plaster use in children with neuropathic pain from burn sequelae. *Pain Med*. 2013;14:422-429.
96. Molan P, Rhodes T. Honey: a biologic wound dressing. *Wounds*. 2015;27(6):141-151.
97. Nisbet HO, Nisbet C, Yarim M, Guler A, Ozak A. Effects of three types of honey on cutaneous wound healing. *Wounds*. 2012;22(11):275-283.
98. Subrahmanyam M. Honey dressing accelerates split-thickness skin graft donor site healing. *Indian J Surg*. 2015;77(suppl 2):S261-S263.
99. Fischer S, Wall J, Pomahac B, Riviello R, Halvorson EG. Extra-large negative pressure would therapy dressings for burns – initial experience with technique, fluid management, and outcomes. *Burns*. 2016;42:457-465.
100. Levi B, Ibrahim A, Mathews K, et al. The use of CO_2 fractional photothermolysis for the treatment of burn scars. *J Burn Care Res*. 2016;37:106-114.
101. Klinger M, Marazzi M, Vigo D, Torre M. Fat injectin for cases of severe burn outcomes: a new perspective of scar remodeling and reduction. *Aesth Plast Surg*. 2008;32:465-469.
102. Maenthaisong R, Chaiyakunapruk N, Niruntraporn S, Kongkaew C. The efficacy of aloe vera used for burn wound healing: a systematic review. *Burns*. 2007;33:713-718.
103. Khorasani F, Hosseinmehr SJ, Azadbakht M, Zamani A, Mahdavr MR. Aloe versus silver sulfadiazine creams for second degree burns: a randomized controlled study. *Surg Today*. 2009;39:587-591.
104. Welling A. A randomized controlled trial to test the analgesic efficacy of topical morphine on minor superficial and partial thickness burns in accident and emergency departments. *Emerg Med J*. 2007;24:408-412.
105. Oremus M, Hanson MD, Whitlock R, et al. A systematic review of heparin to treatment burns injury. *J Burn Care Res*. 2007;28:794-804.
106. Sargent RL. Management of blisters in the partial-thickness burn: an integrative research review. *J Burn Care Res*. 2006;1:66-68.
107. Ang E, Lee ST, Gan CS, et al. Pain control in a randomized, controlled, clinical trial comparing moist exposed burn ointment and conventional methods in patients with partial-thickness burns. *J Burn Care Rehabil*. 2003;24:289-296.

108. Varas RP, O'Keeffe T, Namias N, et al. A prospective, randomized trial of Acticoat versus silver sulfadiazine in the treatment of partial thickness burns: which method is less painful? *J Burn Care Rehabil*. 2005;26:344-347.
109. Letouze A, Volnchet V, Hoecht B, et al. Using a new lipidocolloid dressing in paediatric wounds: results of French and German clinical studies. *J Wound Care*. 2004;13(6):221-225.
110. Tan PWW, Ho WC, Song C. The use of Urgotul™ in the treatment of partial thickness burns and split-thickness skin graft donor sites: a prospective control study. *Int Wound J*. 2009;6:295-300.
111. Alves HRN, Cavalcente de Almeida PC, Grillo VAT, et al. Clinical experiences of using a cellulose dressing on burns and donor site wounds. *J Wound Care*. 2009;18:27-30.
112. White R, Morris C. Mepitel: anon-adherent wound dressing with Safetac technology. *Br J Nurs*. 2009;18:58-64.
113. Edwards J. The use of Silfex in burn wound management. *Br J Community Nursing*. 2009;S32-S36.
114. Uhlig C, Rappp M, Hartmann B, et al. Suprathel- Ann innovative resorbable skin substitute for the treatment of burn victims. *Burns*. 2007;33:221-229.
115. Waldrop K, Serfass A. Clinical effectiveness of non contact low frequency non thermal ultrasound in burn care ostomy. *Ostomy Wound Management*. 2008;54(6):66-69.
116. Samies J, Gehling M. Acoustic pressure wound therapy for management of mixed partial- and full-thickness burns in a rural wound center. *Ostomy Wound Mgmt*. 2008;54(3):56-59.
117. Blanchet B, Jullien V, Vinsonneau C, Tod M. Influence of burns on pharmacokinetics and pharmacodynamics of drugs used in the care of burn patients. *Clin Pharmacokinet*. 2008;47(10):635-654.
118. Han T, Hamatz JS, Greenblatt DJ, Martyn JA. Fentanyl clearance and volume of distribution are increased in patients with major burns. *J Clin Pharmacol*. 2007;47(6):674-680.
119. Faucher L, Furukawa K. Practice guidelines for the management of pain. *J Burn Care Res*. 2006;27(5):659-668.
120. Milne RW, Nation RL, Somogyi AA, Bochner F, Griggs WM. The influence of renal function on the renal clearance of morphine and its glucuronide metabolites in intensive-care patients. *Br J Clin Pharmacol*. 1992;34(1):53-59.
121. Holtman JR Jr, Jellish WS. Opioid-induced hyperalgesia and burn pain. *J Burn Care Res*. 2012;33(6):692-701.
122. Sharar SR, Bratton SL, Carrougher GJ, et al. A comparison of oral transmucosal fentanyl citrate and oral hydromorphone for inpatient pediatric burn wound care analgesia. *J Burn Care Rehabil*. 1998;19(6):516-521.
123. Marshall J, Finn CA, Theodore AC. Impact of a clinical pharmacist-enforced intensive care unit sedation protocol on duration of mechanical ventilation and hospital stay. *Crit Care Med*. 2008;36(2):427-433.
124. Battershill AJ, Keating GM. Remifentanil: a review of its analgesic and sedative use in the intensive care unit. *Drugs*. 2006;66(3):365-385.
125. Koppert W, Sittl R, Scheuber K, et al. Differential modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by S-ketamine and clonidine in humans. *Anesthesiology*. 2003;99(1):152-159.
126. Stanski DR, Hug CC Jr. Alfentanil – a kinetically predictable narcotic analgesic. *Anesthesiology*. 1982;57(6):435-438.
127. Sim KM, Hwang NC, Chan YW, Seah CS. Use of patient-controlled analgesia with alfentanil for burns dressing procedures: a preliminary report of five patients. *Burns*. 1996;22(3):238-241.
128. Fredheim OM, Moksnes K, Borchgrevink PC, Kaasa S, Dale O. Clinical pharmacology of methadone for pain. *Acta Anaesthesiol Scand*. 2008;52(7):879-889.
129. Davis AM, Inturrisi CE. d-Methadone blocks morphine tolerance and N-methyl-D-aspartate-induced hyperalgesia. *J Pharmacol Exp Ther*. 1999;289(2):1048-1053.
130. Williams PI, Sarginson RE, Ratcliffe JM. Use of methadone in the morphine-tolerant burned paediatric patient. *Br J Anaesth*. 1998;80(1):92-95.
131. Morley JS, Watt JW, Wells JC, et al. Methadone in pain uncontrolled by morphine. *Lancet*. 1993;342(8881):1243.
132. Martyn JA, Greenblatt DJ, Quinby WC. Diazepam kinetics in patients with severe burns. *Anesth Analg*. 1983;62(3):293-297.
133. Martyn J, Greenblatt DJ. Lorazepam conjugation is unimpaired in burn trauma. *Clin Pharmacol Ther*. 1988;43(3):250-255.
134. Singleton A, Preston JR, Cochran A. Sedation and analgesia for critically ill pediatric burn patients: the current state of practice. *J Burn Care Res*. 2015;36(3):440-445.
135. Mandema JW, Tuk B, van Steveninck AL, et al. Pharmacokinetic-pharmacodynamic modeling of the central nervous system effects of midazolam and its main metabolite alpha-hydroxymidazolam in healthy volunteers. *Clin Pharmacol Ther*. 1992;51(6):715-728.
136. Meyer WJ 3rd, Nichols RJ, Cortiella J, et al. Acetaminophen in the management of background pain in children post-burn. *J Pain Symptom Mgmt*. 1997;13(1):50-55.
137. Rivosecchi RM, Kellum JA, Dasta JF, et al. Drug class combination-associated acute kidney injury: a review of the literature. *Ann Pharmacother*. 2016;50(11):953-972. doi:10.1177/1060028016657839. Epub 2016 Oct 1.
138. Cuignet O, Pirson J, Soudon O, Zizi M. Effects of gabapentin on morphine consumption and pain in severely burned patients. *Burns*. 2007;33(1):81-86.
139. Mao J, Chen LL. Gabapentin in pain management. *Anesth Analg*. 2000;91(3):680-687.
140. Van Elstraete AC, Sitbon P, Mazoit JX, Benhamou D. Gabapentin prevents delayed and long-lasting hyperalgesia induced by fentanyl in rats. *Anesthesiology*. 2008;108(3):484-494.
141. Rimaz S, Alavi CE, Sedighinejad A, et al. Effect of gabapentin on morphine consumption and pain after surgical debridement of burn wounds: a double-blind randomized clinical trial study. *Arch Trauma Res*. 2012;1(1):38-43.
142. Himmelseher S, Durieux ME. Revising a dogma: ketamine for patients with neurological injury? *Anesth Analg*. 2005;101(2):524-534, table of contents.
143. Green SM, Krauss B. Ketamine is a safe, effective, and appropriate technique for emergency department paediatric procedural sedation. *Emerg Med J*. 2004;21(3):271-272.
144. Levanen J, Makela ML, Scheinin H. Dexmedetomidine premedication attenuates ketamine-induced cardiostimulatory effects and postanesthetic delirium. *Anesthesiology*. 1995;82(5):1117-1125.
145. Ozaki M, Takeda J, Tanaka K, et al. Safety and efficacy of dexmedetomidine for long-term sedation in critically ill patients. *J Anesth*. 2014;28(1):38-50.
146. Talon MD, Woodson LC, Sherwood ER, et al. Intranasal dexmedetomidine premedication is comparable with midazolam in burn children undergoing reconstructive surgery. *J Burn Care Res*. 2009;30(4):599-605.
147. Evers AS, Maze M. *Anesthetic Pharmacology: Physiologic Principles and Clinical Practice: A Companion to Miller's Anesthesia*. Philadelphia, PA: Churchill Livingstone; 2004:479.
148. Sebel PS, Lowdon JD. Propofol: a new intravenous anesthetic. *Anesthesiology*. 1989;71(2):260-277.
149. Ronan KP, Gallagher TJ, George B, Hamby B. Comparison of propofol and midazolam for sedation in intensive care unit patients. *Crit Care Med*. 1995;23(2):286-293.
150. Krajcova A, Waldauf P, Andel M, Duska F. Propofol infusion syndrome: a structured review of experimental studies and 153 published case reports. *Crit Care*. 2015;19:398.
151. Mathru M, Esch O, Lang J, et al. Magnetic resonance imaging of the upper airway. Effects of propofol anesthesia and nasal continuous positive airway pressure in humans. *Anesthesiology*. 1996;84(2):273-279.
152. Filkin SA, Cosgray P, Marvin JA, Engrav L, Heimbach D. Self-administered anesthetic: a method of pain control. *J Burn Care Rehabil*. 1981;2(1):33-34.
153. Ozil D, Vialle R, Thevenin-Lemoine C, Conti E, Annequin D. Use of a combined oxygen/nitrous oxide/morphine chlorylhydrate protocol for analgesia in burned children requiring painful local care. *Pediatr Surg Int*. 2010;26(3):263-267.
154. do Vale AH, Viderira RL, Gomez DS, et al. Effect of nitrous oxide on fentanyl consumption in burned patients undergoing dressing change. *Braz J Anesthesiol*. 2016;66(1):7-11.
155. Hayden PJ, Hartemink RJ, Nocholson GA. Myeloneuropathy due to nitrous oxide. *Burns*. 1983;9(4):267-270.
156. Sweeney B, Bingham RM, Amos RJ, Petty AC, Cole PV. Toxicity of bone marrow in dentists exposed to nitrous oxide. *Br Med J (Clin Res Ed)*. 1985;291(6495):567-569.
157. Singer AJ, Beto L, Singer DD, et al. Association between burn characteristics and pain severity. *Am J Emerg Med*. 2015;33(9):1229-1231.

158. Schwarze H, Kuntscher M, Uhlig C, et al. Suprathel, a new skin substitute, in the management of partial-thickness burn wounds: results of a clinical study. *Ann Plast Surg*. 2008;60(2):181-185.
159. Engrav LH, Colescott PL, Kemalyan N, et al. A biopsy of the use of the Baxter formula to resuscitate burns or do we do it like Charlie did it? *J Burn Care Rehabil*. 2000;21(2):91-95.
160. Sullivan SR, Friedrich JB, Engrav LH, et al. Opioid creep" is real and may be the cause of "fluid creep. *Burns*. 2004;30(6):583-590.
161. Saffle JI. The phenomenon of "fluid creep" in acute burn resuscitation. *J Burn Care Res*. 2007;28(3):382-395.
162. Nilsson A, Kalmman S, Sonesson LK, Arvidsson A, Sjoberg F. Difficulties in controlling mobilization pain using a standardized patient-controlled analgesia protocol in burns. *J Burn Care Res*. 2011;32(1):166-171.
163. Shipton EA, Minkowitz HS, Becker PJ. PCA in burn injuries: the subcutaneous route. *Can J Anaesth*. 1993;40(9):898.
164. Patterson DR, Ptacek JT, Carrougher GJ, Sharar SR. Lorazepam as an adjunct to opioid analgesics in the treatment of burn pain. *Pain*. 1997;72(3):367-374.
165. Ratcliff SL, Brown A, Rosenberg L, et al. The effectiveness of a pain and anxiety protocol to treat the acute pediatric burn patient. *Burns*. 2006;32(5):554-562.
166. Slotkin TA, Seidler FJ, Whitmore WL. Methadone inhibits serotonin and norephinephrine uptake into rat brain synaptosomes and synaptic vesicles in vitro but not in vivo. *Eur J Pharmacol*. 1978;49(4):357-362.
167. Lyons B, Casey W, Doherty P, McHugh M, Moore KP. Pain relief with low-dose intravenous clonidine in a child with severe burns. *Int Care Med*. 1996;22(3):249-251.
168. Fagin A, Palmieri T, Greenhalgh D, Sen S. A comparison of dexmedetomidine and midazolam for sedation in severe pediatric burn injury. *J Burn Care Res*. 2012;33(6):759-763.
169. Gorlin AW, Rosenfeld DM, Ramakrishna H. Intravenous sub-anesthetic ketamine for perioperative analgesia. *J Anaesthesiol Clin Pharmacol*. 2016;32(2):160-167.
170. Byers JF, Bridges S, Kijek J, LaBorde P. Burn patients' pain and anxiety experiences. *J Burn Care Rehabil*. 2001;22(2):144-149.
171. Sharar SR, Carrougher GJ, Selzer K, et al. A comparison of oral transmucosal fentanyl citrate and oral oxycodone for pediatric outpatient wound care. *J Burn Care Rehabil*. 2002;23(1):27-31.
172. Humphries Y, Melson M, Gore D. Superiority of oral ketamine as an analgesic and sedative for wound care procedures in the pediatric patient with burns. *J Burn Care Rehabil*. 1997;18(1 Pt 1):34-36.
173. Borland ML, Bergesio R, Pascoe EM, Turner S, Woodger S. Intranasal fentanyl is an equivalent analgesic to oral morphine in paediatric burns patients for dressing changes: a randomised double blind crossover study. *Burns*. 2005;31(7):831-837.
174. Beers R, Camporesi E. Remifentanil update: clinical science and utility. *CNS Drugs*. 2004;18(15):1085-1104.
175. Ceber M, Salihoglu T. Ketamine may be the first choice for anesthesia in burn patients. *J Burn Care Res*. 2006;27(5):760-762.
176. Himmelseher S, Durieux ME. Ketamine for perioperative pain management. *Anesthesiology*. 2005;102(1):211-220.
177. McCloy R. Asleep on the job: sedation and monitoring during endoscopy. *Scand J Gastroenterol Suppl*. 1992;192:97-101.
178. American Society of Anesthesiologists Task Force. Practice guidelines for sedation and analgesia by non-anesthesiologists. *Anesthesiology*. 2002;96(4):1004-1017.
179. Grunwell JR, Marupudi NK, Gupta RV, et al. Outcomes following implementation of a pediatric procedural sedation guide for referral to general anesthesia for magnetic resonance imaging studies. *Paediatr Anaesth*. 2016;26(6):628-636.
180. Owens VF, Palmieri TL, Comroe CM, et al. Ketamine: a safe and effective agent for painful procedures in the pediatric burn patient. *J Burn Care Res*. 2006;27(2):211-216, discussion 217.
181. Prakash S, Fatima T, Pawar M. Patient-controlled analgesia with fentanyl for burn dressing changes. *Anesth Analg*. 2004;99(2):552-555, table of contents.
182. Nilsson A, Steinvall I, Bak Z, Sjoberg F. Patient controlled sedation using a standard protocol for dressing changes in burns: patients' preference, procedural details and a preliminary safety evaluation. *Burns*. 2008;34(7):929-934.
183. Coimbra C, Choiniere M, Hemmerling TM. Patient-controlled sedation using propofol for dressing changes in burn patients: a dose-finding study. *Anesthesiol Analg*. 2003;97(3):839-842.
184. Schneider JC, Nadler DL, Herndon DN, et al. Pruritus in pediatric burn survivors: defining the clinical course. *J Burn Care Res*. 2015;36:151-158.
185. Reference removed while revising.
186. Carrougher GJ, Martinez EM, McMullen KS, et al. Pruritus in adult burn survivors: postburn prevalence and risk factors associated with increased intensity. *J Burn Care Res*. 2013;34:94-101.
187. Goutos I, Clark M, Upson C, Richardson PM, Ghosh SJ. Review of therapeutic agents for burns pruritus and protocols for management in adult and pediatric patients using the GRADE classification. *Indian J Plast Surg*. 2010;43(suppl):S51-S60.
188. Bauer M, Schwameis R, Scherzer T, et al. A double-blind, randomized clinical study to determine the efficacy of benzocaine 10% on histamine-induced pruritus and UVB-light induced slight sunburn pain. *J Dermatol Treat*. 2015;doi:10.3109/09546634.2014.992384.
189. Matheson JD, Clayton J, Muller MJ. Reduction of itch during burn wound healing. *J Burn Care Rehabil*. 2001;22:76-81.
190. Bernstein JE, Whitney DH, Keyoumars S. Inhibition of histamine-induced pruritus by topical tricyclic antidepressants. *J Am Acad Dermatol*. 1981;5:582-585.
191. Demling R, DeSanti L. Topical doxepin cream significantly decreases itching and erythema in the healed burn wound compared to oral antihistamines. *J Burn Care Rehabil*. 2002;23:581.
192. Httrick H, O'Brien K, Laznick H, et al. Effect of transcutaneous electrical nerve stimulation for the management of burn pruritus: a pilot study. *J Burn Care Rehabil*. 2004;25:236-240.
193. Allison KP, Kiernan MN, Waters RA, Clement RM. Pulsed dye laser treatment of burn scars alleviation or irritation? *Burns*. 2003;29:207-213.
194. Cuignet O, Pirlot A, Ortiz S, Rose T. The effects of electroacupuncture on analgesia with peripheral sensory thresholds in patients with burn scar pain. *Burns*. 2015;41:1298-1305.
195. Li Tang CW, Lau JC, Choe J, Cham CC, Jianan L. A prospective randomized clinical trial to investigate the effect of silicone gel sheeting (Cica-Carfe) on post-traumatic hypertropic scar among the Chinese population. *Burns*. 2006;32:678-683.
196. Vitale M, Fields-Blache C, Luterman A. Severe itching in the patient with burns. *J Burn Care Rehabil*. 1991;12:330-333.
197. Mendham JE. Gabapentin for the treatment of itching produced by burns and wound healing in children: a pilot study. *Burns*. 2004;30:851-853.
198. Goutos I, Eldardire M, Khan AA, Dziewulski P, Richardson PM. Comparative evaluation of antipruritic protocols in acute burns. The emerging value of gabapentin in the treatment of burns pruritus. *J Burn Care Res*. 2010;31:57-63.
199. Kaul I, Amin A, Rosenberg M, Rosenberg L, Meyer W Use of gabapentin and pregabalin for pruritus and neuropathic pain associated with major burn injury: a retrospective chart review. 18th Congress of Inter Soc Burn Inj, Miami, Fl August. 2016.
200. LaSalle L, Rachelska G, Nedelec B. Naltrexone for the management of post-burn pruritus: a preliminary report. *Burns*. 2008;34:797-802.
201. Jung SI, Seo CH, Jang K, et al. Efficacy of naltrexone in the treatment of chronic refractory itching in burn patients: preliminary report of an open trial. *J Burn Care Res*. 2009;30:357-360.
202. Sheridan RL, Hinson M, Nackel A, et al. Development of a pediatric burn pain and anxiety management program. *J Burn Care Rehabil*. 1997;18:455-459.
203. Ulmer JF. Burn pain management: a guideline-bases approach. *J Burn Care Rehabil*. 1998;19:151-159.
204. Patterson D, Sharar S. Burn pain. In: Loeser J, ed. *Bonica's Management of Pain*. 3rd ed. Philadelphia: Lippincott, Williams, Wilkins; 2003:778-787.
205. Faucher L, Furukawa K. Practice guidelines for the management of pain. *J Burn Care Res*. 2006;27:659-668.
206. Patterson DR. Nonopioid based approaches to burn pain. *J Burn Care Rehabil*. 1995;16:372-376.
207. Meyer D. Children's responses to nursing attire. *Pedia Nurs*. 1992;18:157-160.
208. Martin-Herz SP, Thurber CA, Patterson DR. Psychological principles of burn wound pain in children: Part II: treatment applications. *J Burn Care Rehabil*. 2000;21(5):458-472.
209. Thurber CA, Martin-Herz SP, Patterson DR. Psychological principles of burn wound pain in children: Part I: theoretical framework. *J Burn Care Rehabil*. 2000;21(4):376-387.

210. Kavanaugh CK, Lasoft E, Eide Y, et al. Learned helplessness and the pediatric burn patient: dressing change behavior and serum cortisol and beta endorphins. *Adv Pedia*. 1991;38:335-363.
211. Everett JJ, Patterson DR, Chen AC. Cognitive and behavioral treatments for burn pain. *Pain Clin*. 1990;3:133-145.
212. Miller K, Rodger S, Kipping B, Kimble R. A novel technology approach to pain management in children with burns: a prospective randomized controlled trial. *Burns*. 2011;37(3):395-405.
213. Jacobs GD. The physiology of mind-body interactions: the stress response and the relaxation response. *J Altern Complement Med*. 2001;7(1 suppl):S83-S92.
214. Jacobs GD, Friedman R. EEG spectral analysis of relaxation techniques. *Appl Psychophysiol Biofeedback*. 2004;29:245-254.
215. Field T, Peck M, Hernandez-Reif M, et al. Post-burn itching, pain, and psychological symptoms are reduced with massage therapy. *J Burn Care Rehabil*. 2000;21:189-193.
216. Fagerhaugh SY. Pain expression and control on a burn care unit. *Nurs Outlook*. 1974;22:645-650.
217. Knudson-Cooper MS. Relaxation and biofeedback training in the treatment of severely burned children. *J Burn Care Rehabil*. 1981;2.
218. Kueffner M. Passage through hospitalization of severely burned, isolated school-age children. *Commun Nurs Res*. 1976;7:181-197.
219. Wernick RL, Jaremko ME, Taylor PW. Pain management in severely burned adults: a test of stress inoculation. *J Behav Med*. 1981;4:103-109.
220. Whitehead-Pleaux AM, Baryza MJ, Sheridan RL. The effects of music therapy on pediatric patients' pain and anxiety during donor site dressing change. *J Music Ther*. 2006;43:136-153.
221. Elliott CH, Olson RA. The management of children's distress in response to painful medical treatment for burn injuries. *Behav Res Therapy*. 1983;21:675-683.
222. Foertsch CE, O'Hara MW, Stoddard FJ, Kealey GP. Treatment resistant pain and distress during pediatric burn dressing changes. *J Burn Care Rehabil*. 1998;19:219-224.
223. Presner JD, Yowler CJ, Smith LF, Steele AL, Fratianne RB. Music therapy for assistance with pain and anxiety management in burn treatment. *J Burn Care Rehabil*. 2001;22:83-88.
224. Park E, Oh H, Kim T. The effects of relaxation breathing on procedural pain and anxiety during burn care. *Burns*. 2013;39(6):1101-1106.
225. Mohammadi Fakhar F, Rafii F, Jamshidi Orak R. The effect of jaw relaxation on pain anxiety during burn dressings: randomized clinical trial. *Burns*. 2013;39(1):61-67.
226. Melzack R. The tragedy of needless pain. *Sci Amer*. 1990;262(2):27-33.
227. Fordyce WE. *Behavioral Methods for Chronic Pain and Illness*. St. Louis: Mosby Year Book, Inc.; 1976.
228. Ehde DM, Patterson DR, Fordyce WE. The quota system in burn rehabilitation. *J Burn Care Rehabil*. 1998;19:436-439.
229. Kelley ML, Jarvie GJ, Middlebrook JL, McNeer MF, Drabman RS. Decreasing burned children's pain behavior: impacting the trauma of hydrotherapy. *J Appl Behav Anal*. 1984;17(2):147-158.
230. Fratianne RB, Presner JD, Huston MJ, et al. The effect of music-based imagery and musical alternate engagement on the burn debridement process. *J Burn Care Rehabil*. 2001;22:47-53.
231. Tan X, Yowler CJ, Super DM, Fratianne RB. The efficacy of music therapy protocols for decreasing pain, anxiety, and muscle tension levels during burn dressing changes: a prospective randomized crossover trial. *J Burn Care Res*. 2010;31:590-597.
232. Hoffman HG, Patterson DR, Carrougher GJ. Use of virtual reality for adjunctive treatment of adult burn pain during physical therapy: a controlled study. *Clin J Pain*. 2000;16:244-250.
233. van Twillert B, Bremer M, Faber AW. Computer-generated virtual reality to control pain and anxiety in pediatric and adult burn patients during wound dressing changes. *J Burn Care Res*. 2007;28:694-702.
234. Das DA, Grimner KA, Sparnon AL, McRae SE, Thomas BH. The efficacy of playing a virtual reality game in modulating pain for children with acute burn injuries: a randomized controlled trial. *BMC Pediatr*. 2005;5:1.
235. Chan EA, Chung JW, Wong TK, Lien AS, Yang JY. Application of a virtual reality prototype for pain relief of pediatric burn in Taiwan. *J Clin Nurs*. 2007;16:786-793.
236. Sharar S, Carrougher G, Nakamura D, et al. Factors influencing the efficacy of virtual reality distracting analgesia during postburn physical therapy: preliminary results from 3 ongoing studies. *Arch Phys Med Rehabil*. 2007;88:S43-S49.
237. Hoffman H, Patterson D, Seibel E, et al. Virtual reality pain control during burn wound debridement in the hydrotank. *Clin J Pain*. 2008;24:299-304.
238. Maani C, Hoffman H, Morrow M, et al. Pain control during wound care for combat-related burn injuries using custom, articulated arm-mounted virtual reality goggles. *J Cyberther Rehabil*. 2008;1:193-198.
239. Carrougher GJ, Hoffman HG, Nakamura D, et al. The effect of virtual reality on pain and range of motion in adults with burn injuries. *J Burn Care Rehabil*. 2009;30:785-791.
240. Schmitt YS, Hoffman HG, Blough DK, et al. A randomized, controlled trial of immersive virtual reality analgesia, during physical therapy for pediatric burns. *Burns*. 2011;37(1):61-68.
241. Kipping B, Rodger S, Miller K, Kimble R. Virtual reality for acute pain reduction in adolescents undergoing burn wound care: a prospective randomized controlled trial. *Burns*. 2012;38(5):650-657.
242. Hoffman HG, Chambers GT, Meyer WJ 3rd, et al. Virtual reality as an adjunctive non-pharmacologic analgesic for acute burn pain during medical procedures. *Ann Behav Med*. 2011;41(2):183-191, Review. doi:10.1007/s12160-010-9248-7.
243. Hoffman HG, Doctor JN, Patterson DR, Carrougher GJ, Furness TA 3rd. Use of virtual reality as an adjunctive treatment of adolescent burn pain during wound care: a case report. *Pain*. 2000;85:305-309.
244. Morris LD, Louw QA, Grimner-Somers K. The effectiveness of virtual reality on reducing pain and anxiety in burn injury patients. *Clin J Pain*. 2009;25:815-826.
245. Yohannan SK, Tufaro PA, Hunter H, et al. The utilization of Nintendo® Wii™ during burn rehabilitation: a pilot study. *J Burn Care Res*. 2012;33(1):36-45.
246. Parry I, Painting BS, Bagley A, et al. A pilot prospective randomized control trial comparing exercises using videogame therapy to standard physical therapy: 6 months follow up. *J Burn Care Res*. 2015;36:534-544.
247. Mott J, Bucolo S, Cuttle L, et al. The efficacy of an augmented virtual reality system to alleviate pain in children undergoing burns dressing changes: a randomised controlled trial. *Burns*. 2008;34(6):803-808.
248. Patterson DR, Questad KA, Boltwood MD. Hypnotherapy as a treatment for pain in patients with burns: research and clinical considerations. *J Burn Care Rehabil*. 1987;8:263-268.
249. Patterson DR, Everett JJ, Burns GL, Marvin JA. Hypnosis for the treatment of burn pain. *J Consul Clin Psychol*. 1992;60:713-717.
250. Patterson DR, Ptacek JT. Baseline pain as a moderator of hypnotic analgesia for burn injury treatment. *J Consul Clin Psychol*. 1997;65:60-67.
251. Patterson DR, Jensen M. Hypnosis and clinical pain. *Psychol Bull*. 2003;129:495-521.
252. Patterson DR, Adcock RJ, Bombardier CH. Factors predicting hypnotic analgesia in clinical burn pain. *Int J Clin Exper Hypn*. 1997;45:377-395.
253. Patterson DR, Questad KA, DeLateur BJ. Hypnotherapy as an adjunct to narcotic analgesia for the treatment of pain for burn debridement. *Am J Clin Hypn*. 1989;31:156-163.
254. Patterson DR, Tininenko JR, Schmidt AE, Sharar S. Virtual reality hypnosis: a case report. *Int J Clin Exp Hypn*. 2004;52:27-38.
255. Askay SW, Patterson DR, Jensen MP, Sharar SR. A randomized controlled trial of hypnosis for burn wound care. *Rehabil Psychol*. 2007;52:247-253.
256. Wiechman Askay S, Patterson D. A randomized controlled trial of hypnosis for burn wound care. *Rehabil Psychol*. 2007;52(3):247-253.
257. Shakibaei F, Harandi AA, Gholamrezaei A, Samoei R, Pejman S. Hypnotherapy in management of pain and reexperiencing of trauma in burn patients. *Int J Clin Exp Hypn*. 2008;56(2):185-197.
258. Kimball KL, Drews JE, Walker S, Dimick AR. Use of TENS for pain reduction in burn patients. *J Burn Care Rehabil*. 1987;8:28-31.
259. Field T, Peck M, Krugman S, et al. Burn injuries benefit from massage therapy. *J Burn Care Rehabil*. 1998;19(3):241-244.
260. Racine NM, Pillai Riddell RR, Khan M, et al. Systematic review: predisposing, precipitating, perpetuating and present factors predicting anticipatory distress to painful medical procedures in children. *J Pediatr Psychol*. 2016;4(12):159-181.
261. Hanson MD, Gauld M, Wathen N, MacMillan HL. Nonpharmacological interventions for acute wound care distress in pediatric patients with burn injury: a systematic review. *J Burn Care Res*. 2008;29:730-741.

262. Foertsch CE, O'Hara MW, Stoddard FJ, Kealey GP. Parent participation during burn debridement in relation to behavioral distress. *J Burn Care Rehabil*. 1996;17:372-377.
263. de Jong AEE, Middlekoop E, Faber AW, Van Loey NEE. Nonpharmacological nursing interventions for procedural pain relief in adults with burns: a systematic literature review. *Burns*. 2007;33:811-827.
264. Perry S, Heidrick G. Management of pain during debridement: a survey of US burn units. *Pain*. 1982;13:267-280.
265. Kavanagh CK, Lasoff E, Eide Y, et al. Learned helplessness and the pediatric burn patient: dressing change behavior and serum cortisol and B-endorphin. *Adv Pediatr*. 1991;38:335-363.
266. Schreiber S, Galai-Gat T. Uncontrolled pain following physical injury as the core trauma in post traumatic stress disorder. *Pain*. 1993;54:107-110.
267. Thomas C, Brazeal B, Rosenberg L, et al. Phantom Limb Pain in Pediatric Burn Survivors. *Burns*. 2003;29:139-142.

65 Psychiatric Disorders Associated With Burn Injury

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Introduction

All members of the burn treatment team should have a basic knowledge of psychiatric problems because they commonly occur and often play a central role in burn recovery. It is useful to have mental health professionals as integrated members of the team because their expertise and skills are often needed in the management of patients with burns to screen and identify problems and to assist in the treatment of the multitudes of psychiatric and psychological issues concomitant to burns.

Preexisting psychiatric disorders and symptoms are relatively common in the histories of burned patients and frequently appear to have contributed significantly to the etiology of the injury itself.[1–4] The converse is also true.

In addition to premorbid disorders, a number of patients will develop psychiatric symptoms during acute treatment for burns, as also can be seen after other major trauma.[4] Pain, itching, and stress during hospitalization can contribute to problems during acute treatment, such as sleep disorders and depression, starting a vicious circle. Dissociation and anxiety experienced during the burn have been shown to predict later psychopathology.[5,6] While it is understandable to expect patients with major burns to be at risk, even minor burns can result in significant psychological distress and psychiatric symptoms.[7]

At present, there is no profile that can reliably predict and identify which patients will suffer psychiatric symptoms following burns. Furthermore, there is a clear risk that patients will not actively seek help for psychological distress or psychiatric symptoms, and this can have a strong effect on outcome and rehabilitation. All members of the burn team should be aware of this risk and be observant of signs or symptoms.

This chapter will focus on the recognition and treatment of common mental disturbances that can be expected to occur in patients suffering serious burns. This includes specific attention to both pediatric as well as adult patients, and it is important to be aware that symptoms and signs may differ between ages. Also, preexisting psychopathology may alter the expression of a patient's distress and complicate medical management of the patient.

In the following text ICD-10 codes can be found in parentheses after each diagnosis.

Preexisting Factors

Psychiatric morbidity greatly increases the risk of sustaining an injury, either directly (e.g., self-inflicted burns or suicide attempts) or indirectly through problems in impulse control (e.g., conduct disorders), by reducing vigilance or affecting judgment (e.g., substance abuse disorders, depression).[1,7,8] The knowledge of preexisting psychiatric problems is important for burn care mainly for two reasons: first, to better understand and identify psychiatric symptoms occurring during treatment and to recognize them as ongoing or reactivated problems instead of reactions to the injury; and second, to increase awareness of potential difficulties during rehabilitation (for a comprehensive review refer to McKibben et al.[1]).

Patients with preinjury psychiatric disorders have been observed to require longer hospitalization, they more frequently experience complications during treatment and problems with rehabilitation and postburn adjustment, and they have a higher risk of developing other psychiatric disorders (e.g., posttraumatic stress disorder; PTSD).[2–4,9–13]

Psychiatric morbidity is common in burn patients. Two-thirds of all patients with burns have a lifetime history of at least one psychiatric disorder, 50% had a psychiatric disorder in the year before injury, and one-third have an ongoing psychiatric disorder at the time of injury.[1] Patients with preexisting psychiatric morbidity have a higher risk of sustaining a preventable injury, and, in individuals with psychotic disorders, self-inflicted burns are overrepresented.[1]

The most frequent preexisting psychiatric disorder in burn patients is the mood disorder major depression, which is present in up to 42% of individuals, a proportion much higher than in the general population.[1] Smoking (i.e., substance use disorder, tobacco use disorder; Z72.0 or F17.2x), has been shown to increase the risk of burns; smoking more than 10 cigarettes a day increases the risk of burns by up to sixfold.[1] Similarly, other substance use disorders (e.g., the stimulant drug methamphetamine or the use of highly volatile and flammable substances) increase the risk of sustaining a burn.[1,14]

Personality disorders are also overrepresented in burn patients compared to the general population, and persons who score high on the personality traits neuroticism and extraversion appear to have a higher risk of injury.[1] In addition, persons with dementia have a higher age-standardized incidence rate of burns than do those without dementia (22.7 vs. 14.2 per 100,000 inhabitants), and they have a longer length of hospital stay.[15]

Disorders in Children and Adolescents

Psychiatric morbidity can increase the risk for burns in children and adolescents, and specific psychiatric disorders

have been found to occur more frequently in pediatric burn survivors than in the general population. Commonly pediatric burn survivors may not exhibit symptoms of prior psychiatric disorders during the acute phase of treatment due to the impact of injuries and other treatments. When symptoms are evident, continuation of prior treatment or implementation of indicated treatment for a preexisting psychiatric disorder may not only control symptoms but also facilitate patient participation and cooperation with acute care and long-term rehabilitation.

Repeated inhaling of psychoactive volatile hydrocarbons from, for example, glue, fuels, or paint ("sniffing") can be classified as inhalant use disorder (F18.x). This disorder can result in burns because many of the substances are flammable. Inhalant use disorder is most common in adolescents, whereas prevalence declines rapidly in adulthood.[16]

Across cultures attention-deficit/hyperactivity disorder (ADHD, F90.x) in children has a prevalence of about 5%.[16] One of the key features of ADHD is impulsivity (i.e., actions without forethought), which can expose the individual to high-risk situations, and children with ADHD have repeatedly been shown to be at greater risk for burns.[17–19]

Conduct disorders (F91.x) encompass repetitive and persistent behavioral patterns of violations of social norms and rules. Childhood-onset conduct disorder often is concurrent with ADHD, and individuals displaying this subtype (in contrast to adolescent-onset type) often display physical aggression; thrill-seeking and recklessness are frequent personality features.[16] In this context, playing with fire and fire-setting can be symptoms of conduct disorder[16] and can result in burns. Conduct disorders have a prevalence of around 4%, and the childhood-onset subtype has a worse prognosis with risk for adulthood psychiatric morbidity.

In contrast, pyromania (F63.1) is a specific conduct disorder in which deliberate and purposeful fire-setting occurs not as an aggression but in a setting of tension or affective arousal. This repeated fire-setting behavior increases the risk for burns, both for the individuals and those around them. Possibly the prevalence of pyromania may be underestimated; it has been observed that a slight majority of individuals with pyromania restrict their fire-setting to controlled situations, such as controlled fires on their own property, and therefore can remain "undetected."[20] The prevalence of pyromania as a comorbidity has been found to be 3–7%.[16,20] There is limited knowledge about the time course of pyromania. It has been postulated that the disorder is rare in children and begins in late adolescence but that some individuals "switch" to other impulsive, reward-seeking behaviors.[16,20]

Social Considerations in Pediatric Burns

Clearly parental and family characteristics can increase both the risk for burns in children as well as influence their subsequent recovery and outcome. The presence of child abuse or neglect can directly result in pediatric burns.[1,21,22] The presence of parental anxiety, depression, poor coping skills, or lack of social support at the time of injury are associated with poorer functional outcome in pediatric burn survivors.[23,24] Possibly high parent state anxiety in combination with ineffective coping strategies rather than family functioning or burn severity can be most predictive of pediatric burn outcome.[25]

Parents face numerous emotional challenges not only due to the psychological trauma of their children's burns, but also during subsequent treatment and recovery. Parents report more feelings of anxiety and being stressed, depressed, and guilty than the normal reference population even in areas unrelated to their children.[24,26] These stresses can result in psychiatric disorders in parents up to 2 years after the injury, with mothers at greater risk for developing mental health problems and depressive and posttraumatic stress symptoms.[27–29] Increased risk for depression was associated with having an only child or multiple offspring injured and with complicated burn injuries (secondary infection or amputation). Larger burns and the presence of parent–child conflict, parental dissociation, or PTSD symptoms in the child are strongly correlated with parental PTSD symptoms.[30–32] This emphasizes the need for psychological attention to parents of burned children, as well as to the children themselves. As child and parent ratings do not always match, recent studies suggest that burn centers adopt a family perspective and include assessments of both parents and children.[32]

Self-Inflicted Burns and Suicide Attempts

The proportion of self-inflicted burns differs across the world: whereas it is between 1% and 9% in North America and Europe with no clear gender distribution, self-inflicted burns are a major cause of burns in females in the Middle East, Africa, and south Asia, with a prevalence of up to 28%.[33,34] Of patients with self-inflicted burns, those attempting suicide are more likely to have larger burns and longer hospitalizations than those with the intent of self-mutilation.[33] Across cultures psychiatric morbidity is an important additional risk factor, often in conjunction with social stress factors such as marital problems or unemployment.[1]

In-Hospital Contributing Factors and Disorders

Several problems during acute burn treatment can affect the course of treatment and the eventual outcome after burns. Pain, itching, and sleep disorders are caused by both the injury and its treatment. High levels of stress and anxiety may contribute to the development of psychiatric morbidity (e.g., PTSD). In patients with substance-related disorders (F10.x–F19.x), withdrawal symptoms can occur during acute care, and patients with preinjury substance abuse have a higher risk of developing psychiatric symptoms during and after acute care. There is evidence that, in the case of comorbidity of PTSD and substance-related disorders, concurrent treatment of both disorders is necessary to achieve improvement.[35]

After the initial postburn period patients will undergo a series of operative procedures or dressing changes interspersed with physical therapy. Constant pain or the sure knowledge of repeated painful episodes in the near

future and feelings of anxiety and powerlessness are predominant[36–38] because every movement, even shifting position and change of bedclothes, is painful. Therefore treatment and the experience of hospitalization may be as traumatic psychologically as the original burn. Patients who experience high levels of pain not only have a higher risk of poor adjustment and psychiatric problems after discharge, but wound healing also can be affected due to stress.[38,39] Furthermore, high levels of stress, anxiety, and PTSD decrease pain tolerance.[37]

Itching is a common problem during wound healing and scar maturation, and it can cause considerable distress and anxiety.[40,41] Persistent itching can disrupt sleep, which increases stress levels and also impairs everyday functioning and participation in rehabilitation.[42] Anxiolytic, antidepressant, and antipsychotic agents have been used successfully to reduce itch.[41]

Significant sleep problems are common during and after treatment for acute burns.[43–45] The noise and light on the unit and interruptions for treatment will disrupt sleep.[46] Pain, anxiety, and itching can disrupt sleep or affect sleep quality. Symptoms of stress and PTSD (e.g., nightmares) can both cause awakening and a fear of going back to sleep.[44,47] Pain severity during hospitalization has been shown to predict insomnia after discharge, and insomnia in turn predicts long-term pain.[45] Burn patients who experience poor sleep at night will also have lower pain tolerance during the day.[47]

IN-HOSPITAL DISORDERS

Disorientation, confusion, delirium, transient psychosis, depression and anxiety, stress, and sleep disorders are commonly observed during acute burn treatment.[3] Causes of these symptoms are multifactorial: hypoglycemia, sepsis, and/or a variety of other organic problems can contribute. The altered state of consciousness may be transitory, wax and wane over several days, or, with large burns, persist for weeks.

A significant number of burn survivors will experience acute or posttraumatic stress disorder symptoms, including intrusive memories of the injury, during their acute recovery.[1,48,49]

Symptoms of depression and agitation related to excessive pain will subside with adequate pain management. The experience of pain has been found to be a mediating risk factor for PTSD in both pediatric and adult burn patients.[38,50] The recurrence of pain in a scar area following laser treatment or with wound cleaning can lead to recurrence of the PTSD symptoms associated with the original pain.

After severe burns patients are at risk for the development of substance abuse in the wake of PTSD,[3,35] but the use of opioids and other pain medication will not cause dependence per se if adequately administered and tapered when pain levels decrease.[37,51]

Symptoms of delirium and transient psychosis rarely occur among children under the age of 10 years.[52] True hallucinations are uncommon in children, but, when they do occur, the most likely cause is stress, followed by pain and medications.[53] In young burn patients sepsis and metabolic conditions are a more frequent cause of hallucinations than are psychiatric disorders.

In contrast to delirium and psychosis, burn encephalopathy is often observed in children,[54,55] characterized by lethargy, withdrawal, or coma. Electroencephalograms (EEGs) in such cases typically reveal diffuse, nonspecific slow waves. Causative factors probably are the same as those for delirium.[56]

Even young children can experience severe anxiety following burns, with up to a third of patients reporting symptoms of acute stress disorder (ASD) in the immediate aftermath of burns.[57] Mediating factors for the presence of anxiety symptoms appear to be size of burn, parental stress, and the experience of pain. High resting heart rate, poor body image, and parental stress symptoms have been found to be significant risk factors in development of ASD in children.[58]

Similarly to adults, pain in children appears to dramatically increase the risk for developing anxiety symptoms and subsequent anxiety disorders, and appropriate pain management can reduce or resolve anxiety symptoms.[59,60]

DELIRIUM

Delirium (F05) is a state of acute brain dysfunction, and, in burn patients, it is important to consider that it can both be due to the trauma itself as well as a symptom of substance withdrawal. It is a transient and usually reversible syndrome with disturbance of consciousness and cognition compared to previous levels of functioning. Hallucinations and delusions can occur, and patients in delirium can become suicidal or combative. Early symptoms can be restlessness, anxiety, disorientation, or sleep disorders.

Delirium in burn patients has been found to occur more often in individuals with a history of substance abuse or other psychological problems and with larger burns.[61,62]

Other potential causes of disorientation, hallucinations, and agitation may be medications used in the treatment of the acute burn patient, sepsis, and metabolic conditions.[62] These hallucinations can blur the line between delirium and ASD. Sleep deprivation has also been discussed as a cause for delirium in ICU patients.[63]

Acute Stress Disorder and Posttraumatic Stress Disorder

In the course of the progression from the *Diagnostic and Statistical Manual of Nervous and Mental Disorders,* Fourth Edition (DSM-IV) to DSM-5, ASD (F43.0) and PTSD (F43.10) no longer are regarded as anxiety disorders; they are now listed as a separate group called trauma- and stressor-related disorders: an overanxious patient is afraid of what might happen, whereas the patient with PTSD reexperiences and fears what has happened. The patient with PTSD is stuck in a heightened perception of threat and uses avoidant behaviors that maintain the symptoms.

ASD is the most common psychiatric disorder seen in survivors of major burns, in addition to PTSD, and it has a prevalence as high as 19% after burns.[48,64,65] ASD symptoms appear immediately following the trauma, last for at least 3 days, and usually resolve within a month after the trauma.[16]

In contrast to PTSD, dissociative symptoms can be present. Whereas these symptoms previously (i.e., in DSM-IV) had been given a central role for the diagnosis, it is now understood that some individuals develop ASD without dissociative symptoms.[16,66]

In children, repetitive reenactment of the traumatic event in play can be a symptom of intrusion and/or dissociation.

The presence of avoidant symptoms during the acute phase of recovery has been shown to predict chronic posttraumatic disorder in burn patients.[67,68] It is of great importance to recognize symptoms of ASD and PTSD at an early stage because the former has been shown to be a predictor for PTSD, and, once PTSD is established, it usually will persist.[48,69]

PTSD is, in addition to depression and general anxiety disorder (GAD), one of the most common psychiatric disorders seen in survivors of major burns with prevalence rates ranging between 7% and 45%.[2,48,49,65,70,71] In DSM-5 behavioral symptoms of PTSD encompass four instead of the previous three clusters: (B) intrusion, (C) avoidance, (D) negative cognition and mood—this is the new cluster—and (E) arousal (which in DSM-IV was the D cluster).[16] Aggressive, reckless, or self-destructive behaviors are now recognized as aspects of arousal. The DSM-5 definition of PTSD no longer differentiates between acute and chronic PTSD. Instead, two new subtypes of PTSD are identified in DSM-5: PTSD in children younger than 6 years (PTSD preschool subtype) and PTSD with prominent dissociative symptoms (PTSD Dissociative subtype) (for a review of the changes, see reference 66).

About one-third of burn survivors develop PTSD within 2 years of their injury,[72] and this was true for even small burns.[73] Individuals should be interviewed about sleep patterns and startle response because nightmares and altered sleep patterns are usually the symptoms first noted. In fact, in adults, it has been shown that one of the most important piece of information when screening for PTSD is nightmares.[74] Another potential marker for ASD and PTSD is heart rate at admission to the burn unit, although it appears to be mediated by gender.[75] A significant number of burn survivors will experience PTSD symptoms, including intrusive memories of the injury, during their acute recovery.[76,77] Children may express intrusive symptoms by reenactment of the traumatic event, and nightmares may not be directly related to the event.[16]

The presence of avoidant PTSD symptoms during the acute phase of recovery is reported to predict chronic PTSD in burn patients.[67–69,72,78]

Long-Term Postburn Disorders

Pain and previous psychiatric illness are the main factors that have been suggested as reasons for psychiatric problems beyond the time of discharge from the burn care center.[49] Pain and depression seem to be linked in such a way that they can cause each other.[79] Also, acute pain at the time of discharge from the hospital seems to produce long-term suicidal ideation.[80,81] There is a reciprocal relationship between pain with depression and anxiety.[81]

Another predictor of psychiatric problems is the presence of psychiatric or personality disorders preburn.[2] Cognitive processes may play an important role because, for example, burn-related attentional bias has been shown to be strongly associated with PTSD 1 year post injury.[82] Skull burns are associated with cognitive as well as affective disorders post burn,[83] but there does not seem to be a relationship to facial burns or even very large burns.

It has been observed that depressive symptoms were linked to physical limitations at 5 years after injury.[84] The appearance and location of the burn scar may be predictive for PTSD symptoms of avoidance and emotional numbing[85] or depression, especially in women.[86] In contrast, other studies found that neither the severity nor the visibility of burn scars influence long-term adjustment, but rather social introversion, which predicted the development of pathological shame.[87,88] Many patients with PTSD have comorbid depression;[89] both are sequelae of trauma and share a lot of symptoms, but they develop independently of each other.[90] In the trauma literature,[91] as well as in the burns literature,[92] subgroups of patients developing PTSD symptoms in different patterns over time can be identified (e.g., resilient with no or low symptoms, recovery, delayed, and chronic). The chronic group carries more of the above-mentioned medical, social, and psychological risk factors and should, together with those who have delayed onset of symptoms, receive the most attention from the burn rehabilitation team.

General Anxiety Disorder

Many patients continue beyond acute hospitalization to have periods during which they appear extremely anxious and express fear. These periods often recur in association with return to a hospital for reconstructive surgeries. General anxiety disorder (GAD, F41.1) is characterized by excessive worry for more days than not for at least 3 months and difficulty in controlling the anxiety. Typical symptoms are restlessness or the feeling of being on edge, muscle tension, and changes in behavior due to anxiety and worry, such as avoidance of potentially negative events, procrastination, or seeking reassurance.[16]

In the literature, the prevalence of anxiety disorders in adults during the year after burn—usually GAD or agoraphobia without panic—is less than 20%, and those with very small burns had even less anxiety.[7,93] Avoidant coping style was significantly correlated with the level of anxiety at 3 months.[6] In a study of young adults burned as children and with much larger burns than those examined in other studies, all the anxiety disorders were found, and they were twice as common as in matched controls: 12.9% of the subjects had a specific phobia and 6.9% had generalized anxiety.[94]

Not infrequently, anxiety spills over to other situations and/or becomes focused on specific objects; thus, phobias develop that are characterized by excessive persistent fear in response to specific stimuli. In a burned patient, difficulty controlling anxiety, restlessness, and behavioral changes are diagnostic of anxiety disorders since some other symptoms can be related to burn injuries specifically.

Although adults may express anxiety through "panic" symptoms such as sweating, palpitations, trembling, or nausea, children may express anxiety by crying, tantrums, freezing, or clinging. A differential diagnosis of these anxiety disorders distinct from PTSD is difficult and requires a careful interview.

Major Depressive Disorder

Although feeling depressed is a reaction most observers would expect of burned patients, only a relatively small number of patients with burns have been observed to have symptoms of severe depression (F32.x and F33.x).[2,49,64,95,96] In most studies preinjury depression or lower levels of well-being were stronger predictors than burn size for subsequent depression. All the same, those individuals who experience symptoms of depression during hospitalization will continue to do so after discharge so that early recognition and treatment may improve their situation considerably.[95] Depression is also a rare long-term sequela of burns in children: fewer than 50% of the children had ever suffered symptoms of major depression, and, in a sample of adolescent survivors, only 6% met criteria for a major depressive disorder.[96,97]

Symptoms of a major depressive episode according to DSM-5 are as follows: (1) depressed mood, (2) diminished interest or pleasure in activities ("anhedonia"), (3) significant weight or appetite changes, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue, (7) feelings of worthlessness or guilt, (8) diminished ability to think or concentrate, and (9) recurrent thoughts about death.[16] Children and adolescents may display irritable mood instead of depressed mood and a failure to gain weight instead of weight or appetite changes.

This is an extremely difficult diagnosis to make during the acute burn period since many of the criteria are linked to physical symptoms. A number of approaches have been used to determine the incidence among adult survivors of major burns using self-report measures such as the Beck Depression Inventory. A review of the literature on depression in burn survivors found a prevalence of major depression at 1 year post discharge of between 4% and 7%. At more than 1 year post discharge the prevalence ranged between 9% and 23% (for a comprehensive review, refer to Thombs et al.[98]

Even beyond the acute phase, the diagnosis is often complicated by grief. The critical symptoms of major depressive disorder are the first two listed—depressed mood and anhedonia—whereas grief is mainly characterized by feelings of emptiness and loss.[16]

Persistent Depressive Disorder

A smaller percentage of burned patients, around 4%, will develop a milder but more protracted type of depression called persistent depressive disorder, or dysthymia (F34.1).[98,99] In some cases the persistent depressive disorder may be preceded and/or interspersed by major depression. The main differences between major depression and persistent depressive disorder are that diagnostic criteria for the latter do not include the symptoms anhedonia, psychomotor agitation/retardation, and recurrent thoughts about death. The time frame also differs: persistent depressive disorder must be present for at least 2 years in adults or at least 1 year in children and adolescents in order to be diagnosed. Patients often report chronic anger, appetite changes, sleep difficulties, fatigue, low self-esteem, poor concentration, difficulty making decisions, and feelings of hopelessness. The same combination of medication and psychotherapy is recommended for patients with persistent depressive disorder as for major depression.

Substance-Related and Addictive Disorders

There are few studies that indicate the prevalence of substance abuse or alcohol abuse in adults. Recent studies indicate that substance abuse may be one of the most prevalent psychiatric disorders. A Finnish study found that 26% of the surveyed patients had alcohol abuse or dependence, and 6.5% had drug abuse or dependence during a 6-month follow-up after trauma.[49] Another study reported that 25% of former patients had an at-risk drinking pattern 2–7 years after burn injury, and it was predicted by an avoidant coping pattern that involved using alcohol, tobacco, or other drugs to handle problems.[100] Certainly prior abuse is a major risk factor for abuse after burns. Maes et al.[93] reported an incidence of 6% for new-onset psychoactive substance use disorders after trauma. In a study in young adults who were burned as children the prevalence of the use of alcohol and substances was 7.9% for alcohol and 35.7% for other substances; however this rate later fell to 3% for alcohol and 9.9% for other substances.[94] These young adult prevalence rates are lower than the reference population in the United States for alcohol but were higher for substance abuse/dependence, which may reflect the socioeconomic background of the subjects studied.

Comorbidity and Problems Beyond Psychiatric Illness

PTSD and depression are both linked to poor long-term outcomes in adults.[39,70] PTSD and pain together predicted poor functional and increased disability after major burns. PTSD symptoms led to greater physical and psychosocial disability, poorer social functioning, and less vitality.[39] Pain is linked to poor concurrent physical functioning, and depression can predict decreased physical health 2 months post discharge.[80,101]

Adjustment in Children After Burns

A significant number of the children and adolescents who survive major thermal injury develop a variety of significant behavioral and emotional problems at some point in their lives, but good adjustment is achieved by the majority of individuals.[102–106] In studies in adolescent and young adult survivors of pediatric burns, about half

of the individuals met criteria for one or more psychiatric disorders,[94,97] and adult survivors of childhood burns have a significantly higher relative rate of both psychiatric and physical illnesses.[107] About one-fifth of children with burns are reported to have more problems with conduct and peers than does the norm population,[106] and 35% of preschool children with burns were diagnosed with at least one psychological disorder.[108] A recent study also showed that 13.2% of infants and toddlers with burns met the proposed alternative criteria for PTSD.[109] Severity of symptoms and adjustment were associated with family relations and maternal PTSD. Compared to a group of survivors of flood trauma and a community sample, burned children had significantly more phobic disorders, overanxious disorders, enuresis, encopresis, major depression, PTSD, and substance/ethanol abuse.[96,110] Sleep disorders and psychotic disorders were also slightly more common among the burned children.

Parents usually report more problems than do the children themselves or their teachers.[102,111,112] This observation could be explained by increased problems in these children following severe burns that would not be easily observed by persons who do not live with them or that parents became overly sensitive to any indication of difficulty for their children following burns.

Another area of long-term psychiatric outcome following pediatric burns that has received little attention is the development of personality disorders. In the same sample of young adults mentioned earlier,[94] personality disorders were common and significantly associated with comorbid Axis I diagnoses.[113]

Diagnosis (Screening Instruments, SCID)

Two techniques are used to determine the prevalence of psychiatric disorders in burn survivors. The one most commonly used has been the self-report questionnaire, such as the Beck Depression Inventory, Impact of Event Scale-Revised,[114] Davidson Trauma Scale, Brief Symptom Inventory, McGill Pain Questionnaire, and Quality of Life surveys such as the Short Form 36 (SF-36) or the EQ-5D, which has been validated with burn survivors.[115]

For a more complete diagnostic survey, the gold standard is the Structured Clinical Interview for DSM-5 Disorders (SCID-5) interview.

The American Burn Association had a consensus conference in February 2013 to establish a recommendation for uniform psychiatric screening and diagnostic tools for the burn survivor. Wiechman et al. published a list of recommended tools a few months later.[116] The group focused on depression and PTSD symptoms.

Criteria for the screening instruments were that they be validated, easy to use, and free. For depression in adults, the Patient Health Questionnaire (PHQ-2 and 9), Beck Depression Inventory, Brief Symptom Inventory, and SCID were recommended; for childhood depression, the Child Depression Inventory was recommended. For PTSD symptoms in adults, the PTSD Symptom Checklist and in children the UCLA PTSD Index were recommended.

Treatment

DELIRIUM AND AGITATION

Due to the problems associated with phenothiazines, benzodiazepines have been used to a greater extent in recent years for the combative, delirious patient.[117–119] The two most commonly used benzodiazepines are diazepam and lorazepam. Lorazepam (0.03 mg/kg) orally or intravenously can usually be given every 4–8 hours; for a very combative patient it can be given hourly. A third benzodiazepine that is frequently used is midazolam at 0.05 mg/kg IV, typically used in conjunction with morphine for procedures such as tubbing and staple removal. Midazolam is also used for sedation as a continuous infusion for intubated patients. When using the benzodiazepine class of medications, a clinician must balance the desired effects of relaxation with oversedation. Visual and auditory hallucinations may occur if the dose of benzodiazepine is too high. In cases of excessive anxiety in the presence of adequate pain control, lorazepam can be added to a patient's treatment. Nighttime doses usually enhance sleep. Diazepam may be used in place of lorazepam if simultaneous muscle relaxation is desired.[120] Diazepam has an extremely long half-life, 40 hours, and therefore should be used sparingly. To avoid excessive sedation by benzodiazepines, a patient should not be awakened for the next dose.

ASD AND PTSD

Therapy is the same for ASD and PTSD and usually includes a combination of psychotherapy and pharmacotherapy. For a comprehensive description of common aspects of psychotherapy for PTSD, see Schnyder et al.[121] Trauma-focused cognitive behavioral therapy (TFCBT) can relieve PTSD symptoms and typically includes imagined and in vivo exposure, where prolonged exposure is one of the most effective treatment protocols today. Exposure involves in-depth recalling and verbalizing of the event, physically revisiting the site of the accident either in person or, as most recently studied, by means of virtual reality. Another treatment component is cognitive restructuring and skills training, sometimes by role play and cognitive tasks. Training in anxiety management using stabilizing and relaxation techniques is also important for recovery from PTSD. Another evidence-based psychological treatment is eye-movement desensitization and reprocessing (EMDR) where in-depth processing of the memory is achieved by having the patient track a bilateral stimulus with his or her eyes at the same time as the memory is retrieved. In a Cochrane review, TFCBT and EMDR were found more effective in the treatment of PTSD in the long term than were other psychotherapies or waitlist conditions.[122]

Pharmacotherapy developed over the past two decades with the use of selective serotonin reuptake inhibitors (SSRIs), such as sertraline and fluoxetine, as first-line drugs. Other useful medications are tricyclic antidepressants (TCAs); antipsychotics, such as risperidone and quetiapine fumarate; and $\alpha 2$ adrenergic agonists, such as clonidine. SSRI antidepressants, such as fluoxetine, or a TCA like imipramine should be considered for ASD.[123] Both SSRIs and TCAs are helpful in reducing nightmares and improving

sleep patterns. Treatment with an SSRI or TCA should be continued for at least 9 months to a year following the improvement of symptoms because of the risk of relapse.

One of the major issues with the use of TCA is that cardiac arrhythmias, associated with a prolonged PR interval, can be life-threatening.[124] When medication is discontinued, it should be reduced over time to avoid uncomfortable—although not medically threatening—discontinuation symptoms. The relatively long half-life of fluoxetine usually protects patients from any discontinuation symptoms but requires extended vigilance for any drug–drug interactions.

Typically the SSRIs are given in the morning rather than the evening because they may interfere with sleep onset. Side effects of SSRIs include gastrointestinal upset, increased agitation, headaches, sexual symptoms, and sweating. A rare but potentially life-threatening side effect is serotonergic syndrome,[125] characterized by at least three of the following symptoms: delirium, agitation, sweating, fever, hyperreflexia, myoclonus, tremor, incoordination, diarrhea, and shivering. Severe cases can result in hyperpyrexia, shock, or death. The risk of serotonergic syndrome increases when patients are on multiple medications that potentiate central nervous system serotonin, such as an SSRI and a monoamine oxidase inhibitor. There is a reported case of serotonin syndrome in a pediatric burn patient who was receiving fluoxetine and linezolid, a broad-spectrum antibiotic with monoamine oxidase inhibition.[126] Sexual side effects are the most likely reason that a teen or an adult would refuse to take an SSRI.

In an emergency room setting, propranolol has been tried with some success for those with minor injuries. It has been reported to be very helpful in the treatment of PTSD and ASD and to prevent their occurrence following a variety of different types of trauma. Longer-term studies with larger injuries have not shown propranolol to be helpful for the prevention or treatment of ASD or PTSD.[127,128] Benzodiazepines will control some immediate symptoms but are not useful long term.

Concerns that midazolam administration might interfere with this process and actually enhance PTSD could not be substantiated.[129]

OTHER ANXIETY DISORDERS

Most burn patients, certainly those who qualify for the diagnosis of generalized or overanxious disorder, will benefit from lorazepam therapy in addition to psychotherapy. If anxiety is associated with other symptoms of posttraumatic stress, such as hypervigilance or poor sleep, an SSRI[123] or the older TCAs[130] should be considered. The SSRIs have the advantage of being safer drugs for outpatient treatment since an overdose is unlikely to cause the significant cardiac problems that have been attributed to the TCAs.[131]

MAJOR DEPRESSION

Major depression, with or without grief reaction, should be treated by a team approach. The patient should be involved in scheduled daily activities. Psychotherapy should begin to identify and address appropriate issues. Medication with SSRIs or TCAs, as described for acute and posttraumatic stress, is often helpful. Once the symptoms have responded to medication, treatment should continue for 9 months to a year in order to avoid relapse on discontinuation.

Many times the depression is comorbid with PTSD. Therefore medications that affect both are preferred. Fluoxetine and the other SSRIs are the first-line medications for treatment of patients with depressive symptoms.[124,132]

SLEEP DISTURBANCES

After discharge, many burn survivors have significant sleep problems. As in the hospital setting this may be secondary to PTSD symptoms, depression, itch, or pain. Pain in the hospital before discharge will predict insomnia.[45] When sleep disturbance with nightmares is associated with posttraumatic anxiety, as described earlier, antidepressant medications are the drugs of choice. Imipramine and doxepin are both sedating antidepressants that are effective treatments for sleep problems in burn patients. Trazodone and nefazodone are alternative medications for insomnia and do not appear to alter sleep architecture as much as other antidepressants. Mirtazapine is another antidepressant that has been used for insomnia, although little is known about its effects on sleep architecture. Pain and itch are other problems that can interfere with sleep and should be addressed with appropriate analgesic or antipruritic medications.[133] If a patient continues to have significant sleep problems, sleep can be induced with diphenhydramine. Diphenhydramine doses of 1.5 mg/kg are often used throughout the day for itching and may be used alone for sleep at night or as an adjunct to other sleep medications. Usually, doses of 25 or 50 mg in the evening are adequate. Recently quetiapine fumarate (Seroquel) PO has been found to be safe and useful in this setting.

SPECIAL ASPECTS IN PEDIATRIC TREATMENT

As with adults, pediatric patients suffering with psychiatric symptoms can benefit from psychotherapy, with appropriate indicated treatment for their specific problems. A number of specific therapies have been adapted for treatment of anxiety, PTSD, and depression in children and adolescents. In addition, specific treatments for pediatric burn survivors have been developed, such as social skills training addressing disfigurement.[134] In school-aged children there is preliminary support for a brief, early psychological intervention in reducing later internalizing problems.[135]

Early opiate management of burn-related pain is important for decreasing the risk of long-term PTSD in children.[136]

Pediatric burn patients appear to have a much higher rate of adverse reactions to haloperidol, and alternative management of agitation should be considered.[137] Chlorpromazine and thioridazine may be used in place of haloperidol in the dosage range of 25–100 mg per dose. Chlorpromazine and thioridazine have strong sedative effects and interfere with learning but are less likely than haloperidol to produce associated dystonia, pseudo-parkinsonism, and akathisia. If more than 2 mg of haloperidol per day is used, attention must be given to simultaneous administration of 1

or 2 mg/d of benztropine or 2–5 mg/d of trihexyphenidyl in divided doses. Benztropine or trihexyphenidyl are used to avoid dystonia, pseudo-parkinsonism, and akathisia.[117] Occasionally, dystonia takes the form of an oculogyric crisis, which resembles an acute neurological catastrophe[138] and can be a true medical emergency if respiration is impaired. These reactions are usually alleviated by 50 mg IV diphenhydramine.

The treatment of anxiety and depression in children with SSRIs and TCAs requires closer attention to dosage and potential side effects. The usual starting dose of fluoxetine is 5 mg for children weighing less than 40 kg, 10 mg for children between 40 and 60 kg, and the adult dose for any children weighing more than 60 kg. The usual starting dose of imipramine is 25 mg/d unless the patient weighs less than 25 kg. The beginning dose is 12.5 mg for those under 25 kg. The dose can be increased rapidly over the next few days to a dose of 1 mg/kg. If the symptoms are still uncontrolled, the dose may be increased stepwise to 3 mg/kg, but only with frequent checking of the plasma level and electrocardiographic changes with each increment of dose. A steady state is usually not reached until a given dose is maintained for 3–5 days. The preferable time of administration is in the evening to aid with sleep. Major side effects of the TCAs are anticholinergic (dry mouth and dry nasal passages, constipation, urinary hesitance, and occasional esophageal reflux).[117] Autonomic complications such as orthostatic hypotension, palpitations, and hypertension have been reported in adolescents using this medication.[139] Cardiac arrhythmias associated with a prolonged PR interval can be life-threatening.[124,132] Sudden death has been reported for teenagers and children receiving desipramine and other TCAs.[140] Amitriptyline or doxepin may be used in place of imipramine. The dosages are similar; however both these medications may cause more sedation than imipramine.[117]

Following clinical reports of increased suicidal ideation in pediatric patients treated with certain antidepressant medications and a review of clinical trial data, the U.S. Food and Drug Administration instructed all manufacturers to include a "black box" warning with all antidepressant medications.[141] Pediatric patients and their caretakers must be aware of these risks, and clinicians should closely monitor children and adolescents on these medications for possibly increased suicidal ideation and behavior.[142]

NONPHARMACOLOGICAL PREVENTION OF PTSD

Currently there is no evidence-based nonpharmacological method for prevention of PTSD. The dominating approach is psychological first aid that is largely based on consensus agreement and has replaced the much criticized psychological debriefing as the standard intervention for trauma victims.[143] However there are preliminary indications that TFCBT can be effective in preventing PTSD in groups of trauma victims with early signs of high symptomatology.[144] Other complementary and alternative treatment modalities such as meditation, mindfulness, and acupuncture may also be effective, but to date the evidence is not as strong as for the aforementioned modalities.[145,146]

Resilience, Posttraumatic Growth

Although it has become generally accepted knowledge that trauma and injury can lead to psychological and psychiatric problems, the fact that a considerable proportion of individuals do not develop problems after trauma and injury has found much less attention, and, to date, there is only an extremely small number of studies in burn patients.

Resilience and posttraumatic growth (PTG) are two separate constructs. Resilience is a trait that exists before exposure to trauma or adverse events that PTG.[147,148] Resilient individuals have an ability to "bounce back" and regain balance in all aspects of life, as well as having endurance in the face of adverse events.[147–151] Resilience is the most common response pattern seen after burns: approximately 40% of adult patients respond in this way.[92] Three categories of protective factors, which also are predictive of resilience, have been identified:[150] individual characteristics, relationships, and social network.

In contrast, PTG is the development of new behaviors and attitudes that were not present before the event. It is a positive psychological development, the result of struggles in the face of hardship or traumatic events.[147,152] The Posttraumatic Growth Inventory[152] identifies five different aspects of PTG: new possibilities, relating to others, personal strength, spiritual change, and appreciation of life. PTG appears to be somewhat related to the personality traits of optimism and extraversion. Female gender and social support are the strongest predictors of PTG, and higher levels of education and higher socioeconomic status also are predictive.[145,147]

Resilience and PTG can both occur concurrently with distress and lower quality of life; in fact PTG may not occur without some level of distress, but distress diminishes over time in individuals who experience PTG. Longitudinal studies show that PTG levels out at about 6 months after trauma.[147]

INTERVENTIONS TO FOSTER PTG

While alleviating distress does not foster PTG, growth can protect from further distress. The patient's own experiences and psychological development appear to play a central role in PTG. The caregiver's role should be to support and improve coping, strengthen self-image, and enhance social support; caregivers "must be comfortable in allowing the patient to struggle with the event."[147,153] Common aspects of PTG in burn patients appear to be the use of active and flexible coping, social support, enhanced self-image, and the successful search for meaning.[148,154,155]

Conclusion

Preinjury psychiatric morbidity can have a major effect on outcome after a burn. Furthermore, psychiatric symptoms occur commonly as part of the complex systemic response to burn injuries. Psychological and pharmacologic treatment is important in the successful recovery of a burned person and may reduce the risk of long-term psychiatric sequelae of the injury. It is important to note that

psychological adaptation is a lengthy process occurring over months or years. During the postburn years, it is imperative that the burn team assesses the mental and affective states of patients while assessing their physical recovery. In most cases, patients with sleep disorders, depression, or withdrawal from previous activities will not seek psychiatric attention and treatment, although these problems can be ameliorated by treatment. It therefore becomes a responsibility of the expert in burn care and the entire burn team to be aware of frequently occurring problems, to ask the right questions to assess a patient's status, and to assist a patient in receiving psychological and psychiatric assistance.

Complete references available online at
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References

1. McKibben JB, et al. Epidemiology of burn injuries II: psychiatric and behavioural perspectives. *Int Rev Psychiatry*. 2009;21(6):512-521.
2. Dyster-Aas J, et al. Major depression and posttraumatic stress disorder symptoms following severe burn injury in relation to lifetime psychiatric morbidity. *J Trauma*. 2008;64(5):1349-1356.
3. Patterson DR, et al. Psychological effects of severe burn injuries. *Psychol Bull*. 1993;113(2):362-378.
4. Davydow DS, Katon WJ, Zatzick DF. Psychiatric morbidity and functional impairments in survivors of burns, traumatic injuries, and ICU stays for other critical illnesses: a review of the literature. *Int Rev Psychiatry*. 2009;21(6):531-538.
5. Taal LA, Faber AW. Dissociation as a predictor of psychopathology following burns injury. *Burns*. 1997;23(5):400-403.
6. Willebrand M, Andersson G, Ekselius L. Prediction of psychological health after an accidental burn. *J Trauma*. 2004;57(2):367-374.
7. Tedstone JE, Tarrier N. An investigation of the prevalence of psychological morbidity in burn-injured patients. *Burns*. 1997; 23(7-8):550-554.
8. Fauerbach JA, et al. Preinjury psychiatric illness and postinjury adjustment in adult burn survivors. *Psychosomatics*. 1996;37(6):547-555.
9. van der Does AJ, et al. Burn injuries, psychiatric disorders and length of hospitalization. *J Psychosom Res*. 1997;43(4):431-435.
10. Tarrier N, et al. The influence of pre-existing psychiatric illness on recovery in burn injury patients: the impact of psychosis and depression. *Burns*. 2005;31(1):45-49.
11. Modjarrad K, et al. The descriptive epidemiology of intentional burns in the United States: an analysis of the National Burn Repository. *Burns*. 2007;33(7):828-832.
12. Low AJ, Dyster-Aas J, Willebrand M, Ekselius L, Gerdin B. Psychiatric morbidity predicts perceived burn-specific health 1 year after a burn. *Gen Hosp Psychiatry*. 2012;34(2):146-152.
13. Ekeblad F, Gerdin B, Öster C. Impact of personality disorders on health-related quality of life one year after burn injury. *Disabil Rehabil*. 2015;37(6):534-540.
14. Burke BA, et al. Methamphetamine-related burns in the cornbelt. *J Burn Care Res*. 2008;29(4):574-579.
15. Harvey L, Mitchell R, Brodaty H, Draper B, Close J. Dementia: a risk factor for burns in the elderly. *Burns*. 2016;S0305-4179(15):00333-2.
16. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
17. Badger K, Anderson L, Kagan RJ. Attention deficit-hyperactivity disorder in children with burn injuries. *J Burn Care Res*. 2008;29(5):724-729.
18. Ghanizadeh A. Small burns among out-patient children and adolescents with attention deficit hyperactivity disorder. *Burns*. 2008;34(4):546-548.
19. Thomas CR, et al. Attention deficit hyperactivity disorder & pediatric burn injury: a preliminary retrospective study. *Burns*. 2004; 30(3):221-223.
20. Grant JE, Won Kim SJ. Clinical characteristics and psychiatric comorbidity of pyromania. *Clin Psychiatry*. 2007;68(11):1717-1722.
21. Dissanaike S, et al. Burns as child abuse: risk factors and legal issues in West Texas and eastern New Mexico. *J Burn Care Res*. 2010;31(1):176-183.
22. Thombs BD. Patient and injury characteristics, mortality risk, and length of stay related to child abuse by burning: evidence from a national sample of 15,802 pediatric admissions. *Ann Surg*. 2008;247(3):519-523.
23. Tyack ZF, Ziviani J. What influences the functional outcome of children at 6 months post-burn? *Burns*. 2003;29(5):433-444.
24. Meyer WJ, et al. Parental well-being and behavioral adjustment of pediatric survivors of burns. *J Burn Care Rehabil*. 1994;15(1):62-68.
25. Simons MA, Ziviani J, Copley J. Predicting functional outcome for children on admission after burn injury: do parents hold the key? *J Burn Care Res*. 2010;31(5):750-765.
26. Kent L, King H, Cochrane R. Maternal and child psychological sequelae in paediatric burn injuries. *Burns*. 2000;26(4):317-322.
27. Dorn T, et al. Physical and mental health problems in parents of adolescents with burns–a controlled, longitudinal study. *J Psychosom Res*. 2007;63(4):381-389.
28. Fukunishi I. Posttraumatic stress symptoms and depression in mothers of children with severe burn injuries. *Psychol Rep*. 1998;83(1): 331-335.
29. El Hamaoui Y, et al. Depression in mothers of burned children. *Arch Womens Ment Health*. 2006;9(3):117-119.
30. Rizzone LP, et al. Posttraumatic stress disorder in mothers of children and adolescents with burns. *J Burn Care Rehabil*. 1994;15(2): 158-163.
31. Hall E, et al. Posttraumatic stress symptoms in parents of children with acute burns. *J Pediatr Psychol*. 2006;31(4):403-412.
32. Egberts MR, van de Schoot R, Boekelaar A, et al. Child and adolescent internalizing and externalizing problems 12 months postburn: the potential role of preburn functioning, parental posttraumatic stress, and informant bias. *Eur Child Adolesc Psychiatry*. 2016;25(7):791-803.
33. Tuohig GM, et al. Self-inflicted patient burns: suicide versus mutilation. *J Burn Care Rehabil*. 1995;16(4):429-436.
34. Poeschla B, Combs H, Livingstone S, et al. Self-immolation: socioeconomic, cultural and psychiatric patterns. *Burns*. 2011;37(6): 1049-1057.
35. Difede J, et al. Treatments for common psychiatric conditions among adults during acute, rehabilitation, and reintegration phases. *Int Rev Psychiatry*. 2009;21(6):559-569.
36. Wikehult B, et al. Evaluation of negative emotional care experiences in burn care. *J Clin Nurs*. 2008;17(14):1923-1929.
37. Connor-Ballard PA. Understanding and managing burn pain: Part 2. *Am J Nurs*. 2009;109(5):54-62, quiz 63.
38. Wiechman Askay S, Patterson DR. What are the psychiatric sequelae of burn pain? *Curr Pain Headache Rep*. 2008;12(2):94-97.
39. Corry NH, Klick B, Fauerbach JA. Posttraumatic stress disorder and pain impact functioning and disability after major burn injury. *J Burn Care Res*. 2010;31(1):13-25.
40. Goutos I, Dziewulski P, Richardson PM. Pruritus in burns: review article. *J Burn Care Res*. 2009;30(2):221-228.
41. Shaw RJ, et al. Psychiatric medications for the treatment of pruritus. *Psychosom Med*. 2007;69(9):970-978.
42. Patel T, Ishiuji Y, Yosipovitch G. Nocturnal itch: why do we itch at night? *Acta Derm Venereol*. 2007;87(4):295-298.
43. Rose M, et al. Factors altering the sleep of burned children. *Sleep*. 2001;24(1):45-51.
44. Lawrence JW, et al. The 1998 Clinical Research Award. Sleep disturbance after burn injury: a frequent yet understudied complication. *J Burn Care Rehabil*. 1998;19(6):480-486.
45. Smith MT, et al. Sleep onset insomnia symptoms during hospitalization for major burn injury predict chronic pain. *Pain*. 2008;138(3):497-506.
46. Gabor JY, Cooper AB, Hanly PJ. Sleep disruption in the intensive care unit. *Curr Opin Crit Care*. 2001;7(1):21-27.
47. Raymond I, et al. Quality of sleep and its daily relationship to pain intensity in hospitalized adult burn patients. *Pain*. 2001;92(3): 381-388.
48. McKibben JB, et al. Acute stress disorder and posttraumatic stress disorder: a prospective study of prevalence, course, and predictors in a sample with major burn injuries. *J Burn Care Res*. 2008;29(1): 22-35.
49. Palmu R, Suominen K, Vuola J, et al. Mental disorders after burn injury: a prospective study. *Burns*. 2011;37(4):601-609.
50. Saxe GN, et al. Pathways to PTSD, part I: Children with burns. *Am J Psychiatry*. 2005;162(7):1299-1304.
51. Sheridan R, Stoddard F, Querzoli E. Management of background pain and anxiety in critically burned children requiring protracted mechanical ventilation. *J Burn Care Rehabil*. 2001;22(2): 150-153.
52. Blakeney P, Meyer W. Psychological aspects of burn care. *Trauma Q*. 1994;II(2):166-179.
53. Thomas C Presentation on hallucinations. in *ABA*.
54. Haynes BW Jr, Bright R. Burn coma: a syndrome associated with severe burn wound infection. *J Trauma*. 1967;7(3):464-475.
55. Antoon AY, Volpe JJ, Crawford JD. Burn encephalopathy in children. *Pediatrics*. 1972;50(4):609-616.
56. Stoddard F. Psychiatric management of the burned patient. In: Martyn JA, ed. *Acute Care of the Burn Patient*. Orlando FL.: Grune and Stratton; 1990:256-272.
57. Stoddard FJ, et al. Acute stress symptoms in young children with burns. *J Am Acad Child Adolesc Psychiatry*. 2006;45(1):87-93.
58. Saxe G, et al. Risk factors for acute stress disorder in children with burns. *J Trauma Dissociation*. 2005;6(2):37-49.
59. Ratcliff SL, et al. The effectiveness of a pain and anxiety protocol to treat the acute pediatric burn patient. *Burns*. 2006;32(5):554-562.

60. Saxe G, et al. Separation anxiety as a mediator between acute morphine administration and PTSD symptoms in injured children. *Ann N Y Acad Sci*. 2006;1071:41-45.
61. Blank K, Perry S. Relationship of psychological processes during delirium to outcome. *Am J Psychiatry*. 1984;141(7):843-847.
62. Agarwal V, et al. Prevalence and risk factors for development of delirium in burn intensive care unit patients. *J Burn Care Res*. 2010;31(5):706-715.
63. Weinhouse GL, et al. Bench-to-bedside review: delirium in ICU patients – importance of sleep deprivation. *Crit Care*. 2009;13(6):234.
64. Van Loey NE, Van Son MJ. Psychopathology and psychological problems in patients with burn scars: epidemiology and management. *Am J Clin Dermatol*. 2003;4(4):245-272.
65. Giannoni-Pastor A, Eiroa-Orosa FJ, Fidel Kinori SG, et al. Prevalence and predictors of posttraumatic stress symptomatology among burn survivors: a systematic review and meta-analysis. *J Burn Care Res*. 2016;37(1):e79-e89.
66. Friedman MJ, Resick PA, Bryant RA, et al. Considering PTSD for DSM-5. *Depress Anxiety*. 2011;28(9):750-769.
67. Van Loey NE, et al. Predictors of chronic posttraumatic stress symptoms following burn injury: results of a longitudinal study. *J Trauma Stress*. 2003;16(4):361-369.
68. Lawrence JW, Fauerbach JA. Personality, coping, chronic stress, social support and PTSD symptoms among adult burn survivors: a path analysis. *J Burn Care Rehabil*. 2003;24(1):63-72, discussion 62.
69. Difede J, Barocas D. Acute intrusive and avoidant PTSD symptoms as predictors of chronic PTSD following burn injury. *J Trauma Stress*. 1999;12(2):363-369.
70. Zatzick D, Roy-Byrne PP. From bedside to bench: how the epidemiology of clinical practice can inform the secondary prevention of PTSD. *Psychiatr Serv*. 2006;57(12):1726-1730.
71. Ter Smitten MH, de Graaf R, Van Loey NE. Prevalence and comorbidity of psychiatric disorders 1–4 years after burn. *Burns*. 2011;37(5):753-761.
72. Bryant RA. Predictors of post-traumatic stress disorder following burns injury. *Burns*. 1996;22(2):89-92.
73. Shakespeare V. Effect of small burn injury on physical, social and psychological health at 3–4 months after discharge. *Burns*. 1998;24(8):739-744.
74. Low AJ, et al. The presence of nightmares as a screening tool for symptoms of posttraumatic stress disorder in burn survivors. *J Burn Care Res*. 2006;27(5):727-733.
75. Gould NF, McKibben JB, Hall R, et al. Peritraumatic heart rate and posttraumatic stress disorder in patients with severe burns. *J Clin Psychiatry*. 2011;72(4):539-547.
76. Ehde DM, et al. Post-traumatic stress symptoms and distress following acute burn injury. *Burns*. 1999;25(7):587-592.
77. Yu BH, Dimsdale JE. Posttraumatic stress disorder in patients with burn injuries. *J Burn Care Rehabil*. 1999;20(5):426-433, discussion 422-425.
78. Lawrence JW, Fauerbach J, Munster A. Early avoidance of traumatic stimuli predicts chronicity of intrusive thoughts following burn injury. *Behav Res Ther*. 1996;34(8):643-646.
79. Ullrich PM, Askay SW, Patterson DR. Pain, depression, and physical functioning following burn injury. *Rehabil Psychol*. 2009;54(2):211-216.
80. Edwards RR, et al. Acute pain at discharge from hospitalization is a prospective predictor of long-term suicidal ideation after burn injury. *Arch Phys Med Rehabil*. 2007;88(12 suppl 2):S36-S42.
81. Edwards RR, et al. Symptoms of depression and anxiety as unique predictors of pain-related outcomes following burn injury. *Ann Behav Med*. 2007;34(3):313-322.
82. Sveen J, Dyster-Aas J, Willebrand M. Attentional bias and symptoms of posttraumatic stress disorder one year after burn injury. *J Nerv Ment Dis*. 2009;197(11):850-855.
83. Nayeb-Hashemi N, et al. Skull burns resulting in calvarial defects: cognitive and affective outcomes. *Burns*. 2009;35(2):237-246.
84. Pallua N, Kunsebeck HW, Noah EM. Psychosocial adjustments 5 years after burn injury. *Burns*. 2003;29(2):143-152.
85. Fukunishi I. Relationship of cosmetic disfigurement to the severity of posttraumatic stress disorder in burn injury or digital amputation. *Psychother Psychosom*. 1999;68(2):82-86.
86. Wiechman SA, et al. Rates, trends, and severity of depression after burn injuries. *J Burn Care Rehabil*. 2001;22(6):417-424.
87. Taal LA, Faber AW. Posttraumatic stress and maladjustment among adult burn survivors 1–2 years postburn. *Burns*. 1998;24(4):285-292.
88. Taal L, Faber AW. Posttraumatic stress and maladjustment among adult burn survivors 1 to 2 years postburn. Part II: the interview data. *Burns*. 1998;24(5):399-405.
89. Kessler RC, et al. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1995;52(12):1048-1060.
90. Shalev AY, et al. Prospective study of posttraumatic stress disorder and depression following trauma. *Am J Psychiatry*. 1998;155(5):630-637.
91. deRoon-Cassini TA, Mancini AD, Rusch MD, et al. Psychopathology and resilience following traumatic injury: a latent growth mixture model analysis. *Rehabil Psychol*. 2010;55(1):1-11.
92. Sveen J, Ekselius L, Gerdin B, et al. A prospective longitudinal study of posttraumatic stress disorder symptom trajectories after burn injury. *J Trauma*. 2011;71(6):1808-1815.
93. Maes M, et al. Psychiatric morbidity and comorbidity following accidental man-made traumatic events: incidence and risk factors. *Eur Arch Psychiatry Clin Neurosci*. 2000;250(3):156-162.
94. Meyer WJ, et al. Prevalence of major psychiatric illness in young adults who were burned as children. *Psychosom Med*. 2007;69(4):377-382.
95. Ptacek JT, Patterson DR, Heimbach DM. Inpatient depression in persons with burns. *J Burn Care Rehabil*. 2002;23(1):1-9.
96. Stoddard F. Psychiatric management of the burned patient. In: Martyn JA, ed. *Acute Care of the Burn Patient*. Orlando, FL: Grune and Stratton; 1990:256-272.
97. Thomas CR, et al. Psychiatric disorders in long-term adjustment of at-risk adolescent burn survivors. *J Burn Care Res*. 2009;30(3):458-463.
98. Thombs BD, Bresnick MG, Magyar-Russell G. Depression in survivors of burn injury: a systematic review. *Gen Hosp Psychiatry*. 2006;28(6):494-502.
99. Madianos MG, et al. Psychiatric disorders in burn patients: a follow-up study. *Psychother Psychosom*. 2001;70(1):30-37.
100. Sveen J, Öster C. Alcohol consumption after severe burn: a prospective study. *Psychosomatics*. 2015;56(4):390-396.
101. Thombs BD, et al. Symptoms of depression predict change in physical health after burn injury. *Burns*. 2007;33(3):292-298.
102. Blakeney P, et al. Psychosocial sequelae of pediatric burns involving 80% or greater total body surface area. *J Burn Care Rehabil*. 1993;14(6):684-689.
103. Blakeney P, et al. Long-term psychosocial adaptation of children who survive burns involving 80% or greater total body surface area. *J Trauma*. 1998;44(4):625-632, discussion 633-634.
104. LeDoux J, et al. Relationship between parental emotional states, family environment and the behavioural adjustment of pediatric burn survivors. *Burns*. 1998;24(5):425-432.
105. Zeitlin RE. Long-term psychosocial sequelae of paediatric burns. *Burns*. 1997;23(6):467-472.
106. Willebrand M, Sveen J, Ramklint MD, et al. Psychological problems in children with burns – parents' reports on the Strengths and Difficulties Questionnaire. *Burns*. 2011;37(8):1309-1316.
107. Stone J, Gawaziuk JP, Khan S, et al. Outcomes in adult survivors of childhood burn injuries as compared with matched controls. *J Burn Care Res*. 2016;37(2):e166-e173.
108. De Young AC, Kenardy JA, Cobham VE. Prevalence, comorbidity and course of trauma reactions in young burn-injured children. *J Child Psychol Psychiatry*. 2012;53(1):56-63.
109. Graf A, Schiestl C, Landolt MA. Posttraumatic stress and behavior problems in infants and toddlers with burns. *J Pediatr Psychol*. 2011;36(8):923-931.
110. Stoddard FJ, Norman DK, Murphy JM. A diagnostic outcome study of children and adolescents with severe burns. *J Trauma*. 1989;9(4):471-477.
111. Blakeney P, et al. Social competence and behavioral problems of pediatric survivors of burns. *J Burn Care Rehabil*. 1993;14(1):65-72.
112. Meyer WJ 3rd, et al. Inconsistencies in psychosocial assessment of children after severe burns. *J Burn Care Rehabil*. 1995;16(5):559-568, discussion 557–558.
113. Thomas C, et al. Personality disorders and traits in young adult survivors of pediatric burn injury. *J Pers Disord*. 2012;In press.
114. Sveen J, et al. Validation of a Swedish version of the Impact of Event Scale-Revised (IES-R) in patients with burns. *J Anxiety Disord*. 2010;24(6):618-622.

115. Oster C, et al. Validation of the EQ-5D questionnaire in burn injured adults. *Burns*. 2009;35(5):723-732.
116. Wiechman S, Meyer W, Edelman L, et al. Psychological outcomes. *J Burn Care Res*. 2013;34(4):363-368.
117. Schatzberg AF, Cole JO. *Manual of Clinical Psychopharmacology*. 2nd ed. Washington, DC: American Psychiatric Press; 1991.
118. Still J, et al. Neuroleptic malignant syndrome in a burn patient. *Burns*. 1998;24(6):573-575.
119. Coffey BJ. Anxiolytics for children and adolescents: traditional and new drugs. *J Child Adolesc Psychopharmacol*. 1990;1(1):57-83.
120. Martyn JA, Greenblatt DJ, Quinby WC. Diazepam kinetics in patients with severe burns. *Anesth Analg*. 1983;62(3):293-297.
121. Schnyder U, Ehlers A, Elbert T, et al. Psychotherapies for PTSD: what do they have in common? *Eur J Psychotraumatol*. 2015;6:28186.
122. Bisson JI, Roberts NP, Andrew M, et al. Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. *Cochrane Database Syst Rev*. 2013;(12):CD003388.
123. Tcheung WJ, et al. Early treatment of acute stress disorder in children with major burn injury. *Pediatr Crit Care Med*. 2005;6(6):676-681.
124. Ryan ND. Heterocyclic antidepressants in children and adolescents. *J Child Adolesc Psychopharmacol*. 1990;1(1):21-31.
125. Chiu S, Leonard HI. Antidepressants I: selective serotonin reuptake inhibitors. In: Martin A, et al, eds. *Pediatric Psychopharmacology: Principles and Practice*. New York: Oxford University Press; 2003:274.
126. Thomas CR, et al. Serotonin syndrome and linezolid. *J Am Acad Child Adolesc Psychiatry*. 2004;43(7):790.
127. Sharp S, et al. Propranolol does not reduce risk for acute stress disorder in pediatric burn trauma. *J Trauma*. 2010;68(1):193-197.
128. McGhee LL, et al. The effect of propranolol on posttraumatic stress disorder in burned service members. *J Burn Care Res*. 2009;30(1):92-97.
129. McGhee LL, et al. The relationship of intravenous midazolam and posttraumatic stress disorder development in burned soldiers. *J Trauma*. 2009;66(4 suppl):S186-S190.
130. Robert R, et al. Imipramine treatment in pediatric burn patients with symptoms of acute stress disorder: a pilot study. *J Am Acad Child Adolesc Psychiatry*. 1999;38(7):873-882.
131. Glassman AH. The newer antidepressant drugs and their cardiovascular effects. *Psychopharmacol Bull*. 1984;20(2):272-279.
132. Glassman AH, Bigger JT Jr. Cardiovascular effects of therapeutic doses of tricyclic antidepressants. A review. *Arch Gen Psychiatry*. 1981;38(7):815-820.
133. Raymond I, Ancoli-Israel S, Choiniere M. Sleep disturbances, pain and analgesia in adults hospitalized for burn injuries. *Sleep Med*. 2004;5(6):551-559.
134. Blakeney P, et al. Efficacy of a short-term, intensive social skills training program for burned adolescents. *J Burn Care Rehabil*. 2005;26(6):546-555.
135. Kramer DN, Landolt MA. Early psychological intervention in accidentally injured children ages 2–16: a randomized controlled trial. *Eur J Psychotraumatol*. 2014;5.
136. Sheridan RL, Stoddard FJ, Kazis LE, et al. Long-term posttraumatic stress symptoms vary inversely with early opiate dosing in children recovering from serious burns: effects durable at 4 years. *J Trauma Acute Care Surg*. 2014;76(3):828-832.
137. Ratcliff SL, et al. The use of haloperidol and associated complications in the agitated, acutely ill pediatric burn patient. *J Burn Care Rehabil*. 2004;25(6):472-478.
138. Huang V, Figge H, Demling R. Haloperidol complications in burn patients. *J Burn Care Rehabil*. 1987;8(4):269-273.
139. Teicher MH, Glod CA. Neuroleptic drugs: indications and guidelines for their rational use in children and adolescents. *J Child Adolesc Psychopharmacol*. 1990;1(1):33-56.
140. Popper CW, Elliott GR. Sudden death and tricyclic antidepressants: clinical considerations for children. *J Child Adolesc Psychopharmacol*. 1990;1(2):125-132.
141. Kondro W. FDA urges "black box" warning on pediatric antidepressants. *Can Med Assoc J*. 2004;171(8):837-838.
142. Bridge JA, et al. The risks and benefits of antidepressant treatment for youth depression. *Ann Med*. 2005;37(6):404-412.
143. Pratchett LC, Daly K, Bierer LM, et al. New approaches to combining pharmacotherapy and psychotherapy for posttraumatic stress disorder. *Expert Opin Pharmacother*. 2011;12:2339-2354.
144. Qi W, Gevonden M, Shalev A. Prevention of post-traumatic stress disorder after trauma: current evidence and future directions. *Curr Psychiatry Rep*. 2016;18(2):20.
145. Smith BW, Ortiz JA, Steffen LE, et al. Mindfulness is associated with fewer PTSD symptoms, depressive symptoms, physical symptoms, and alcohol problems in urban firefighters. *J Consult Clin Psychol*. 2011;79(5):613-617.
146. Williams JW Jr, Gierisch JM, McDuffie J, et al. VA evidence-based synthesis program reports. An overview of complementary and alternative medicine therapies for anxiety and depressive disorders: supplement to efficacy of complementary and alternative medicine therapies for posttraumatic stress disorder [Internet]; 2011. Washington (DC): Department of Veterans Affairs.
147. Wiechman Askay S, Magyar-Russell G. Post-traumatic growth and spirituality in burn recovery. *Int Rev Psychiatry*. 2009;21(6):570-579.
148. Baillie SE, Sellwood W, Wisely JA. Post-traumatic growth in adults following a burn. *Burns*. 2014;40(6):1089-1096.
149. Zautra AJ. Resilience: one part recovery, two parts sustainability. *J Pers*. 2009;77(6):1935-1943.
150. Ong AD, Bergeman CS, Boker SM. Resilience comes of age: defining features in later adulthood. *J Pers*. 2009;77(6):1777-1804.
151. Bonanno GA, et al. Resilience to loss and chronic grief: a prospective study from preloss to 18-months postloss. *J Pers Soc Psychol*. 2002;83(5):1150-1164.
152. Tedeschi RG, Calhoun LG. The Posttraumatic Growth Inventory: measuring the positive legacy of trauma. *J Trauma Stress*. 1996;9(3):455-471.
153. Calhoun LG, Tedeschi RG. *Facilitating Posttraumatic Growth: a Clinician's Guide*. Mahwah, NJ: Lawrence Erlbaum Associates; 1999.
154. Rosenbach C, Renneberg B. Positive change after severe burn injuries. *J Burn Care Res*. 2008;29(4):638-643.
155. Zhai J, et al. What does posttraumatic growth mean to Chinese burn patients: a phenomenological study. *J Burn Care Res*. 2010;31(3):433-440.

66 Psychosocial Recovery and Reintegration of Patients With Burn Injuries

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Introduction

Burn survivors may deal with diverse psychosocial issues in the recovery from a major burn injury. Common concerns include adapting to physical limitations and permanent changes; dealing with grief and loss; experiencing traumatic stress, anxiety, pain, sleep disturbance, depression, and body image concerns; and other adjustment issues. Approximately 30% of survivors experience long-term psychosocial difficulties.[1,2] Psychological healing occurs across time commensurate with physical healing in a relatively predictable and consistent pattern.[3] Awareness of this process permits survivors and their family members to anticipate the development of psychosocial issues, view concerns as normal reactions to the trauma instead of symptoms of psychological impairment, and facilitates coping with these issues. The goal of the recovery process is to attain optimal psychological, emotional, and social functioning (Figs. 66.1 and 66.2). Therefore, availability of psychosocial support is important for the recovery of the burn survivor and the adjustment of the family.

This chapter provides an overview of psychosocial issues that burn survivors and their families may experience during the phases of the recovery. There is also a review of important psychosocial constructs that can affect recovery such as assisting with grief and loss; cultural sensitivity; psychological distress; acute and posttrauma distress; resilience and recovery; body image concerns, stigmatization and social integration; social belongingness; long-term quality of life; and interventions beyond acute care. The medical management of pain and anxiety are presented in chapter 4 in this book.

Integrating Psychological Treatment With Physical Treatment

Comprehensive burn treatment requires a coordinated interdisciplinary team approach for physical and psychosocial recovery to occur concurrently. Mental health professionals on a burn team provide direct patient care and work indirectly through consultation with other caregivers to address survivors' psychosocial concerns and to assist family members with their adjustment. Integrating the family into the treatment plan from the beginning facilitates successful outcomes.

PREINJURY ADJUSTMENT

Shortly after being admitted to the burn unit, a clinical interview is done to gather information regarding variables that may influence the patient's recovery and treatment. Information about the burn injury, previous stressful events, risk factors, preburn physical and psychological health, coping skills, family and social support, and the family's strengths and weaknesses are important factors to take into account when developing treatment plans.[4,5] Gathering information about factors that contributed to the circumstances of the burn is emphasized in instances of suspected maltreatment and neglect.[6] Because patients will be dependent to some extent on family during recovery, it is essential to identify risk factors in the family system. Risk factors that may predispose individuals to burn injury and that may affect postburn recovery include physical illness, substance abuse, psychiatric illness, behavioral problems, poverty, inadequate social support, and heightened family disruption.[5,7–9] Part of the clinical interview involves initiation of a therapeutic alliance with those who are most likely to be involved in assisting a patient's recovery.

ADMISSION CRISIS

When people with burns are admitted to the intensive care unit (ICU), they may be frightened, confused, experience shock and disbelief, have pain and anxiety, and fear dying. While the physiological emergency is treated medically, the psychological crisis must also be addressed. The goals at this time are to establish therapeutic rapport with the patient, decrease anxiety, and assess strengths and needs of the patient. The first two tasks are addressed immediately by orienting the patient, focusing on immediate priorities, and assuring the patient that the burn team is composed of knowledgeable experts who will provide excellent care. The patient's heightened anxiety can be expected to interfere with his or her comprehension, so it is usually necessary to repeat statements of reassurance. To prevent a patient from becoming emotionally overwhelmed, it may be necessary initially to avoid or limit talking about trauma-related content. Children in this early stage of recovery may exhibit signs of cognitive and emotional regression, and it is important to respond to them on that level. Techniques such as deep breathing, relaxation with

Fig. 66.1 Quinceañera cutting cake with parents. (From Herndon DN, ed. *Total burn care*. London: WB Saunders; 2007.)

Fig. 66.2 A relaxing day before attending college.

focused imagery, and hypnotherapy may decrease patients' anxiety.

Family members are often traumatized and may experience difficulty eating, sleeping, or concentrating, and feel a loss of control and a generalized sense of incompetence and helplessness. Providing psychosocial support and education about recovery may facilitate the coping of the family. They may need frequent repetition of information and direction in providing comfort to the patient. The psychotherapeutic goals to be accomplished with the family include establishing a therapeutic relationship and diminishing anxiety. This can be facilitated by assisting with orientation to the hospital, providing information about normal reactions to trauma, and validating that their distress is normal and temporary, which helps communicate empathy and understanding. Learning about the injury and its treatment helps restore the family's sense of competence and provides opportunities for them to experience the reality of their roles in helping the patient. The manner in which an individual and a family will ultimately adjust to the long-term sequelae of a burn is often determined in the early stages of recovery.

CRITICAL CARE PHASE

This phase involves intensive medical and surgical care until the majority of open wounds are covered, and it is an important phase psychologically. Organic factors resulting from the injury and treatment can contribute to psychological symptoms of disorientation, confusion, sleep disturbance, transient psychosis, and delirium. Helpful interventions include frequent orientation to person, place, time; placing comforting objects in patient's view to see and touch; and making the environment as soothing as possible. Visits from family and friends can provide familiarity, reassurance, and comfort the patient. A schedule that approximates a regular wake–sleep cycle helps patients begin to feel normal.

Reassurance from staff about normal aspects of recovery, the treatment plan, and how staff plans to help improve function can decrease anxiety and provide a sense of hope. When a patient is alert the psychotherapist can facilitate grief work to help the patient adjust to the effects of the burn. Patients with altered mental states may be able to hear although not respond, and discretion should be used regarding what is said near them. Psychological interventions are aimed at diminishing anxiety and increasing comfort instead of correcting the person's perception of reality.[10]

Pain and anxiety management are crucial in this stage of recovery. Providing good pain control enhances psychological recovery. Routine and scheduled assessments of background and procedural pain[11–13] and anxiety[11,13] validates a patient's concerns but also set an expectancy of relief. The use of standardized scales provides the message that experiencing a range of pain is normal. When staff assess comfort routinely, patients are less likely to feel anxious about their pain management. Clinicians, researchers, and burn survivors have noted that patient recall of satisfaction with acute pain management in the hospital has indicated the need to improve this salient aspect of burn care. Perhaps this may be accomplished by combining a standard pain medication regimen with individualized adjustments based on behavioral observation and patient-reported pain.[14] Similarly, survivors have voiced dissatisfaction with various aspects of care and aftercare, including pain management and the means by which they observed and coped with their injuries.[15] These are ongoing areas of focus and psychosocial intervention.

Psychological interventions for pain and anxiety should be used in conjunction with pharmacological management. Anticipatory anxiety may influence a person's perception of pain. Cognitive and behavioral interventions that enhance a patient's mastery or control can decrease pain and anxiety. Patients often tolerate procedures better when the reasons for each procedure are explained. They may feel more comfortable participating in their own care and gain some mastery over pain when they are allowed to remove their own dressings or participate in wound debridement. The presence of a supportive person during procedures can

be effective in decreasing pain. Instructing a family member on how to comfort his or her loved one is important during these procedures.

Other effective interventions in decreasing pain and distress associated with burn treatment include deep breathing, progressive relaxation, visual imagery, biofeedback, hypnosis, virtual reality, mindfulness exercises, and relaxed jaw.[16] Hypnosis induces a relaxed and focused state of awareness that can be extremely helpful in facilitating comfort for patients. Hypnotic inductions and suggestions must be modified to facilitate a patient's use of imagery. Some individuals will respond well to suggestions of imagining a "favorite place." Older children may respond well to storytelling, with suggestions for comfort and mastery interwoven into the story.[17] Survivors may benefit from interventions that redirect their attention away from the painful procedure. Studies found immersive virtual reality, in which individuals' attention was immersed in a computer-generated world, was effective in reducing pain during wound care[18–20] and in the tub room.[21] This intervention may also be helpful during physical therapy.[22,23] Mott and colleagues reported augmented reality, where a character viewed on a screen, was effective in decreasing pain ratings of children with burns during prolonged wound care.[24] Music therapy is an excellent adjunct to analgesia during burn care with children.[25–27] Fratianne and colleagues mentioned that music therapy significantly decreased the perception of pain in children during wound care;[28] whereas a sensory-focused intervention was more effective with adult burn survivors.[29] Child life interventions such as medical play that gives children control by having them role play and manipulate medical equipment, preoperative preparation about procedures or surgeries, and procedural support can facilitate coping in children and adolescents and decrease anxiety during burn care. The child's age and development need to be considered when selecting the intervention.[30]

Although over time family members may become more at ease with hospital routines, they will continue to have difficulty coping, feel anxious, and need updates about their patient's present and future status,[31] and they may develop new concerns as they are given new roles and responsibilities. Being away from support systems can be difficult. It is helpful to provide information about what to expect in the immediate future, to facilitate patient interaction, and provide honest information while allowing family members to protect themselves from overwhelming despair. Staff can find ways to allow family members to nurture their loved one and can assist them in becoming comfortable in caring for their patient's needs. Taking the time to treat the family is a very important part of treating the patient. This facilitates the family's resumption of feelings of competence and control, promotes hope, and encourages them to join with the burn team in the healing and rehabilitation of the patient. Psychotherapeutic work with the family should also identify and plan for management of family issues that may impede a patient's recovery and rehabilitation.

IN-HOSPITAL RECUPERATION PHASE

This phase involves burn survivors becoming physically and emotionally stronger as they face new challenges. Patients begin to comprehend the extent of their injury and may experience difficulty adapting to physical limitations and changes in their physical appearance. They may feel apprehensive about the future, continue to grieve losses, experience a loss of control and autonomy due to being dependent on others, and feel ambivalent about resuming self-care. The team can help motivate the survivor to participate in his or her treatment and assume responsibility for recovery. Individuals who desire optimal recovery need to comply with the medical team's instructions, many of which require significant physical discomfort. Pain continues to be a concern as patients become increasingly active in rehabilitative exercises. Pain and anxiety management are important to regain optimal physical functioning, and the interventions mentioned previously can facilitate pain and anxiety management.

Emotional lability and cognitive and behavioral regression may occur with younger children. Children often have difficulty expressing verbally their thoughts and feelings and may exhibit behavioral outbursts. Parents may be relieved to find that such behaviors are normal, and they often require guidance with implementation of treatment plans that target and positively reinforce desirable behaviors. Emotional reactions such as frustration, anger, and feelings of hopelessness can be difficult for family members to cope with. Hopelessness can occur when patients feel a lack of control and eventually give up trying, which can lead to depression. Research found that depressive symptoms may decrease during the initial hospitalization,[32] and depression during hospitalization is associated with physical functioning the first year post burn.[33] Psychotherapeutic work may involve helping the patient experience control, combat feelings of hopelessness and helplessness, facilitate healthy expression of emotions, achieve success, and feel rewarded while progressing through difficult procedures. Early in this phase, as the patient begins to ask about the future, the psychotherapist can describe the predictable pattern of emotional vicissitudes indicating that they are normal and can be endured and managed. Staff can demonstrate positive regard and acceptance of the patient while also helping the patient exercise control over destructive behaviors. Responses to questions should be honest but hopeful regarding the expectations of treatment and recovery. Interventions aimed at facilitating grief work, coping with body image concerns, management of anxiety and depression, and social skills training to facilitate social interactions are helpful.

Much psychotherapeutic work during this phase is accomplished with patient and family together. Families must learn to assist the patient's adjustment to the new situation, and the family system must accommodate as well. Research suggests it is important to strengthen the family unit, facilitate family closeness, and support attempts to organize their lives to incorporate additional duties involved in providing continued care for the patient.[34,35] Families will have to adapt to changes in their relationships and in the home environment that are necessary for the patient's recovery and rehabilitation after discharge.

REINTEGRATION PHASE

Preparing for a patient's discharge to outpatient status and eventually home begins upon admission to the burn unit.

A major objective is to facilitate a person's reintegration to life at home with the family and back to his or her community. Community reintegration is the process of becoming involved in the community, school, work, and leisure activities.[36] Returning home signifies social interactions with the immediate family as well as the extended family, friends, and strangers. Individuals must prepare for those encounters. They often feel anxious, fear social rejection, worry about being accepted, and are concerned about receiving social support.[37] Returning to a cohesive and supportive family environment[35,38] and loyal friends[39] can make this transition much smoother.

Psychotherapeutic activities involve education and preparation of patient and family about difficulties that may be encountered at discharge. Coping skills that can help should be discussed and practiced. Survivors and families often deny that they will have problems; however, psychotherapists can help prepare patients by offering suggestions to address problems that others have experienced. Issues such as recurrence of posttraumatic stress symptoms, anxiety and pain management, sleep disturbance, irritability, or fear of resuming sexual activities should be discussed prior to discharge.

There are now a spectrum of programs available to the survivor and some for the family. These professional programs help individuals and families through all the phases of recovery from major burn injuries. The Model System Knowledge Translation Center has a large number of print and downloadable forms containing useful information on a wide-range of burn-specific topics available in English and Spanish.

The Phoenix Society for Burn Survivors Inc. is "a nonprofit organization dedicated to empowering anyone affected by a burn injury."[40] This organization has several videos providing information and instruction on new skills, such as social skills, training survivors how to conduct supportive therapy, image enhancement, and school reentry.[40]

Cognitive-behavioral therapists have developed several techniques for treating negative body image and social anxiety related to a physical difference. Likely the most important is teaching a specific set of social skills.[41–43] Social skills programs are available to facilitate positive reintegration into society, improve social comfort, and increase confidence in social interactions. Social skills include having a short precise answer to explain "what happened," guiding the topic of conversation, using confident body language and eye contact, and assertively confronting confused and rude behavior. After mastering these skills through in-therapy practice, the survivor is encouraged to practice the skills by engaging in social activities. This practice helps break the social avoidance–depression cycle that may maintain the burn survivor's negative body image.

The program Be Your Best, by Barbara Kammerer Quayle and The Phoenix Society for Burn Survivors Inc., was developed to help burn survivors with community reintegration.[44] The UBelong Social Skills program includes skills to increase social comfort and confidence. Acquiring such skills can make encountering new people and situations and handling stares and unwelcome comments easier. They can help survivors and their loved ones navigate such encounters with added confidence.[44,45] Additionally Changing Faces, by James Partridge, a program dedicated to assisting persons with facial disfigurement, and recommends a brief social skills training program called 3-2-1-GO![46,47] Each of these programs provides strategies to prepare patients and their loved ones to answer questions related to the burn and to deal with staring and stigmatization. The patient may benefit from rehearsal using these skills on brief outings outside the hospital. If difficulties are encountered, the patient can consult with the burn team for direction and support to develop an alternate plan. Support groups for inpatients, outpatients, and their families can be extremely helpful in the process of anticipating difficulties at discharge and rehearsing solutions while also providing emotional support.

Reintegration of the patient into the family is also an area where the burn team can provide assistance. Patients are usually pleased to go home, but upon arrival, may find that their role in the family has changed significantly. The spouse–partner or parent–child relationship may now be one of survivor–caregiver, and the patient may feel helpless or burdensome. Staff can offer advice to families on ways to make the transition home go more smoothly. Tips such as spending time listening to the patient and trying to better understand his or her burn and hospital experience, limiting visitors so the patient can rest, working through feelings of guilt or blame, asking for help from friends and family, and utilizing relaxation techniques for pain management can aid both the patient and family in an easier return home.[48]

The burn team may also prepare the community to which a patient will return. Instructing those unfamiliar with burns in what to say or do to ease a survivor's reentry may assist with reintegration.[49–51] Variables that may affect burn survivors' ability to return to work once they are discharged from the hospital include size and severity of burn,[52,53] duration of hospitalization,[53,54] location of burn,[52,53] physical impairment,[53–56] pain,[55,56] prior employment history,[52,53,56] lack of vocational training,[57] work environment impediments,[54] and psychosocial difficulties.[53–57] Variables found to assist with return to work were psychosocial support, positive thinking, and vocational training.[56,57] Quinn and colleagues found that 66% of burn survivors returned to work within the first 2 years post burn.[53] In a study of young adults who sustained burns during childhood, Meyer and colleagues found 65% of the sample were employed either full- or part-time.[58] Individuals who do worked reported improved quality of life.[59,60]

Factors that affect adults returning to work can also influence school reentry for children. Staley and colleagues reported that children with small burns returned to school within the first week or month post burn, and most performed well academically.[61] However pediatric burn survivors often require assistance to return to school so they can learn, develop, and form peer relationships. Many burn centers in the United States have developed school reentry programs. These programs are designed to educate staff and students about aspects of burns, provide generic information about treatment and recovery, emphasize the child's abilities and needs, clarify ways in which the child may require assistance, address the importance of normalizing school activities, and providing peer support and acceptance. Working with the family and the school, a burn professional develops a plan to integrate the child back into

school. Usually, part of the process includes the burn professional visiting the child's classroom, explaining the nature of burns and rehabilitation, engendering compassion and support for the survivor, and answering questions. Burn professionals running school reentry programs have received a good deal of positive feedback from schools and families, but the long-term efficacy of school reentry programs has not been empirically demonstrated.[51,62] A few studies found interventions such as on-site school visits[62] and educational videos/DVDs[62,63] are beneficial. The Journey Back, by The Phoenix Society for Burn Survivors, is a comprehensive program providing generic materials designed to help pediatric burn survivors, families, and school communities with the re-entry process.[64] Another program, developed by Shriners Hospitals for Children–Cincinnati, is the Remember Me Program, which keeps the pediatric burn patient in touch with his or her classmates during the lengthy burn-related hospitalization. A teddy bear is placed in the child's seat while he is absent, and communication with and from classmates is encouraged.[65]

REHABILITATION PHASE, POSTDISCHARGE

When survivors transition to the outpatient setting and home, they continue to have physical and psychosocial needs. Rehabilitation may require several months to years, wounds may be vulnerable to breakdown, and individuals may need to use special splints and pressure garments' and continue to exercise. Grief work often continues as survivors cope with losses and delayed grief reactions can occur. Symptoms of posttraumatic stress may recur upon leaving the protective hospital environment. Body image concerns may become more acute as survivors confront stigmatizing reactions from others. Family's social and emotional resources may become taxed as the family transitions into becoming the patient's primary caregivers.

The ratings of significant others on a standardized behavioral scale suggested that young adult survivors of childhood burns who were an average of 14 years post burn were doing well. However on standardized psychiatric interviews, a high percentage of survivors reported experiencing psychiatric disorders specifically related to social situations,[66] and personality disorders[67] warranting diagnoses. Similar results were found in a study of adolescents who were an average 10 years post burn.[68] In these studies survivors[44,48] were rated by a physical therapist to have no physical limitations that prevented caring for themselves and participating in ordinary activities, their anxieties were severe enough to limit their achievement to full capacity.[68] Even if most burn survivors eventually function satisfactorily by external criteria, clinically, they may be suffering significant distress that is not easily observable. A psychosocial goal is to understand the sources of survivors' distress and to develop interventions that enable survivors to become full participants in society. It would be extremely valuable to patients leaving the hospital, as well as to their social network, employers, and care providers, if there were a set of predictors that could reliably estimate when and to what degree functional improvement could be expected over time. Fauerbach and colleagues evaluated functional impairment of survivors from discharge and across 2 years and found psychological impairment was predicted by prior alcohol abuse, psychological distress, and psychological function both before the burn and at discharge.[69] These data can inform providers and adult patients about factors that could be modified to effect more desirable outcomes.

Assisting With Grief Following Trauma

Traumatic events are frightening experiences that create uncertainty, anxiety, and a sense of threat for victims and their families.[70,71] An individual who experiences a burn injury may face multiple changes and losses, including separation from one's support network and home environment, uncertainty regarding the length of hospitalization and process, changes with physical appearance, and in certain circumstances, death of loved ones. On the burn unit, these issues often become the focus of psychosocial intervention. Successful grief therapy requires that mental health professionals have an understanding of the traumatic event and knowledge of the individual's past experiences with loss and coping styles and cultural and religious beliefs.[70] Mental health professionals can assist re-establishing a sense of equilibrium following trauma by facilitating the grieving process.

The terms "bereavement," "grief," and "complicated grief" merit clarification. *Bereavement* refers to coping with the death of a loved one, whereas *grief* is a broader term referring to coping with loss in general.[72] Grief reactions are individually unique and age dependent.[71,73] *Complicated grief* occurs in adults when the grieving process is compromised by trauma. Prigerson and Jacobs described complicated bereavement as difficulty comprehending and accepting the death of a loved one, persistent and intense longing for the deceased, intrusive thoughts about the deceased, and avoidance of painful memories.[74] Children can also experience childhood traumatic grief when there is traumatic loss or bereavement.[71,75,76] This construct evolved from the literature in child development and trauma and occurs when trauma symptoms interfere with the child's ability to grieve normally. The child may engage in avoidance behaviors that interfere with the normal grieving process.[71,75,76] Traumatic grief can co-occur with psychiatric disorders such as depression and posttraumatic stress disorder (PTSD).[71,75,77] The prevalence of burn survivors and family members who experience traumatic grief is unknown. Clinical experience suggests that many burn survivors progress through the grieving process without complications and are resilient when faced with loss. Brown and Goodman found that children who retained a positive memory and ongoing presence of their loved one were able to grieve normally.[71]

On the burn unit, mental health professionals may need to inform the burn survivor about multiple losses and life changes, which may include changes in appearance, loss of body parts, the death of others such as family and friends, loss of a pet, or loss of a home. In some circumstances it requires informing, supporting, and preparing the family for bereavement of the burn trauma victim. This is a delicate process that requires appropriate timing and psychosocial planning. Important factors to consider when planning the disclosure process with patients and families include the patient's medical stability and ability to participate in

conversations; the readiness of the patient and family to hear the news; identification of what they know about the trauma and the factors related to the traumatic event; their wishes regarding disclosure; and knowledge of their cultural, religious and spiritual needs.[78] Bronson and Price discussed important principles to keep in mind when working with grieving children after burn trauma. They suggest a process that includes supportive and compassionate truth-telling, acceptance, respectfulness of individual differences and feelings, and giving the individual an opportunity to say good-bye.[79] If death occurs on the burn unit, staff can psychologically support the family by obtaining desired spiritual assistance, assisting them with paperwork for the burial process, allowing them quiet private time with the deceased, and providing distraught family with memory items if they wish to have them.

Cultural Sensitivity

Burn survivors come from diverse cultures, and burn care teams must be sensitive to how cultural issues can affect survivors and families in all the phases of the recovery process. "Culture" refers to the socially transmitted expectations, beliefs, traditions, and behavioral patterns of a given community at a point in time.[80] Factors influencing culture include country of origin, geographical location within the country, ethnicity, and socioeconomic background. Staff must also be aware of their own biases, values, and assumptions that stem from their cultures.[81,82]

Acculturation is the process by which individuals from one culture embrace patterns, customs, beliefs, values, and the language of the dominant culture.[83,84] Patients and their families on first arriving at a burn care facility must rapidly adapt to the culture of the hospital environment. Even if the hospital is within their own community, they experience some level of culture shock and acculturation. This process is even more complicated for those who are transported for care to communities far removed from their homes and perhaps in another country. For some patients, this traumatic situation is the first time they have traveled to another country and the first time they have had to deal with differences in language, currency, living accommodations, and foods. Individuals' concepts of time and space, appropriate hospitality, importance of greetings, how nonverbal gestures are interpreted, and ways of expressing gratitude may differ greatly among cultures. Ideas of what caused the burn injury and what is necessary for healing to occur also are determined by cultural values.[85,86]

Coping with such a multitude of unfamiliar experiences in a traumatic situation is an extraordinary challenge that can inhibit a patient's or family's ability to participate in the recovery process. The burn team must be aware of cultural differences and make culturally appropriate accommodations to a patient's treatment plan. Cultural traditions can be incorporated into treatment plans to enhance participation toward recovery. For example, if a Latino family believes that the burn incident was a result of an "evil eye," they may request a cleansing ritual.[83] It is impossible for providers to know the beliefs and expectations of every culture; however, cultural sensitivity and a willingness to learn are necessary for good patient–provider communication and improve outcome. Staff can acknowledge their lack of familiarity and ask the patient/family whether there is anything the team can do to help meet their cultural, spiritual, and religious needs. The question conveys respect for cultural differences and a desire to help through the acculturation process.

Knowledge and sensitivity of cultural practices is also important when focusing on safety and prevention education with patients and families. Epidemiological research has focused on identification of sociodemographic risk factors and cultural practices that have contributed to burn injuries in developed and developing countries and found differences among these countries.[87–91] The highest incidence of severe burns occurs in low- and middle-income countries,[92] with children being at highest risk.[87] In developing countries, factors such as poverty, crowding, food preparation practices, unstable cooking methods, and inconsistent supervision practices place young children at high risk for scald burns.[88,93,94] Identification of modifiable risk factors and cultural practices can facilitate education about prevention for burn survivors and their families. A recent study of children 5 and younger from Mexico who received medical care in a U.S. hospital found the primary causes of burns were flame and scald injuries. Flame burns were caused by explosions of flammable substances and house fires, and scalds were attributed to falling in large containers of hot liquids placed on the ground and spills.[91]

Postburn Psychological Distress and Long-Term Outcome

There are many disturbing aspects of a major burn injury including memories and emotions from the burn injury event and its circumstances, the initial sight of the wound, and pain both at rest and during unavoidable wound care and rehabilitation. Further challenges accrue as healing progresses, such as changes in appearance and function as skin contracts and scars progress through the maturation phases. There are additional disturbances from expected or actual reactions of family, friends, associates, and strangers as these members of the social sphere view the wounds, the scars throughout maturation phases, rehabilitation splints and garments, and the like. Each of these stressors, when exceeding individual and group resilience factors, imposes a burden on the person (distress within mind–body self) and between the person and his or her social network (reciprocal distress between/within the patient and those affected individuals within the embedded social network).

Among the most common manifestations of psychosocial distress for burn survivors following an injury are sleep disturbance,[95,96] depression,[97,98] body image dissatisfaction,[99] and acute and posttraumatic distress.[96,100] Not unexpectedly, the average level of psychological distress among those with major burns was significantly higher than that of a normative sample.[34]

ACUTE AND POSTTRAUMA DISTRESS

Acute stress disorder (ASD) and Post-traumatic stress disorder (PTSD) following exposure to trauma may occur. According to the *Diagnostic and Statistical Manual of Mental*

Disorders (DSM-5), individuals with trauma disorders experience intrusion symptoms, negative mood, dissociative symptoms, avoidance behaviors, and increased arousal.[101] The prevalence rate of ASD among adult burn survivors has varied between 10% and 23%,[100,102,103] whereas the rate among pediatric survivors has been between 8% and 31%.[11,104,105] It is estimated that 15–45% of adult burn survivors meet the criteria for PTSD in the first year post burn,[103] and almost 50% meet the criteria for at least one of the PTSD symptoms clusters.[99,106] The current and lifetime incidences of PTSD in pediatric burn survivors are 7% and 30% respectively;[107] and in young adults who sustained childhood burns, they were 9% and 21% respectively.[66]

Posttrauma distress has been found to be associated with greater lengths of acute hospitalization,[106] enhanced sense of distress, and impaired adjustment to injury.[108] In the population of patients surviving severe burns, certain aspects of pretrauma adjustment (history of mood disorder) and coping style[109] can influence the risk of developing PTSD following trauma exposure.[5] Individual factors (avoidance of reminders) and aspects of the injury (injury severity, facial injury) have been associated with poorer outcome.[110] Those with high levels of trait neuroticism appear to be at greater risk of PTSD symptomatology following burn injury, whereas high levels of extraversion appear protective against PTSD.[52,111]

It might be assumed that PTSD is related to greater initial injury; however, PTSD among burn survivors has not been found to be related to severity of injury.[112] On the other hand, high levels of acute posttrauma stress symptomatology have been shown to be positively related to perception of more intense pain among hospitalized burn patients.[113,114] High emotional distress and ASD symptoms during hospitalization are risk factors for PTSD in adults 2 years post burn.[103,115] However, in a long-term follow-up study of children who experienced ASD symptoms during their initial hospitalization and a non-ASD matched comparison group, there was no significant difference in the prevalence of lifetime PTSD between the groups. Eight percent of the children in the ASD group and 5% in the non-ASD group met diagnostic criteria for PTSD. Children were an average of 5 years post burn.[116]

Chronicity of Postburn Psychological Distress: From In-Hospital Through Long-Term Follow-Up

Prospective longitudinal research has shown that the level of distress one reports experiencing during acute hospitalization tends to persist across at least 2 years of follow-up. Analyses of 2-year longitudinal data quite consistently identified 3–4 groups of survivors whose level of distress (posttrauma distress, body image dissatisfaction/social discomfort, generalized distress) formed trajectories characterized as chronically severe, moderately severe hovering around cutoff for clinical disorder, a subclinical group, and a group essentially without symptoms.[103,117,118] The stability of these trajectories is illustrated in that, across the 2-year follow-up, only 5–10% of participants reported a reliable and clinically significant change in distress that moved them from one trajectory to another.[103] Of the 5–10% of participants who changed from one trajectory to another, about half reported less distress (improved) and half reported increased distress (worsened). The stability in distress trajectories among survivors of major burns is largely unique relative to other trauma-exposed samples. These other populations tend to show recovery trajectories of early recovery (~6 months), mid-term recovery (~12 months), and a chronic trajectory, and some studies found a delayed-onset trajectory with early low symptom severity followed by increasing symptoms beginning about 6 months out.[119] Thus, some research to date has identified varied forms of psychological distress, their prevalence, the stability of distress level over long-term follow-up, and the enduring impact of early psychological distress on longitudinal psychological and social adjustment. These replicated findings highlight the need for identifying early survivors with high levels of distress to attempt to circumvent the suffering, impairment, and disability that may ensue.

The goal of rehabilitation is to enable full social-environmental integration, including access to social opportunities and physical space (absence of physical barriers). The National Institute of Disability and Independent Living Rehabilitation Research (NIDLRR) formerly the National Institute of Disability Rehabilitation Research (NIDRR) presents a paradigm for conceptualizing and conducting rehabilitation research that places environmental factors on an equal footing with person factors.[120] Burn-related research has begun to progress beyond identifying forms of distress and quantifying their prevalence, largely on the basis of targeted federal funding by the NIDLRR through its multicenter Burn Model System database and both multicenter and site-specific projects.[121] There are at least three key questions to address as research focus shifts to developing new psychological, behavioral, and social treatments: What are the mechanisms by which early distress levels are maintained across long-term follow-up? Is the best approach to prevent distress by (a) reducing risk factors, (b) enhancing resilience factors, or (c) reducing risk and enhancing resilience? Also, can high levels of distress, once developed, be effectively reduced and maintained at low levels? Finally, can the factors that initiate and maintain low distress levels be influenced by medical, psychological, or social factors in a way that can provide relief to those experiencing distress?

Theory-Guided Research as the Next Step in Enhancing Psychological and Social Adjustment

Unfortunately there has not been enough burn-specific research in which a priori aims were explicitly stated addressing the questions just listed. It is proposed that, in order to promote such research, a common theory and language should be adopted in the field. Specifically, learning-based theories grounded in biology and neuroscience[122] are the best formulated theories, and treatments developed with these theories have acquired the strongest evidence

base in other trauma-related fields.[123] Thus it is suggested that burn researchers utilize theories and associated design/methods to more effectively guide treatment development in burns and to conceptualize the related research aims. Our general approach to assessment is a behavioral approach based on learning principles (e.g. conditioning, cognitive restructuring, and social learning theories) where adjustment is the target of intervention. Assessment and treatment are integrally related, and both occur simultaneously throughout the recovery and rehabilitation process. In this section, posttrauma distress is examined, but similar explication will be necessary for each problem area being addressed, such as body image dissatisfaction, social stigmatization, and social rejection.

Formulating Psychological Distress Following Burn Injury: Using Posttrauma Distress as an Illustration

Classical conditioning can be used to describe the process involved in the development of trauma symptoms. The traumatic event can be conceptualized as the unconditioned stimulus (UCS) that causes an unconditioned response (UCR) such as fight–flight, freeze, and distress. Reexperiencing the trauma is the conditioned stimulus (CS) and elicits a conditioned response (CR) such as flight–fight, freeze, and distress. Failure to extinguish the CR when a CS is presented may lead to maladaptive behavior. In addition, there are preinjury variables that may contribute to a person's difficulty coping, including early life experiences, previous traumas, learned behaviors, genetic predisposition, and personality characteristics.

Maintenance occurs when approaching cues, reminders, and triggers (CS) cause increased distress (feelings of horror/helplessness) (CR) and, if perceived intolerable, can lead to escape, avoidance, and withdrawal behaviors. The avoidance response is reinforced by lessening the distress and more likely to continue as the habit strengthens with each exposure and avoidance pairing. Three key motives have been observed in adult burn survivors, and these have been conceptualized as: *Approach* (move toward threat; Fight), *Avoidance* (move away from threat; Flight), and *Approach-Avoidance* conflict or ambivalence (alternately moving toward then away from threat; Freeze). The behaviors associated with these motives are the classic survival responses.[115] For example, re-experiencing symptoms of ASD/PTSD can be understood as CS that elicit basic survival motivations and behaviors (CR) that were elicited by the life-threatening event itself (UCS).

We propose use of cognitive-behavioral interventions designed to lessen the trauma-related distress target symptoms of re-experiencing (memories, flashbacks, nightmares), avoidance behaviors (flight from cues/contexts), and hyperarousal (anticipation or expectation of further threat/harm). It is proposed that an important component of the cognitive and emotional processing of traumatic events is to provide or renew the sense that memories, even horrific ones, can no longer harm us directly, are the means by which we can learn from the past, and can help us to be more prepared for the future. The ability to plan for the future will reduce the likelihood of recurrence and provide one the means for helping others to acquire this knowledge without having to go through a similar episode.

Social learning occurs by watching another person behave in novel ways as they respond to social situations of importance to the observer. When observing a person whom we hold in high esteem as that person achieves a desired outcome (reduced distress), the observer is more likely to acquire and practice that behavior. Social learning can help one to learn new methods of healthy coping. Seeing someone skillfully use social skills to defuse a negative comment can be helpful. Such learning enhances one's comfort and confidence in intentionally overcoming the distress associated with trauma memories and social stigmatization.

RESILIENCE AND RECOVERY

Resilience is the capability to adjust well when dealing with difficult situations. While some individuals adapt well, others experience difficulty.[119] When exposed to a traumatic event or significant stressors, coping is affected by the individual's characteristics and social structures. Social support in the form of emotional, material, and cognitive support is important in the adjustment process. These facets of social support can be facilitated and maintained by different systems, including family, community, state, national, and international systems.[119]

BODY IMAGE, STIGMATIZATION, AND SOCIAL INTEGRATION

Body image is one's self-evaluation of one's physical appearance.[124] Negative body image or body dissatisfaction is the belief that one is unattractive. Body image is highly correlated with self-esteem, particularly among adolescents and young adults. Negative body image is a component of or is highly associated with a number of psychiatric disorders including depression, social anxiety, eating disorders, and drug abuse.[124] Due to the fact that burn survivors may be permanently scarred by their injuries, it is commonly hypothesized that burn survivors are at high risk of developing a negative body image.[125–128] Body image is a consequence of the interaction between a person and his or her social environment.[124,129] In order to understand the challenge of adapting one's body image to having burn scars, it is necessary to be familiar with the appearance norms of the burn survivor's culture. These sociocultural norms establish criteria for the importance of appearance, how one should appear, and the room for deviation allowed from the norms.[124,127,129,130]

SOCIAL BELONGINGNESS AS CORE SURVIVAL NEED

Belongingness is understood as one of the core needs driving human social behavior. Individuals are particularly sensitive to being excluded, especially when this is on the basis of one's appearance and function that cannot be readily changed.[131] The *pivotal sociometer theory* posits that self-esteem is a marker for the degree of belonging one is

experiencing.[131] As belonging improves (inclusion in an activity), self-esteem increases. When belonging declines (excluded from an activity), self-esteem diminishes. A recent meta-analysis confirmed expectations that, following social exclusion, negative mood increases and both positive mood and self-esteem decline.[132] Exclusion-related social pain stimulates neural structures that also affect mood and self-esteem and thus motivate adaptive coping to these threats to social belonging.[132]

An elegant series of experiments found that the group of participants who were made to feel excluded, relative to those who were not made to feel excluded afterward attended more to positive memories and interpreted ambiguous stimuli more positively.[133] Of note, this automatic emotion regulation process was observed among individuals with high self-esteem and low depression but not among those with low self-esteem or high depression.[133] In addition, a study was conducted among participants whose self-esteem was strongly based on appearance and who were subjected to social exclusion. Those with high self-esteem sought to reconnect to those who had excluded them, whereas those with low self-esteem avoided social contact.[134] Taken together, these findings suggests that high self-esteem along with low depression is a good marker for resilience, whereas low self-esteem in the presence of high depression is a good marker for vulnerability. These means of estimating vulnerability (low self-esteem, high depression) and resilience (high self-esteem, low depression) may serve as a means of discerning in the acute phase those burn survivors at high versus low risk for having difficulty reintegrating into social roles and public settings.

Perceived discrimination, similar in nature and impact to social exclusion, has also been linked to poor health outcomes.[135] A systematic review found strong evidence that discrimination increases the stress response and concluded that it is associated with increased engagement in health risk behavior and decreased participation in protective health behaviors.[136] Discrimination is a form of exclusion that is omnipresent culturally and globally, is distressing, and negatively impacts health and adjustment.[135]

APPEARANCE, SOCIAL STIGMATIZATION, AND SOCIAL EXCLUSION

Appearance norms are communicated to the individual through both mass media and interpersonal behavior. Via mass media (magazines, television, and the Internet), people are exposed to hundreds of images daily of "beautiful people" technologically enhanced through processes such as airbrushing, soft-focus camera shots, and manipulated digital images. The message, implicit or explicit, of cosmetic product advertisements is that you are an inadequate person unless you are very attractive, and that a particular product will enhance your appearance. There is also interpersonal pressure to conform to appearance norms. One review of the literature on appearance concluded that people tend to both make positive assumptions about "good-looking" people and treat them more favorably than less attractive people.[137] On the other hand people who deviate from the beauty standard are more likely to experience stigmatization and discrimination behavior.[138] For example, children are most frequently teased about their appearance in comparison to all other aspects of their person or behavior.

The most troubling challenge for many people re-entering society following major burns is their own appraisal of scars and related changes in appearance and function and their expectations of what others will think and do. Social stigmatization is a process in which people are socially rejected (put out) and ostracized (kept out) based on a negative stereotype.[139] People with visible differences have long been stigmatized in the mass media. In many movies and video games, the villain is a person with a physical difference, often burn scars. Stigmatizing interpersonal behaviors experienced by burn survivors include an absence of friendliness and courtesy, staring, pointing, startled and disgusted reactions, ignoring, avoidance, confused behavior, teasing, bullying, and discrimination.[126,127,138,140] There is evidence that people with visible differences are more likely than people without visible differences to experience stigmatizing interpersonal behavior. For example, when interacting with an actor who had makeup applied that looked like a real disfigurement, participants were less likely to offer assistance or sit or stand close, and they limited their interactions. Job interviewers rated actors without such disfigurements as more fit for the position than those with a mock visible difference.[141–143]

This emphasis on an attractive appearance is an onerous barrier to inclusion and social participation for those with a visible difference. In addition, acquired disfigurement can be difficult to incorporate into preinjury body image.[144] Body image, a facet of self-esteem, is formed at the nexus at which individual differences intersect with social group norms.[145] Consequently, injury-related disfigurement creates distress over both an altered body image and social exclusion based on appearance. Burn injuries cause an immediate change in appearance, and to complicate matters, uncertainty about final appearance outcome persists as healing is followed by months or years of scar maturation during which appearance typically becomes worse before improving.[146] This change in appearance thus represents an amalgam of threats to safety, body image/self-esteem, and social belonging.

What are the psychosocial consequences for burn survivors living in a highly beauty-conscious society? Few studies have investigated the frequency of body image dissatisfaction and perceived stigmatization and their correlates among burn survivors.

Studies that have compared the body image of burn survivors to a nonburn comparison group have found no normative differences.[147,148] In one study comparing a group of long-term pediatric burn survivors to an age-matched nonburn comparison group on a body image measure, there was no difference between the males in the two groups. Among the females, on average, the burn group had higher body image scores than the comparison group.[148] This surprising finding needs to be interpreted with caution given that it has not been replicated. Much more remains to be done in order to discern whether, with whom, and at what point in recovery burn survivors are most affected by altered appearance. Furthermore, there remains much to do in order to firmly establish what person, injury, and social factors may protect against body image dissatisfaction or promote recovery from it.

FACTORS AFFECTING BODY IMAGE DISSATISFACTION AND SOCIAL DISCOMFORT

Physical appearance is an almost universal criterion for group membership.[149] The greater the degree to which one fits in with the group culture, including normative appearance, the greater likelihood one has of being included. This is problematic in that burn scars often change appearance in a manner that unnecessarily disrupts inclusion and may lower the belonging and self-esteem of some burn survivors. Recent studies among burn survivors investigated the theory that social exclusion of individuals with differences in appearance is motivated by the fear of disease or injury[149] or emotions.[150] It seems plausible to consider that there may be two stages of observer's reactions to altered appearance. The first is likely genetically determined and is the fear of external signs on the body that might connote disease. This reaction is automatic and largely beyond conscious choice. The second reaction is more likely to involve a higher order of cognition that is acquired through social norms, parental training, and peer conformity. This higher level of cognitive processing and emotion regulation involves conscious appraisal of appearance alterations and takes into consideration social norms for appropriate behavior.

In regards to risk factors for negative body image, severity of burn scarring has proved to have a modest relationship with body image among both adult and child burn survivors. Across studies, the correlation between burn severity and body image has ranged from 0.00 to 0.40.[99,148,151,152] One study suggested that the relationship between perceived scar severity and body image is moderated by importance of appearance.[153] For those burn survivors who placed little value on physical appearance, self-rated scar severity had no relationship with body image. For those burn survivors who highly valued physical appearance, scar severity was highly predictive of body image dissatisfaction. All studies investigating the relationship between scar severity and body image have been limited by the lack of a reliable, standardized measure of scar severity. Many studies to date have used proxy variables to measure scar severity, such as total body surface area (TBSA), TBSA-full thickness (TBSA-FT), and location or number of burn-related surgeries.

Within the literature there has been a theoretical debate regarding the relationship between burn scar location and body image. The "visible hypothesis" posits that socially visible scars, such as scars on the face, will be highly related to body image dissatisfaction because burn survivors with visible scars will experience more frequent stigmatizing reactions from others. The "hidden scar" hypothesis posits that because the person has fewer opportunities to learn how to deal with the reactions of others, he or she will live in fear of the scar being revealed and thus have a negative body image. There is little empirical evidence for either hypothesis. In the studies that have tested these formulations, the correlation between facial scarring and body image ranged from 0.00 to 0.20.[151] Gender has also been investigated as a possible risk factor. In comparison to men, women burn survivors tend to have lower body image satisfaction; however the gender difference in burn survivors has not been as great or as consistent across studies as it is in the general population. Across studies the strongest correlates of body image among burn survivors has been social and emotional variables such as social support, perceived social stigmatization, importance of appearance, and depression (*r's* ranging from 0.30 to 0.60).[99,148,151,152,154]

In regards to stigmatization a few studies have focused on pediatric burn survivors. Among pediatric burn survivors, there is some evidence that appearance-related stigmatization is a common concern. In a survey of 250 pediatric burn survivors, 60% of participants reported being bullied within the last 6 months. Twenty-five percent of the sample indicated that bullying was a "big problem."[155] However, to date, there is not enough evidence to conclude that burn survivors experience stigmatizing interpersonal behavior more frequently than the general population. First, appearance-related teasing appears to be very common in the general population. In a survey of adolescents in Britain, 52% of the sample had experienced distress related to appearance-related teasing, and 10% reported at least one incidence of avoiding going to school fearing appearance-related teasing.[128] No studies have been completed directly comparing the experience of burn survivors with stigmatizing behaviors to a comparison group. Two studies comparing the frequency with which children with craniofacial differences experienced teasing and other victimization behavior to a comparison group found no differences between groups.[156,157]

To date there is no empirical evidence that burn survivors as a group experience higher levels of negative body image or more stigmatizing behavior than nonburn comparison groups. However relatively few studies have been completed, and these findings need to be replicated before they are accepted as fact. Over the past decade, a number of new standardized measures and structured interviews have been validated to measure body image, perceived stigmatization, and social comfort among people with visible differences.[153,158–160] Hopefully these instruments will facilitate future body image research among burn survivors. Clinical experience suggests that approximately 20–30% of burn survivors struggle with body image and social integration issues. For these burn survivors, the emotional pain that results from body image dissatisfaction and social discomfort can be very intense.

DISTRESS OF FAMILIES OF BURN SURVIVORS

Long-term impact on families of burn survivors has not been well studied, but clinical experience and scant empirical data indicate the sequelae to be significant. Family members may continue to experience symptoms of post-traumatic stress after a patient has returned home.[31] Parents of survivors of massive injuries appear extraordinarily stressed even several years after their children's recoveries.[4,161] A series of studies found that parents of pediatric burn patients reported significant depressive symptoms at 2 years post injury, and they attributed their distress to their children.[4,162] Although parental distress appears to improve with time for most, parents of the most troubled burned children continued across time to be troubled themselves.[162] Parents also express concern for their other children, whom some felt had been slighted of attention and time while the child with a burn injury required a lot of the family's attention. Even free medical and surgical care did

not eliminate the burden of direct and indirect costs of burn injury, and many families experience financial difficulties attendant to the injury and treatment of their child.[4]

LONG-TERM OUTCOME: QUALITY OF LIFE

After survival is assured, quality of life is arguably the most important outcome to individuals who are seriously ill or injured. Health-related quality of life has been defined as a multifactorial construct that involves an individual's degree of satisfaction and level of health and functioning in several core domains including: physical-behavioral (ability to perform self-care behaviors) and psychological well-being (subjective sense of contentment and the absence of emotional distress), social and role functioning (ability to fulfill family, work, and community responsibilities), and personal perception of health (satisfaction with one's health status).[163] Research has found that participation in a comprehensive wellness and exercise program helps improve physical and psychosocial well-being for burn survivors.[164–168]

Quality of life has been investigated using general health questionnaires or measures that focus on specific behaviors. Recent research has begun to focus on the overall quality of life.[169–171] As with self-report behavioral scales, most long-term (>2 years) burn survivors appear to have eventually developed satisfactory adjustment and are within normal range on domain subscales of the SF-36, a widely used measure that assesses general health quality of life.[163,169,171] Using a measure that examined specific behaviors, young adults who sustained burns as children rated their overall quality of life lower than the normative group.[170]

Many burn survivors question if they can have meaningful relationships and have questions about intimacy and sexual activity. Meyer and colleagues examined the sexual attitudes and behaviors of adult burn survivors and found that, overall, they felt positive about their sexual experiences; however gender differences were evident, with the women reporting an easier time finding partners.[172] Bianchi found that there was no relationship between burn severity and sexual esteem for male survivors.[173]

The past couple of decades of our burn-related research has consistently shown that early psychological distress (i.e., in-hospital) can have an enduring impact on physical, psychological, and social health and function.[34,100,174] For example, psychological distress while in the hospital was found to be associated with significantly greater impairment of physical and psychological function and slower rates of recovery over the course of the first year following a major burn injury, even when preburn physical and psychological health and function were statistically controlled.[174] In a second longitudinal study following burn survivors over the first year of recovery, psychological distress was highly correlated with poor quality of life throughout the study.[175] In addition, body image dissatisfaction upon leaving the hospital is associated with prolonged periods of poorer mental health-related quality of life among adult patients following disfiguring burns, and this was independent of general distress, injury severity, and preinjury psychosocial adjustment.[99] Furthermore, posttrauma distress during the late inpatient phase is predictive of significant problems with adjustment during subsequent phases of recovery.[108,176] These and other quality-of-life outcome studies clearly establish the enduring impact of early distress on early, mid-term, and long-term psychosocial adjustment. In conclusion, the quality-of-life research points to the importance of early detection and treatment of psychosocial problems among burn survivors.

INTERVENTIONS FOR BURN SURVIVORS BEYOND ACUTE CARE

Moving beyond general social support, psychologists and psychiatrists specializing in burn recovery have been working to develop theoretically based, empirically testable interventions that can be tailored to the individual needs of both pediatric and adult patients. As stated earlier, the psychosocial sequelae of a burn are quite varied. In order to create effective individual treatment plans there need to be effective treatment protocols for treating specific common problems. Within recent years detailed psychotherapy treatment programs have been described to treat PTSD[177] and ASD[178] and to teach social skills training for coping with disfigurement.[42,43] However much more research is needed to empirically demonstrate the efficacy of these interventions among burn survivors and other groups with physical differences.[179]

Cognitive therapy for the treatment of body image and social integration concerns of people with visible differences is an example of a tailored psychotherapy.[42,43,180,181] Although much has been learned about the risk and protective factors for body image issues and social adjustment, there are few empirically validated treatments.[154] The therapy is based on a detailed conceptualization of how a survivor's social environment, thoughts, behaviors, and emotions interact to maintain the survivor's distress. Given the sociocultural premium placed on appearance, it is understandable that some burn survivors adapt personal values that prioritize physical appearance. Consequently these individuals may ruminate about the discrepancy between their appearance and the ideal (their lost appearance). Self-conscious about appearance, these individuals may act in ways that confirm their belief that their appearance is socially unacceptable. For example, they may minimize or avoid social interactions with others. This social avoidance may be interpreted by others as curt or rejecting behavior by the burn survivor. Thus brief awkward social encounters turn into self-confirming experiences that validate survivors' beliefs that their burn scars make them socially inadequate persons.

Many burn survivors lack access to mental health care in general and access to mental health providers with expertise in treating burn survivors in particular. Most burn survivors who suffer psychological symptoms of distress following discharge from a burn center and who desire treatment must rely on mental health professionals in the community. However, it may be difficult for them to find helpful resources. In a study of young adults who sustained burns during childhood, none were receiving professional help for their difficulties as adults.[66] Burn survivors do not always qualify for financial assistance because their "disabilities" are declared insufficient to require such aid. Even when they can afford such treatment, they may be unable

to find a mental health professional to work with them who is knowledgeable about burn care.

Given the limited access to effective psychotherapy, perhaps more effective strategies for improving psychosocial outcomes for burn survivors are those interventions that create more accepting and tolerant social environments. Programs or organizations with the mission of engendering social acceptance for burn survivors and other people with physical differences include school reentry programs, burn camps, the Phoenix Society for Burn Survivors in the United States,[40] and Changing Faces based in the United Kingdom.[46,47] Burn camps provide an opportunity for pediatric burn survivors to interact and socialize with other burn survivors and participate in recreational activities in a supportive environment. These camps may increase self-esteem and also help to build confidence and diminish anxiety.[182,183] Some camps were designed to provide mental health and rehabilitation services to children once they have left the hospital, whereas other camps are for recreational purposes only.[184] A recent study revealed that increased years of attendance at burn camp was positively correlated with lower rates of somatic, separation, and total anxiety symptoms.[185] Adolescents in another study credited the burn camp experience with helping them with identity formation and reflection, improved social interactions, and increased initiative and cooperation with others. Results suggested that burn camp participation not only helped burn-injured youth deal with their burns, but also assisted them in the development of social and basic life skills.[186] Increased posttraumatic growth has also been a documented outcome of long-term tenure at burn camp, as well as attendance at young adult retreats that serve burn-injured youth ages 16–21.[187] These programs provide assistance with the transition to adulthood and provide burn survivor support beyond the burn camp setting.

The Phoenix Society for Burn Survivors in conjunction with multiple burn centers coordinates the Soar Program, which provides peer support for hospitalized patients and their families. "In addition, they host the annual World Burn Congress, a conference that brings together burn survivors, their families, firefighters, and burn care professionals to address the aftercare and reintegration issues of burn survivors."[40] The Phoenix Society for Burn Survivors and the American Burn Association also have a joint Aftercare and Reintegration Committee. This group is devoted to improving psychological health and social reintegration following burns.

As mentioned previously, Changing Faces is another charity based in the United Kingdom and is dedicated to creating "a culture of inclusion for people with disfigurement."[47] In addition to providing counseling and supporting research, it organizes sustained political campaigns in support of the civil and human rights of people with visible differences. For example the group has organized the ongoing "face equality" campaign with the goal of challenging "media, advertisers, and the film industry to adopt more factual and unbiased portrayals of people with disfigurements, actively avoiding language and imagery that creates prejudice." In addition, the campaign has asked politicians and policy-makers to "ensure that facial prejudice and discrimination are effectively outlawed by improving anti-discrimination law and promoting best practice."[47]

Summary

Most burn survivors do eventually adapt well and resume lives of productive activity with satisfactory self-esteem and social interactions. Empirical data indicate that the first year or so postburn is fraught with discomfort and distress, but much of the difficulty is transient. The process of psychological adaptation often continues for several years. Symptoms of disturbance that linger among burn survivors are likely to be such that only intimate friends and family members will observe them, so it is valuable for persons with expertise in burn care adaptation to periodically assess survivors and provide an opportunity for intervention.

That most burn survivors do amazingly well should never be interpreted as indicative of ease in adaptation. We must never diminish the pain and suffering they endure from physical and psychological wounds. As psychotherapists to a large number of burn survivors, we know very well the struggles survivors can experience. They have moments of true despair and hopelessness, moments of rage, and moments of joy. Fortunate psychotherapists can know them through all extremes: looking for glimmers of hope, validating anger, celebrating victories, and gaining deep respect for resilience of human beings.

Acknowldgments

We would like to acknowledge Patricia E. Blakeney, PhD, and John W. Lawrence, PhD, who contributed to the previous psychosocial chapter(s) for this book.

Complete references available online at
www.expertconsult.inkling.com

References

1. Faber A, Klasen H, Sauer E, et al. Psychological and social problems in burn patients after discharge: a follow-up study. *Scand J Plast Reconstr Surg*. 1987;21(3):307-309.
2. Malt U. A long-term psychosocial follow-up study of burned adults. *Acta Psychiatr Scand Suppl*. 1989;80(355):94-102.
3. Meyer W, Murphy L, Robert R, et al. Changes in adaptive behavior among pediatric burn survivors over time. Proceedings American Burn Association 30th Annual Meeting. 1998 Abstract #84; 19(1Part2): S177.
4. Blakeney P, Meyer W, Moore P, et al. Social competence and behavioral problems of pediatric survivors of burns. *J Burn Care Rehabil*. 1993;14:65-72.
5. Fauerbach JA, Lawrence JW, Haythornthwaite J, et al. Preinjury psychiatric illness and postinjury adjustment in adult burn survivors. *Psychosomatics*. 1996;37(6):547-555.
6. Thombs BD. Patient and injury characteristics, mortality risk, and length of stay related to child abuse by burning: evidence from a national sample of 15,802 pediatric admissions. *Ann Surg*. 2008;247(3):519-523.
7. Noyes R, Frye S, Slyment D, et al. Stressful life events and burn injuries. *J Trauma*. 1979;19(3):141-144.
8. Knudson-Cooper M. Emotional care of the hospitalized burned child. *J Burn Care Rehabil*. 1982;3:109-116.
9. Darko D, Wachtel T, Ward H, et al. Analysis of 585 burn patients hospitalized over a 6-year period. Part III: psychosocial data. *Burns*. 1986;12:395-401.
10. Blakeney P, Meyer WJ. Psychological aspects of burn care. *Trauma Q*. 1994;11(2):166-179.
11. Ratcliff SL, Brown A, Rosenberg L, et al. The effectiveness of a pain and anxiety protocol to treat the acute pediatric burn patient. *Burns*. 2006;32:554-562.
12. Wiechman Askay S, Patterson DR, Sharar SR, et al. Pain management in patients with burn injuries. *Intl Rev Psychiatry*. 2009;21(6):522-530.
13. Patterson DR, Jensen MP, Wiechman SA, et al. Virtual reality hypnosis for pain associated with recovery from physical trauma. *Intl J Clin Exper Hypnosis*. 2010;58(3):288-300.
14. McGhee LL, Maani CV, Garza TH, et al. The intra-operative administration of ketamine to burned U.S. service members does not increase the incidence of post-traumatic stress disorder. *Military Med*. 2014;179(8):41-46.
15. Dahl O, Wickman M, Wengstrom Y. Adapting to life after burn injury-Reflections on Care. *J Burn Care Res*. 2012;33:595-606.
16. Mohammadi FF, Rafii F, Jamshidi OR. The effect of jaw relaxation on pain anxiety during burn dressings: randomised clinical trial. *Burns*. 2013;39(1):61-67.
17. Kuttner L. Favorite stories: a hypnotic pain-reduction technique for children in acute pain. *Am J Clin Hypn*. 1985;28:289-295.
18. Das DA, Grimmer KA, Sparnon AL, et al. The efficacy of playing a virtual reality game in modulating pain for children with acute burn injuries: a randomized controlled trial. *BMC Pediatr*. 2005;5(1): 1-10.
19. Patterson DR, Wiechman SA, Jensen M, et al. Hypnosis delivered through immersive virtual reality for burn pain: a clinical case series. *J Clinical Exper Hypnosis*. 2006;54(2):130-142.
20. Sharar SR, Carrougher GJ, Nakamura D, et al. Factors influencing the efficacy of virtual reality distraction analgesia during postburn physical therapy: preliminary results from 3 ongoing studies. *Arch Phys Med Rehabil*. 2007;88(12 suppl 2):S43-S49.
21. Gonzalez M, Hoffman HG, Peña R, et al. Water-friendly adjunctive virtual reality pain distraction for pediatric burn patients during wound debridement in the ICU tubroom. Proceedings of the American Burn Association 48th Annual Meeting. 2016 Abstract # 62;37(3): S97.
22. Schmitt YS, Hoffman HG, Blough DK, et al. A randomized, controlled trial of immersive virtual reality analgesia, during physical therapy for pediatric burns. *Burns*. 2011;37(1):61-68.
23. Carrougher GJ, Hoffman HG, Nakamura D, et al. The effect of virtual reality on pain and range of motion in adults with burn injuries. *J Burn Care Rehabil*. 2009;30:785-791.
24. Mott J, Bucolo S, Cuttle L, et al. The efficacy of an augmented virtual reality system to alleviate pain in children undergoing burns dressings changes: a randomized controlled trial. *Burns*. 2008;34:803-808.
25. Prensner JD, Yowler CJ, Smith LF, et al. Music therapy for assistance with pain and anxiety management in burn treatment. *J Burn Care Rehabil*. 2001;22(1):83-88.
26. Jung Tae S, Sun Hwa K. The effects of self-selected music on anxiety and pain during burn dressing changes. *J Korean Acad Nurs*. 2006; 36(1):159-168.
27. Protacio J. Patient-directed music therapy as adjunct during burn wound care. *Crit Care Nurs*. 2010;30(2):74-76.
28. Fratianne RB, Prensner JD, Huston MJ, et al. The effect of music-based imagery and musical alternate engagement on burn debridement process. *J Burn Care Rehabil*. 2001;22:47-53.
29. Haythornthwaite JA, Lawrence JW, Fauerbach JA. Brief cognitive interventions for burn pain. *Ann Behav Med*. 2001;23(1):42-49.
30. Brewer S, Gleditsh SL, Syblik D, et al. Pediatric anxiety: child life intervention in day surgery. *J Pediatric Nurs*. 2006;21(1):13-22.
31. Cella D, Perry S, Kulchycky S, et al. Stress and coping in relatives of burn patients: a longitudinal study. *Hosp Comm Psychiatry*. 1988;39(2):159-166.
32. Ptacek JT, Patterson DR, Heimbach DM. Inpatient depression in persons with burns. *J Burn Care Rehabil*. 2002;23:1-9.
33. Ullrich PM, Wiechman A, Patterson DR. Pain, depression, and physical functioning following burn injury. *Rehabilitation Psychol*. 2009;54(2):211-216.
34. Patterson D, Ptacek J, Cromes F, et al. Describing and predicting adjustment in burn survivors. *J Burn Care Rehabil*. 2000;21(6): 490-498.
35. Rosenberg L, Blakeney P, Thomas CR, et al. The importance of family environment for young adults burned during childhood. *Burns*. 2007;33(5):541-546.
36. Esselman PC, Ptacek JT, Kowalske K, et al. Community integration after burn injuries. *J Burn Care Rehabil*. 2001;22:221-227.
37. Blakeney P, Partridge J, Rumsey N. Community integration. *J Burn Care Rehabil*. 2007;28(4):598-601.
38. Landolt MA, Grubenmann S, Meuli M. Family impact greatest: predictors of quality of life and psychological adjustment in pediatric burn survivors. *J Trauma Injury Infect Crit Care*. 2002;53:1146-1151.
39. Orr DA, Reznikoff M, Smith GM. Body image, self-esteem, and depression in burn-injured adolescents and young adults. *J Burn Care Rehabil*. 1989;10:454-461.
40. Phoenix Society for Burn Survivors at http://www.phoenix-society.org.
41. Rumsey N, Bull R, Gahagan D. A preliminary study of the potential of social skills for improving the quality of social interaction for the facially disfigured. *Soc Behav*. 1986;1(2):143-145.
42. Robinson E, Rumsey N, Partridge J. An evaluation of the impact of social interaction skills training for facially disfigured people. *Br J Plastic Surg*. 1996;49(5):281-289.
43. Blakeney P, Thomas C, Holzer C 3rd, et al. Efficacy of a short-term, intensive social skills training program for burned adolescents. *J Burn Care Rehabil*. 2005;26(6):546-555.
44. Quayle BK. Be your best. In: *The Journey Back*. Grand Rapids, MI: The Phoenix Society for Burn Survivors, Inc; 2006:27-35.
45. https://www.phoenix-society.org/our-programs/UBelong.
46. James Partridge of Changing Faces. Personal communication, 2005.
47. Changing Faces, http://www.changingfaces.org.uk/Home.
48. Rimmer RB. Family reintegration after burn injury. Presented at the Aftercare Reintegration Committee Forum. Proceedings of the American Burn Association 48th Annual Meeting. 2016 Abstract# 209;37(3):S171.
49. Doctor ME. Returning to school after a severe burn. In: Boswick JA Jr, ed. *The art and science of burn care*. Rockville, MD: Aspen; 1987:323-328.
50. Dobner D, Mitani M. Community reentry program. *J Burn Care Rehabil*. 1988;9(4):420-421.
51. Blakeney P. School reintegration. In: Tarnowski KJ, ed. *Behavioral aspects of pediatric burns*. New York: Plenum Press; 1994:217-241.
52. Hwang Y, Chen-Sea M, Chen C. Factors related to return to work and job modification after a hand burn. *J Burn Care Rehabil*. 2009;30:661-667.
53. Quinn T, Wasiak J, Cleland H. An examination of factors that affect return to work following burns: a systematic review of the literature. *Burns*. 2010;36(7):1021-1026.
54. Esselman PC, Wiechman Askay S, Carrougher GJ, et al. Barriers to return to work after burn injuries. *Arch Phys Med Rehabil*. 2007;88(2):S50-S56.

55. Schneider JC, Bassi S, Ryan CM. Barriers impacting employment after burn injury. *J Burn Care Rehabil*. 2009;30:294-300.
56. Mackey SP, Diba R, McKeown D, et al. Return to work after burns: a qualitative research study. *Burns*. 2009;35:338-342.
57. Oster C, Kildal M, Ekselius L. Return to work after burn injury: burn-injured individuals' perception of barriers and facilitators. *J Burn Care Rehabil*. 2010;31:540-550.
58. Meyer WJ III, Blakeney P, Russell W, et al. Psychological problems reported by young adults who were burned as children. *J Burn Care Rehabil*. 2004;25:98-106.
59. Druery M, Brown TLH, Muller M. Long term functional outcomes and quality of life following severe burn injury. *Burns*. 2005;31:692-695.
60. Dyster-Aas J, Kildal M, Willebrand M. Return to work and health-related quality of life after burn injury. *J Rehabil Med*. 2007;39:49-55.
61. Staley M, Anderson L, Greenhalgh D, Warden G. Return to school as an outcome measure after a burn injury. *J Burn Care Rehabil*. 1998;20(1):91-94.
62. Blakeney P, Moore P, Meyer W, et al. Efficacy of school reentry programs. *J Burn Care Rehabil*. 1995;16:469-472.
63. Rosenberg L, Rosenberg M, Bishop B, et al. Assisting pediatric burn survivors from other countries returning to school. Proceedings for the American Burn Association 37th Annual Meeting. 2005 Abstract #216;26(2):S153.
64. Phoenix Society. *The journey back*. Grand Rapids, MI: The Phoenix Society for Burn Survivors, Inc; 2006:1-159.
65. Dunlap D, Kagan RJ, Arnold S, Gottschlich M. "Remember Me" program: bridging the gap between hospital and school. *J Burn Care Res*. 2013;34(2):99-103.
66. Meyer WJ, Blakeney P, Thomas CR, et al. Prevalence of major psychiatric illness in young adults who were burned as children. *Psychosomatic Med*. 2007;69(4):377-382.
67. Thomas CR, Russell W, Robert RS, et al. Personality disorders in young adult survivors of pediatric burn injury. *J Pers Dis*. 2012;26(2):255-266.
68. Thomas CR, Blakeney P, Holzer CE III, et al. Psychiatric disorders in long-term adjustment of at-risk adolescent burn survivors. *J Burn Care Res*. 2009;30:458-463.
69. Fauerbach JA, Heltshe S, Lezotte DL, et al. Early predictors of long term impairment following burn injury. *J Burn Care Res*. 2006;27(2):S64.
70. Clements PT, DeRanieri JT, Vigil GJ, et al. Life after death: grief therapy after the sudden traumatic death of a family member. *Persp Psychiatric Care*. 2004;40(4):149-154.
71. Brown EJ, Goodman RF. Childhood traumatic grief: an exploration of the construct in children bereaved on September 11. *J Clin Child Adolesc Psychol*. 2005;34(2):248-259.
72. Stroebe MS, Hansson RO, Stroebe W, et al. *Handbook of bereavement research: consequences, coping, and care*. Washington, DC: American Psychological Association; 2001.
73. Wilsey SA, Shear MK. Descriptions of social support in treatment narratives of complicated grievers. *Death Stud*. 2007;31:801-819.
74. Prigerson HG, Jacobs SC. Caring for bereaved patients. *JAMA*. 2001;286:1369-1376.
75. Cohen JA, Mannarino AP. Treatment of childhood traumatic grief. *J Clin Child Adolesc Psychol*. 2004;33(4):819-831.
76. Brown EJ, Amaya-Jackson L, Cohen J, et al. Childhood traumatic grief: a multi-site empirical examination of the construct and its correlates. *Death Stud*. 2008;32:899-923.
77. Boelen PA, Van Den Bout J, de Keijser J. Traumatic grief as a disorder distinct from bereavement related depression and anxiety: a replication study with bereaved mental health care patients. *Am J Psychiatry*. 2003;160:1339-1342.
78. Robert R, Rosenberg L, Amrhein C, et al. Pediatric patients, their families, and truth-telling. Association for the Care of Children's Health, 34th Annual Conference 1999: Long Beach, CA.
79. Bronson M, Price S. Grief, loss and healing after burn trauma: helping children. *Burn Support News*. 2007;4:13-15.
80. Marsella AJ, Yamada AM. Culture and mental health: an introduction and overview of foundations, concepts, and issues. In: Cuellar I, Paniagua FA, eds. *Handbook of multicultural mental health: assessment and treatment of diverse populations*. New York: Academic Press; 2000:3-24.
81. Sue DW, Bernier JE, Durran A, et al. Position paper: cross-cultural counseling competencies. *Counseling Psychologist*. 1982;10:45-52.
82. Battaglia B. Meeting the demands of cross cultural counseling. *Cross Cultural Connections*. 2001;6(4):3.
83. Paniagua FA. *Assessing and treating culturally diverse clients*. 2nd ed. Thousand Oaks, CA: Sage; 1998:5-19.
84. Cuellar I. Acculturation and mental health: ecological transactional relations of adjustment. In: Cuellar I, Paniagua FA, eds. *Handbook of multicultural mental health: assessment and treatment of diverse populations*. New York: Academic Press; 2000:45-62.
85. Angel RJ, Williams R. Cultural models of health and illness. In: Cuellar I, Paniagua FA, eds. *Handbook of multicultural mental health: assessment and treatment of diverse populations*. New York: Academic Press; 2000:25-44.
86. Gomez-Beloz A, Chavez N. The botánica as a culturally appropriate health care options for Latinos. *J Altern Complement Med*. 2001;7(5):537-546.
87. Forjuoh SN. Burns in low and middle income countries: a review of available literature on descriptive epidemiology, risk factors, treatment, and prevention. *Burns*. 2006;32(5):529-537.
88. Peck M, Kruger GE, van der Merwe AE, et al. Burns and fires from non-electric domestic appliances in low and middle income countries: the scope of the problem. *Burns*. 2008;34:303-311.
89. Dissanaike S, Rahimi M. Epidemiology of burn injuries: highlighting cultural and socio-demographic aspects. *Intl Rev Psychiatry*. 2009;21(6):505-511.
90. McKibben JBA, Ekselius L, Girasek DC, et al. Epidemiology of burn injuries II: psychiatric and behavioural perspectives. *Intl Rev Psychiatry*. 2009;21(6):1-10.
91. Patel DD, Rosenberg L, Rosenberg M, et al. The epidemiology of burns in young children from Mexico treated at a U.S. hospital. *Burns*. 2016; (accepted), http://dx.doi.org/10.1016/j.burns.2016.06.008.
92. Atiyeh BS, Costagliola M, Hayek SN. Burn prevention mechanisms and outcomes: pitfalls, failures and successes. *Burns*. 2009;35(2):181-193.
93. Cruz S, Calfa A. Estudio epidemiológico de quemaduras en niños menores de 6 años admitidos en la corporación de ayuda al niño quemado de la ciudad de Antofagasta. *Revista Ciencia y Salud*. 2001;5:17-26.
94. Delgado J, Ramirez-Cardich ME, Gilman RH, et al. Risk factors for burns in children: crowding, poverty, and poor maternal education. *Inj Prev*. 2002;8(1):38-41.
95. Ehde DM, Patterson DR, Wiechman SA, et al. Posttraumatic stress symptoms and distress following acute burn injury. *Burns*. 1999;25:587-592.
96. Ehde DM, Patterson DR, Wiechman SA, et al. Posttraumatic stress symptoms and distress 1 year after burn injury. *J Burn Care Rehabil*. 2000;21:105-111.
97. Wiechman SA, Ptacek JT, Patterson DR, et al. Rates, trends, and severity of depression after burn injuries. *J Burn Care Rehabil*. 2001;22(6):417-424.
98. Thombs BD, Bresnick MG, Magyar-Russell G, et al. Symptoms of depression predict change in physical health after burn injury. *Burns*. 2007;33:292-298.
99. Fauerbach JA, Heinberg LJ, Lawrence JW, et al. Effect of early body image dissatisfaction on subsequent psychological and physical adjustment after disfiguring injury. *Psychosomatic Med*. 2000;62(4):576-582.
100. Difede J, Ptacek JT, Roberts J, et al. Acute stress disorder after burn injury: a predictor of posttraumatic stress disorder? *Psychosom Med*. 2002;64(5):826-834.
101. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. (DSM-5). Washington, DC: American Psychiatric Association; 2013:271-286.
102. Harvey AG, Bryant RA. Acute stress disorder across trauma populations. *J Nerve Ment Dis*. 1999;187(7):443-446.
103. McKibben JB, Bresnick MG, Wiechman Askay SA, Fauerbach JA. Acute stress disorder and posttraumatic stress disorder: a prospective study of prevalence, course, and predictors in a sample with major burn injuries. *J Burn Care Res*. 2008;29(1):22-35.
104. Saxe G, Stoddard F, Chawla N, et al. Risk factors for acute stress disorder in children with burns. *J Trauma Dissociation*. 2005;6(2):37-49.
105. Stoddard FJ, Saxe G, Ronfeldt H, et al. Acute stress symptoms in young children with burns. *J Am Acad Child Adolesc Psychiatry*. 2006;45(1):87-93.
106. Fauerbach JA, Lawrence J, Richter D, et al. Preburn psychiatric history affects posttrauma morbidity. *Psychosomatics*. 1997;38(4):374-385.
107. Stoddard FJ, Norman DK, Murphy JM, et al. Psychiatric outcome of burned children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 1989;28(4):589-595.

108. Fauerbach J, Lawrence J, Munster A, et al. Prolonged adjustment difficulties among those with acute post trauma distress following burn injury. *Behav Med*. 1999;22:359-378.
109. Kildal M, Willebrand M, Andersson G, et al. Coping strategies, injury characteristics and long-term outcome after burn injury. *Injury*. 2005;36(4):511-518.
110. Davydow DS, Katon WJ, Zatzick DF. Psychiatric morbidity and functional impairments in survivors of burns, traumatic injuries, and ICU stays: a review of the literature. *Intl Rev Psychiatry*. 2009;21(6):531-538.
111. Willebrand M, Andersson G, Kildal M, et al. Injury-related fear-avoidance, neuroticism and burn-specific health. *Burns*. 2006;32(4):408-415.
112. Bryant RA. Predictors of posttraumatic stress disorder following burn injury. *Burns*. 1996;22:89-92.
113. Williams D, Kiecolt-Glaser J. Self-blame, compliance and distress among burn patients. *J Person Soc Psychol*. 1987;53:187-193.
114. Taal LA, Faber AW. Post traumatic stress, pain and anxiety in adult burn victims. *Burns*. 1998;23:545-549.
115. Fauerbach JA, McKibben J, Bienvenu OJ, et al. Psychological distress following major burn injury. *Psychosomatic Med*. 2007;69:473-482.
116. Rosenberg L, Rosenberg M, Robert R, et al. Does acute stress disorder predict subsequent posttraumatic stress disorder in pediatric burn survivors? *J Clin Psychiatry*. 2015;76(11):1564-1568.
117. Thombs BD, Notes LD, Lawrence JW, et al. From survival to socialization: a longitudinal study of body image in survivors of severe burn injury. *J Psychosom Res*. 2008;64(2):205-212. doi:10.1016/j.jpsychores.2007.09.003.
118. Mason ST, Corry N, Gould NF, et al. Growth curve trajectories of distress in burn patients. *J Burn Care Res*. 2010;31(1):64-72.
119. Southwick SM, Sippel L, Krystal J, et al. Why are some individuals more resilient than others: the role of social support. *World Psychiatry*. 2016;15(1):77-79.
120. National Institute of Disability and Rehabilitation Research. *Long range plan and the new paradigm*. Washington DC: U.S. Department of Education; 1999.
121. Klein MB, Lezotte DL, Fauerbach JA, et al. The National Institute on Disability and Rehabilitation Research burn model system database: a tool for the multicenter study of the outcome of burn injury. *J Burn Care Res*. 2007;28(1):84-96.
122. Morrison FG, Ressler KJ. From the neurobiology of extinction to improved clinical treatments. *Depression Anxiety*. 2014;31:279-290.
123. Shalev AY, Ankri Y, Gilad M, et al. Long-term outcomes of early interventions to prevent posttraumatic stress disorder. *J Clin Psychiatry*. 2016;e1–e8.
124. Thompson JK, Heinberg LJ, Altabe M, et al. *Exacting beauty: theory, assessment, and treatment of body image disturbance*. Washington, DC: American Psychological Association; 1999.
125. Blakeney P, Robert R, Meyer WJ. Psychological and social recovery of children disfigured by physical trauma: elements of treatment supported by empirical data. *Intl Rev Psychiatry*. 1998;10(3):196-200.
126. Macgregor FC. Facial disfigurement: problems and management of social interaction and implications for mental health. *Aesthetic Plastic Surg*. 1990;14(4):249-257.
127. Pruzinsky T, Doctor M. Body images and pediatric burn injury. In: Tarowski KJ, ed. *Behavioral aspects of pediatric burns*. New York: Plenum; 1994:169-191.
128. Lovegrove E, Rumsey N. Ignoring it doesn't make it stop: adolescents, appearance, and bullying. *Cleft Palate Craniofac J*. 2005;42(1):33-44.
129. Thompson A, Kent G. Adjusting to disfigurement: process involved in dealing with being visibly different. *Clin Psychology Rev*. 2001;21(5):663-682.
130. Walters E. Problems faced by children and families living with visible differences. In: Lansdown R, Rumsey N, Bradbury E, Carr T, Partridge J, eds. *Visibly different*. Oxford: Butterworth–Heineman; 1997:112-120.
131. Macdonald G, Leary MR. Why does social exclusion hurt? The relationship between social and physical pain. *Psychol Bull*. 2005;131(2):202-223.
132. Smart Richman L, Leary MR. Reactions to discrimination, stigmatization, ostracism, and other forms of interpersonal rejection: a multimotive model. *Psychol Rev*. 2009;116(2):365-383.
133. DeWall CN, Deckman T, Pond RS Jr, Bonser I. Belongingness as a core personality trait: how social exclusion influences social functioning and personality expression. *J Personal*. 2011;79(6):1281-1314.
134. Park LE, Maner JK. Does self-threat promote social connection? The role of self-esteem and contingencies of self-worth. *J Pers Social Psychol*. 2009;96(1):203-217.
135. Parker R. Stigma, prejudice and discrimination in global public health. *Cad Saúde Pública*. 2012;28(1):164-169.
136. Pascoe EA, Smart Richman L. Perceived discrimination and health: a meta-analytic review. *Psychol Bull*. 2009;135(4):531-554.
137. Dion K, Berscheid E, Walster E. What is beautiful is good. *J Pers Social Psychol*. 1972;24(3):285-290.
138. Bull RHC, Rumsey N. *The social psychology of facial appearance*. New York: Springer-Verlag; 1988.
139. Link BG, Phelan JC. Conceptualizing stigma. *Ann Rev Sociol*. 2001;27:363-385.
140. Lawrence JW, Fauerbach JA, Heinberg L, et al. The reliability and validity of the Perceived Stigmatization Questionnaire (PSQ) and the Social Comfort Questionnaire (SCQ) among an Adult Burn Survivor Sample. *Psychol Assess*. 2006;18:106-111.
141. Bull R, Stevens J. Effect of unsightly teeth on helping behavior. *Perceptual Motor Skills*. 1980;51(2):438.
142. Rumsey N, Bull R, Gahagan D. The effect of facial disfigurement on the proxemic behavior of the general public. *J Appl Soc Psychol*. 1982;12(2):137-150.
143. Piliavin IM, Piliavin JA, Rodin J. Costs, diffusion, and the stigmatized victim. *J Pers Social Psychol*. 1975;32(3):429-438.
144. Rybarczyk B, Edwards R, Behel J. Diversity in adjustment to a leg amputation: case illustrations of common themes. *Disabil Rehabil*. 2004;26(14-15):944-953.
145. Tiggemann M. Sociocultural perspectives on human appearance and body image. In: Cash TF, Smolak L, eds. *Body image: a handbook of science, practice and prevention*. 2nd ed. New York: Guilford; 2011:12-19.
146. Linares HA. From wound to scar. *Burns*. 1996;12(5):339-352.
147. Pope SJ, Solomons WR, Done DJ, Cohn N, Possamai AM. Body image, mood and quality of life in young burn survivors. *Burns*. 2007;36(6):747-755.
148. Lawrence JW, Rosenberg LE, Fauerbach JA. Comparing the body esteem of pediatric sur*vivors* of burn injury with the body esteem of an age-matched comparison group without burns. *Rehabil Psychol*. 2007;52(4):370-379.
149. Oaten M, Stevenson RJ, Case TI. Disease avoidance as a functional basis for stigmatization. *Philosoph Trans R Soc B*. 2011;366:3433-3452.
150. Willebrand M, Sveen J. Injury-related fear avoidance and symptoms of posttraumatic stress in parents of children with burns. *Burns*. 2016;42:414-420.
151. Lawrence JW, Fauerbach JA, Heinberg L, Doctor M. Visible vs hidden scars and their relation to body esteem. *J Burn Care Rehabil*. 2004;25(1):25-32.
152. Thombs BD, Notes LD, Lawrence JW, et al. From survival to socialization: a longitudinal study of body image in survivors of severe burn injury. *J Psychosomatic Res*. 2008;64(2):205-212.
153. Lawrence JW, Fauerbach JA, Thombs BD. A test of the moderating role of importance of appearance in the relationship between perceived scar severity and body-esteem among adult burn survivors. *Body Image*. 2006;3(2):101-111.
154. Corry N, Pruzinsky T, Rumsey N. Quality of life and psychosocial adjustment to burn injury: social functioning, body image, and health policy perspectives. *Intl Rev Psychiatry*. 2009;21(6):539-548.
155. Rimmer RB, Foster KN, Bay CR, et al. The reported effects of bullying on burn-surviving children. *J Burn Care Rehabil*. 2007;28(3):485-489.
156. Broder HL, Smith FB, Strauss RP. Developing a behavior rating scale for comparing teachers' ratings of children with and without craniofacial anomalies. *Cleft Palate Craniofac J*. 2001;38(6):560-565.
157. Carroll P, Shute R. School peer victimization of young people with craniofacial conditions: a comparative study. *Psychol Health Med*. 2005;10(3):291-304.
158. Lawrence JW, Heinberg LJ, Roca R, et al. Development and validation of the Satisfaction with Appearance Scale: assessing body image among burn-injured patients. *Psychol Assess*. 1998;10(1):64-70.
159. Carr T, Moss T, Harris D. The DAS24: a short form of the Derriford Appearance Scale DAS59 to measure individual responses to living with problems of appearance. *Br J Health Psychol*. 2005;10(Pt 2):285-298.
160. Lawrence JW, Rosenberg LE, Rimmer RB, et al. Perceived stigmatization and social comfort: validating the constructs and their measurement among pediatric burn survivors. *Rehabil Psychol*. 2010;55(4):360-371.

161. Blakeney P, Meyer W 3rd, Robert R, et al. Long-term psychosocial adaptation of children who survive burns involving 80% or greater total body surface area. *J Trauma*. 1998;44(4):625-634.
162. Meyer W, Blakeney P, Moore P, et al. Parental well-being and behavioral adjustment of pediatric burn survivors. *J Burn Care Rehabil*. 1994;15:62-68.
163. Ware JE, Snow KK, Kosinski M, et al. *SF-36 health survey: manual and interpretation guide*. Boston, MA: Nimrod; 1993.
164. Suman OE, Spies RJ, Celis MM, Mlcak RP, Herndon DN. Effects of a 12-wk resistance exercise program on skeletal muscle strength in children with burn injuries. *J Appl Physiol*. 2001;91:1168-1175.
165. Suman OE, Mlcak RP, Herndon DN. Effects of exercise training on pulmonary function in children with thermal injury. *J Burn Care Rehabil*. 2002;23:288-293.
166. Suman OE, Herndon DN. Effects of cessation of a structured and supervised exercise conditioning program on lean mass and muscle strength in severely burned children. *Arch Phys Med Rehabil*. 2007;88(12 suppl 2):S24-S29. PubMed PMID: 18036977.
167. De Lateur BJ, Magyar-Russell G, Bresnick MG, et al. Augmented exercise in the treatment of deconditioning from major burn injury. *Arch Phys Med Rehabil*. 2007;88(12 suppl 2):S18-S23.
168. Rosenberg M, Celis MM, Meyer IIIW, et al. Effects of a hospital based wellness and exercise program on quality of life of children with severe burns. *Burns*. 2013;39:599-609.
169. Sheridan RL, Hinson MI, Liang MH, et al. Long-term outcome of children surviving massive burns. *JAMA*. 2000;283(1):69-73.
170. Rosenberg M, Blakeney P, Robert R, et al. Quality of life of young adults who survived pediatric burns. *J Burn Care Rehabil*. 2006;27:773-778.
171. Baker C, Russell WJ, Meyer W III, et al. Physical and psychologic rehabilitation outcomes for young adults burned as children. *Arch Phys Med Rehabil*. 2007;88(12 suppl 2):S57-S64.
172. Meyer WJ, Russell W, Thomas CR, et al. Sexual attitudes and behaviour of young adults who were burned as children. *Burns*. 2011;37(2):215-221.
173. Bianchi TLG. Aspects of sexuality after burn injury: outcomes in men. *J Burn Care Rehabil*. 1977;18:183-186.
174. Fauerbach JA, Lezotte D, Cromes GF, et al. 2004 American Burn Association Clinical Research Award. Burden of burn: a norm-based inquiry into the influence of burn size and distress on recovery of physical and psychosocial function. *J Burn Care Rehabil*. 2005;26(1):21-32.
175. Cromes GF, Holavanahalli R, Kowalske K, et al. Predictors of quality of life as measured by the Burn Specific Health Scale in persons with major burn injury. *J Burn Care Rehabil*. 2002;23(3):229-234.
176. Saxe G, Stoddard F, Sheridan R. PTSD in children with burns: a longitudinal study. *J Burn Care Rehabil*. 1998;19(1 Pt 2):S206.
177. Foa EBE, Keane TME, Friedman MJE, Cohen JAE. *Effective treatments for PTSD: practice guidelines from the International Society for Traumatic Stress Studies*. 2nd ed. New York: Guilford; 2009.
178. Bryant RA, Harvey AG. *Acute stress disorder: a handbook of theory, assessment, and treatment*. Washington, DC: American Psychological Association; 2000.
179. Bessell A, Moss TP. Evaluating the effectiveness of psychosocial interventions for individuals with visible differences: a systematic review of the empirical literature. *Body Image*. 2007;4(3):227-238.
180. Cash TF. *The body image workbook: an 8-step program for learning to like your looks*. New York: New Harbinger; 1997.
181. Rosen JC. Improving body image in obesity. In: Thompson JK, ed. *body image, eating disorders, and obesity: an integrative guide for assessment and treatment*. Washington, DC: American Psychological Association; 2001:425-440.
182. Cox ER, Call SB, Williams NR, et al. Shedding the layers: exploring the impact of the burn camp experience on adolescents campers' body image. *J Burn Care Rehabil*. 2004;25:141-147.
183. Rimmer RB, Fornaciari GM, Foster KN, et al. Impact of a pediatric residential burn camp experience on burn survivors' perceptions of self and attitudes regarding the camp community. *J Burn Care Rehabil*. 2007;28:334-341.
184. Doctor ME. Burn camps and community aspects of burn care. *J Burn Care Rehabil*. 1992;13:68-76.
185. Rimmer RB, Bay RC, Alam NB, et al. Burn-injured youth may be at increased risk for long-term anxiety disorders. *J Burn Care Res*. 2014;35(2):154-161.
186. Rimmer RB, Pressman MS, Takach OP, et al. Burn-injured adolescents report gaining multiple developmental benefits and improved life skills as a result of burn camp attendance. *J Burn Care Res*. 2012;33(4):552-560.
187. Rimmer RB, Bay R, Wise D, et al. Post-traumatic growth in adolescent burn survivors as compared to survivors of serious childhood illness. Proceedings for the American Burn association 48th Annual Meeting. 2016;37(3): Abstract No. 209.