CHAPTER e23

Infectious Complications of Burns

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The skin is an essential component of the nonspecific immune system, protecting the host from potential pathogens in the environment. Breaches in this protective barrier thus represent a form of immunocompromise that predisposes a patient to infection. Thermal burns may cause massive destruction of the integument as well as derangements in humoral and cellular immunity, permitting the development of infection caused by environmental opportunists and components of the host's skin flora.

EPIDEMIOLOGY

Over the last decade, the estimated incidence of burn injuries in the United States has declined steadily; however, >1 million burn injuries are brought to medical attention each year. Although many burn injuries are minor and require little or no intervention, 50,000 persons are hospitalized for these injuries, 60% of whom require intensive care in a specialized burn center and 20,000 of whom have major burns involving at least 25% of the total body surface area. The majority of burn patients are men. Infants account for ~10% of all reported cases. Scalds, structural fires, and flammable liquids and gases are the major causes of burns, but electrical, chemical, and smoking-related sources are also important. Burns predispose to infection by damaging the protective barrier function of the skin, thus facilitating the entry of pathogenic microorganisms, and by inducing systemic immunosuppression. It is therefore unsurprising that multiorgan failure and infectious complications are the major causes of morbidity and death in serious burn injuries. As many as 10,000 patients in the United States die of burn-related infections each year, and 6 of the top 10 complications recently identified by the American Burn Association's 10-year review are infectious. These 10 most common complications are pneumonia (4.6%), septicemia (2.7%), cellulitis/traumatic injury (2.6%), respiratory failure (2.5%), wound infection (2.2%), other infection (2.0%), renal failure (1.5%), line infection (1.4%), acute respiratory distress syndrome (1.2%), and arrhythmia (1.0) (*www.ameriburn.org/2007NBRAnnual Report.pdf*).

PATHOPHYSIOLOGY

Loss of the cutaneous barrier facilitates entry of the patient's own flora and of organisms from the hospital environment into a burn wound. Initially, the wound is colonized with gram-positive bacteria from the surrounding tissue, but the number of bacteria grows rapidly beneath the burn eschar, reaching ~8.4×10^3 cfu/g on day 4 after the burn. The avascularity of the eschar, along with the impairment of local immune responses, favors further bacterial colonization and proliferation. By day 7, the wound is colonized with other microbes, including gram-positive bacteria, gram-negative bacteria, and yeasts derived from the gastrointestinal and upper respiratory flora. Invasive infection—localized and/or systemic—occurs when these bacteria penetrate viable tissue. In addition, a role for biofilms has been recognized in experimental animal models of burn-wound infection. (Biofilms are surface-associated communities of bacteria, often embedded in a matrix, that allow the microbes to persist and to resist the effects of host immunity and antimicrobial agents.)

Streptococci and staphylococci were the predominant causes of burn-wound infection in the preantibiotic era and are still important pathogens. With the advent of antimicrobial agents, *Pseudomonas aeruginosa* became a major problem in burn-wound management. Less common anaerobic bacteria typically are found in infections from electrical burns or when open wound dressings are used. The widespread use of topical and more effective antimicrobial drugs has resulted in a decline in bacterial wound infections and the emergence of fungi (particularly *Candida albicans*, *Aspergillus* species, and the agents of mucormycosis) as increasingly important pathogens in burn-wound patients. Herpes simplex virus has been found in burn wounds, especially those on the neck and face and those associated with inhalation injury. Autopsy reports on patients with severe thermal burns over the last decade have identified an association of *P. aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* with death; this association is independent of the percentage of the total body surface area covered by burns, the percentage of burns that are full-thickness (as opposed to partial-thickness), inhalation injury, and day of death after a burn. In addition, members of the *Acinetobacter calcoaceticus-baumannii* complex are among the most common pathogens at some burn centers.

The cascade of events that follows a severe burn injury and that leads to multiorgan system failure and death is thought to represent a two-step process; i.e., the burn injury itself, with ensuing hypovolemia and tissue hypoxia, is followed by invasive infection arising from large amounts of devitalized tissue. The frequency of infection parallels the extent and severity of the burn injury. Severe burn injuries cause a state of immunosuppression that affects innate and adaptive immune responses. The substantial impact of immunocompromise on infection is due to effects on both the cellular and the humoral arms of the immune system. For example, decreases in the number and activity of circulating helper T cells, increases in the number and activity of suppressor T cells, decreases in production and release of monocytes and macrophages, and diminution in levels of immunoglobulin follow major burns. Neutrophil and complement functions also have been shown to be impaired after burns. The increased levels of multiple cytokines detected in burn patients are compatible with the widely held belief that the inflammatory response becomes dysregulated in these individuals; bacterial cell products play a potent role in inducing proinflammatory mediators that contribute to this uncontrolled systemic inflammatory response. Increased permeability of the gut wall to bacteria and their components (e.g., endotoxin) also contributes to immune dysregulation and sepsis. Thus, a burn patient is predisposed to infection at remote sites (see below) as well as at the sites of burn injury. Another contributor to secondary immunosuppression after burn injuries is the endocrine system; increasing levels of vasopressin, aldosterone, cortisol, glucagon, growth hormone, catecholamines, and other hormones that directly affect lymphocyte proliferation, secretion of proinflammatory cytokines, natural killer cell activity, and suppressor T cells are seen.

CLINICAL MANIFESTATIONS

Since clinical indications of wound infection are difficult to interpret, wounds must be monitored carefully for changes that may reflect infection. A margin of erythema frequently surrounds the sites of burns and by itself is not usually indicative of infection. Signs of infection include the conversion of a partial-thickness to a full-thickness burn, color changes (e.g., the appearance of a dark

brown or black discoloration of the wound), the new appearance of erythema or violaceous edema in normal tissue at the wound margins, the sudden separation of the eschar from subcutaneous tissues, and the degeneration of the wound with the appearance of a new eschar.

Early surgical excision of devitalized tissue is now widely performed, and burn-wound infections can be classified in relation to the excision site as (1) burn-wound impetigo (infection characterized by loss of epithelium from a previously reepithelialized surface, as seen in a partial-thickness burn that is allowed to close by secondary intention, a grafted burn, or a healed skin donor site), (2) burn-related surgical wound infection (purulent infection of excised burn and donor sites that have not yet epithelialized, accompanied by positive cultures), (3) burn-wound cellulitis (extension of infection to surrounding healthy tissue; Fig. e23-1), and (4) invasive infection in unexcised burn wounds (infection that is secondary to a partial- or full-thickness burn wound and is manifested by separation of the eschar or by violaceous, dark brown, or black discoloration of the eschar; Fig. e23-2). The appearance of a green discoloration of the wound or subcutaneous fat (Fig. e23-3) or the development of ecthyma gangrenosum (see Fig. e7-35) at a remote site points to a diagnosis of invasive *P. aeruginosa* infection.

Changes in body temperature, hypotension, tachycardia, altered mentation, neutropenia or neutrophilia, thrombocytopenia, and renal failure may result from invasive burn wounds and sepsis. However, because profound alterations in homeostasis occur as a consequence of burns per se and because inflammation without infection is a normal component of these injuries, the assessment of these changes is complicated. Alterations in body temperature, for example, are attributable to thermoregulatory dysfunction; tachycardia and hyperventilation accompany the metabolic changes induced by extensive burn injury and are not necessarily indicative of bacterial sepsis.

In light of the difficulty of evaluating burn wounds solely on the basis of clinical observation and laboratory data, wound biopsies are necessary for definitive diagnosis of infection. The timing of these biopsies can be guided by clinical changes, but in some centers burn wounds are biopsied routinely at regular intervals. The biopsy specimen is examined for histologic evidence of bacterial invasion, and quantitative microbiologic cultures are performed.

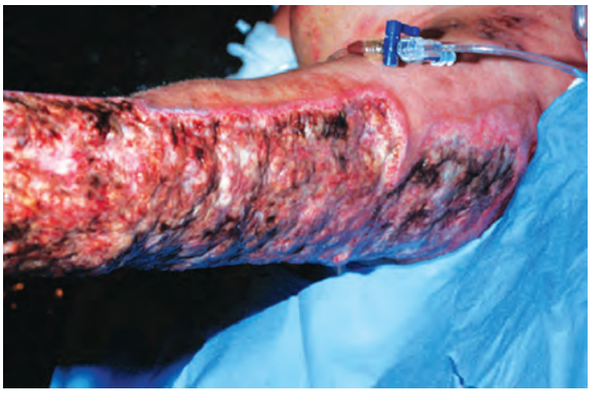

Figure e23-2 A severe upper-extremity burn infected with *Pseudomonas aeruginosa*. The wound requires additional debridement. Note the dark brown to black discoloration of the eschar. *(Courtesy of Dr. Robert L. Sheridan, Massachusetts General Hospital, Boston; with permission.)*

The presence of $>10^5$ viable bacteria per gram of tissue is highly suggestive of invasive infection and of a dramatically increased risk of sepsis. Histopathologic evidence of invasion of viable tissue and the presence of microorganisms in unburned blood vessels and lymphatics are more definitive indicators of infection. A blood culture positive for the same organism seen in large quantities in biopsied tissue is a reliable indicator of burn sepsis. Surface cultures may provide some indication of the microorganisms present in the hospital environment but are not indicative of the etiology of infection. This noninvasive technique might be of use in determining the flora present in excised burn areas or in areas where the skin is too thin for biopsy (e.g., over the ears, eyes, or digits).

In addition to infection of the burn wound itself, a number of other infections due to the immunosuppression caused by extensive burns and the manipulations necessary for clinical care put burn

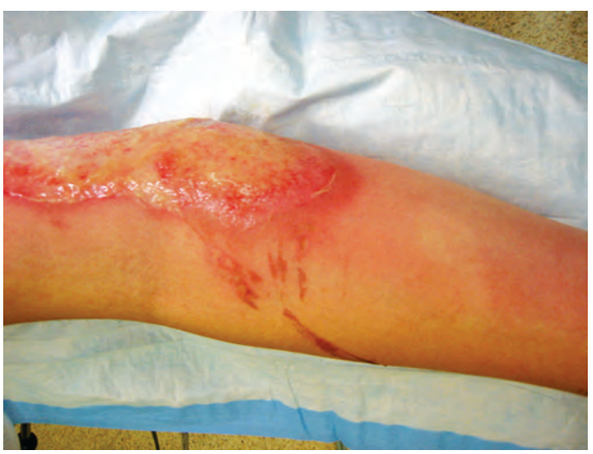

Figure e23-1 Cellulitis complicating a burn wound of the arm and demonstrating extension of the infection to adjacent healthy tissue. *(Courtesy of Dr. Robert L. Sheridan, Massachusetts General Hospital, Boston; with permission.)*

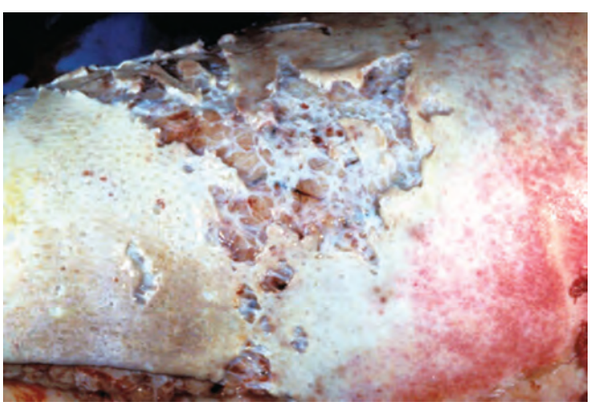

Figure e23-3 A burn wound infected with *Pseudomonas aeruginosa*, with liquefaction of tissue. Note the green discoloration at the wound margins, which is suggestive of *Pseudomonas* infection. *(Courtesy of Dr. Robert L. Sheridan, Massachusetts General Hospital, Boston; with permission.)*

patients at risk. Pneumonia, now the most common infectious complication among hospitalized burn patients, is most often nosocomially acquired via the respiratory route; among the risk factors associated with secondary pneumonia are inhalation injury, intubation, full-thickness chest wall burns, immobility, and uncontrolled wound sepsis with hematogenous spread. Septic pulmonary emboli also may occur. Suppurative thrombophlebitis may complicate the vascular catheterization necessary for fluid and nutritional support in burns. Endocarditis, urinary tract infection, bacterial chondritis (particularly in patients with burned ears), and intraabdominal infection also complicate serious burn injury.

TREATMENT Burn-Wound Infections

The ultimate goal of burn-wound management is closure and healing of the wound. Early surgical excision of burned tissue, with extensive debridement of necrotic tissue and grafting of skin or skin substitutes, greatly decreases mortality rates associated with severe burns. In addition, the four widely used topical antimicrobial agents—silver sulfadiazine cream, mafenide acetate cream, silver nitrate cream, and nanocrystalline silver dressings—dramatically decrease the bacterial burden of burn wounds and reduce the incidence of burn-wound infection; these agents are applied routinely to partial- and full-thickness burns. The bactericidal properties of silver are related to its effect on respiratory enzymes on bacterial cell walls; its interaction with structural proteins causes keratinocyte and fibroblast toxicity that can delay wound healing if silver-based compounds are used indiscriminately. All four agents are broadly active against many bacteria and some fungi and are useful before bacterial colonization is established. Silver sulfadiazine often is used initially, but its value can be limited by bacterial resistance, poor wound penetration, or toxicity (leukopenia). Mafenide acetate has broader activity against gram-negative bacteria. The cream penetrates eschars and thus can prevent or treat infection beneath them; its use without dressings allows regular examination of the wound area. The foremost disadvantages of mafenide acetate are that it can inhibit carbonic anhydrase, resulting in metabolic acidosis, and that it elicits hypersensitivity reactions in up to 7% of patients. This agent is used most often when gram-negative bacteria invade the burn wound and when treatment with silver sulfadiazine fails. The activity of mafenide acetate against gram-positive bacteria is limited. Nanocrystalline silver dressings provide broader antimicrobial coverage than does any other available topical preparation, exhibiting activity against methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci, moderate ability to penetrate eschars, and limited toxicity. In addition, this approach provides controlled and prolonged release of nanocrystalline silver into the wound, limiting the number of dressing changes and therefore reducing the risk of nosocomial infections as well as the cost of treatment. Mupirocin, a topical antimicrobial agent used to eradicate nasal colonization with MRSA, is being used increasingly in burn units where MRSA is prevalent. The efficacy of mupirocin in reducing burn-wound bacterial counts and preventing systemic infections is comparable to that of silver sulfadiazine.

In recent years, rates of fungal infection have increased in burn patients. When superficial fungal infection occurs, nystatin may be mixed with silver sulfadiazine or mafenide acetate as topical therapy. A small study found that nystatin powder (6 million units/g) was effective for treatment of superficial and deep burn-wound infections caused by *Aspergillus* or *Fusarium* species. In addition to these products, moisture-retention ointments with antimicrobial properties can promote rapid autolysis, debridement, and moist healing of partial-thickness wounds.

When invasive wound infection is diagnosed, topical therapy should be changed to mafenide acetate. Subeschar clysis (the direct instillation of an antibiotic, often piperacillin, into wound tissues under the eschar) is a useful adjunct to surgical and systemic antimicrobial therapy. Systemic treatment with antibiotics active against the pathogens present in the wound should be instituted. In the absence of culture data, treatment should be broad in spectrum, covering organisms commonly encountered in that particular burn unit. Such coverage usually is achieved with an antibiotic active against gram-positive pathogens (e.g., vancomycin, 1 g IV every 12 h) and with a drug active against *P. aeruginosa* and other gram-negative rods (e.g., ceftazidime, 2 g IV every 8 h). In penicillin-allergic patients, ciprofloxacin (400 mg IV every 12 h) may be substituted for ceftazidime. In settings where MRSA is not prevalent, oxacillin (2 g IV every 4 h) may be substituted for vancomycin. Patients with burn wounds frequently have alterations in metabolism and renal clearance mechanisms that mandate the monitoring of serum antibiotic levels; the levels achieved with standard doses are often subtherapeutic.

Treatment of infections caused by emerging resistant pathogens remains a challenge in the care of burn patients. MRSA, resistant enterococci, multidrug-resistant gram-negative rods, and Enterobacteriaceae producing extended-spectrum β-lactamases have been associated with burn-wound infections and identified in burn-unit outbreaks. Strict infection-control practices (including microbiologic surveillance in burn units) and appropriate antimicrobial therapy remain important measures in reducing rates of infection due to resistant organisms.

In general, prophylactic systemic antibiotics have no role in the management of burn wounds and can, in fact, lead to colonization with resistant microorganisms. In some studies, antibiotic prophylaxis has been associated with increased secondary infections of the upper and lower respiratory tract and the urinary tract as well as with prolonged hospitalization. An exception involves cases requiring burn-wound manipulation. Since procedures such as debridement, excision, and grafting frequently result in bacteremia, prophylactic systemic antibiotics are administered at the time of wound manipulation; the specific agents used should be chosen on the basis of data obtained by wound culture or data on the hospital's resident flora.

The use of oral antibiotics for selective digestive decontamination (SDD) to decrease bacterial colonization and the risk of burn-wound infection is controversial and has not been widely adopted. In a randomized, double-blind, placebo-controlled trial in patients with burns involving >20% of the total body surface area, SDD was associated with reduced mortality rates in the burn intensive care unit and in the hospital and also with a reduced incidence of pneumonia. The effects of SDD on the normal anaerobic bowel flora must be taken into consideration before this approach is used.

All burn-injury patients should undergo tetanus booster immunization if they have completed primary immunization but have not received a booster dose in the last 5 years. Patients without prior immunization should receive tetanus immune globulin and undergo primary immunization.

FURTHER READINGS

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