

Infection in Burns

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on Behalf of the Scientific Study Committee of the Surgical Infection Society

Abstract

Background: Developments in critical care and surgical approaches to treating burn wounds, together with newer antimicrobial treatments, have significantly reduced the morbidity and mortality rates associated with this injury.

Methods: Review of the pertinent English-language literature.

Results: Several resistant organisms have emerged as the maleficent cause of invasive infection in burn patients, including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, *Pseudomonas*, *Acinetobacter*, non-*albicans Candida* spp., and *Aspergillus*. Advances in antimicrobial therapies and the release of new classes of antibiotics have certainly added to the armamentarium of therapeutic resources for the clinician.

Conclusion: Strict infection control measures, constant wound surveillance with regular sampling of tissues for quantitative culture, and early excision and wound closure remain the principal adjuncts to control of invasive infections in burn patients.

INVASIVE INFECTION is now the chief reason for death and morbidity after burn injury, with it being responsible for 51% of the deaths [1,2]. The importance of prevention, surveillance, and sampling for infections in this immunocompromised group has been well established; however, there is a dearth of standard-of-care guidelines and novel approaches. In this review, we discuss the epidemiology of burn infections, define degrees of severity of infection, outline the major organisms associated with burn wounds, and describe the specific organs and tissues susceptible to infection. We also discuss strategies for surveillance, sampling, and infection control in the burn intensive care unit (ICU).

Epidemiology

Every year, approximately half a million Americans sustain burn injuries requiring medical intervention. Most of these do not require admission to a hospital. However, around 40,000 of these people are admitted, with 75% of them needing specialized treatment at a certified burn center. Advances in modern medical care incorporating aggressive fluid

resuscitation, alleviation of the hypermetabolic response, adequate and effective surgical grafting and coverage of burn wounds, pulmonary toilet and ventilation, nutritional support, and infection control measures have ensured that the majority of patients reaching the hospital will survive. The total annual number of burn-related deaths is approximately 3,400 [3]. Sepsis and the accompanying invasive infection continue to be the primary reason for death after the first 24 h, with these often culminating in the demise of the patient after the first 2 wks of admission. Over the last 10 years, the most frequent clinical complications reported in patients admitted to a certified burn center were pneumonia (3.5%), cellulitis (3%), and urinary tract infection (2.6%). The frequency of pneumonia was greater in patients who had been injured by fire and those with four or more days of mechanical ventilation [4].

Classification

Burn wound impetigo, also referred to as graft ghostings and folliculitis when the scalp is involved, usually is caused by bacterial colonization rather than invasive

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infection. The result is a loss of epithelium from an area that had re-epithelialized.

Burn wound colonization may be diagnosed when bacteria are present at low concentrations ($<10^5$ colony-forming units [CFU]) on the wound's surface. No surrounding erythema or cellulitis is evident, but deterioration of the wound surface can be observed.

Infection is defined as the presence of high concentrations ($>10^5$ organisms/g of tissue) of bacteria in the burn wound and scab. However, no evidence exists that the infection is invasive. The presence of cellulitis is the foundation of the clinical diagnosis. Burn wound cellulitis can be observed when the area of erythema extends beyond what would be expected for the injury alone. It is the result of infection of the otherwise-healthy tissues surrounding the wound and often is accompanied by increased warmth within the area, pain or tenderness, advancing swelling, or induration. Occasionally, lymphangitis may be observed, but this is less common.

Invasive infection of burn wounds is a surgical emergency because of the high concentrations of bacteria ($>10^5$ CFU) in the wound and surrounding area, together with new areas of necrosis in unburned tissues. This situation often is accompanied by signs of sepsis and changes in the burn wound such as black, blue, or brown discoloration of the eschar. **Urgent resuscitation measures are required, along with broad-spectrum antimicrobial agents, antifungals, and surgical debridement of the affected area.** Specimens of this tissue must undergo histopathologic and microbiologic analysis to assist in the identification of the causative organism(s). Those patients with a delay in presentation or removal of burned tissues are at greatest risk of this condition [5].

Unfortunately, because of the natural pathophysiology of burns, definitions developed by the American College of Chest Physicians and Society of Critical Care Medicine for inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock inadequately describe the septic responses of the burn patient. Large burns, those covering $\geq 20\%$ of the total body surface area, compromise the barrier function of the skin that prevents entry of microorganisms, triggering a prolonged, constant exposure to host immune response mediators that is not observed in other critical illnesses. The profound biphasic immune response, described as hyperinflammation followed by severe immunodepression, has a clinical presentation that mimics SIRS, sepsis, and the already-mentioned states. This finding led to the formation of a consensus conference in 2007 by members of the American Burn Association, who determined the definition of sepsis for burn patients that is used today [1]. The group also adjudicated that the terms and clinical descriptions of SIRS, severe sepsis, and septic shock were not useful for the burn patient population. The definition of sepsis developed by the American Burn Association Consensus Conference to Define Sepsis and Infection in Burns is provided [1].

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. Whereas there is need for clinical interpretation, the diagnosis needs to be tied to the discovery of an infection. The definition is age-dependent with adjustments necessary for children.

The trigger includes at least three of the following:

- I. Temperature $>39^\circ\text{C}$ or $<36.5^\circ\text{C}$
- II. Progressive tachycardia
 - A. Adults >110 beats/min (bpm)
 - B. Children >2 SD [standard deviations] above age-specific norm (85% age-adjusted maximum heart rate)
- III. Progressive tachypnea
 - A. Adults >25 bpm if not ventilated
 - i. Minute ventilation >12 L/min when ventilated
 - B. Children >2 SD above age-specific norm (85% age-adjusted maximum respiratory rate)
- IV. Thrombocytopenia (will not apply until 3 d after initial resuscitation)
 - A. Adults $<100,000/\text{mL}$
 - B. Children <2 SD below age-specific norm
- 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 h)
- VI. Inability to continue enteral feedings >24 h
 - A. Abdominal distension
 - B. Enteral feeding intolerance (residual >150 mL/h in children or $2\times$ feeding rate in adults)
 - C. Uncontrollable diarrhea ($>2,500$ mL/d for adults or >400 mL/d in children)
- VII. 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

Sources of Infection

Although the leading infective bacterium in burn wounds is *Staphylococcus aureus*, a recent study showed that the leading causes of death from infection now are multiply resistant organisms, including *Pseudomonas* and *Acinetobacter* [2]. The following are the organisms most frequently responsible for infections after burns.

Gram-positive bacteria

Staphylococcus aureus remains the chief cause of burn wound infection [6]. Over recent decades and with the liberal use of broad-spectrum antibiotics, methicillin-resistant *S. aureus* (MRSA) has become the predominant pathogen in the ICU. Colonization with either of these bacteria in an uninjured individual usually is asymptomatic, but they are a source of opportunistic infection that can lead to severe illness and death [7]. *Staphylococcus aureus* produces toxic byproducts such as proteinases, collagenases, and hyaluronidase that allow it to invade local tissues and disseminate hematogenously, causing generalized systemic infection and sepsis [8]. Methicillin-resistant *S. aureus* now is one of the leading organisms causing invasive infection in burns across the world, with burn units reporting rates of infection greater than 50% [9,10]. In addition to causing

pneumonia, sepsis, and other sequelae related to invasive burn wound infection, staphylococci are a significant cause of graft loss when the burden of infective organisms exceeds 10^5 CFU [11].

Although vancomycin has been the stand-alone treatment for MRSA infections, over recent years, resistant strains such as vancomycin-intermediate *S. aureus* have been isolated. Other new antimicrobials such as linezolid (an oxazolidinone), tigecycline, daptomycin, quinupristin-dalfopristin, and dalbavancin have been developed specifically to tackle this problem. When using vancomycin for burns, which often involve major changes in fluid status and renal function, maintaining a therapeutic concentration with a trough normally between 10–15 mcg/mL is imperative. Daily monitoring of vancomycin concentrations enables any needed alterations in dosing.

Streptococcus. Although once the leading cause of burn wound infection, streptococci now are easily eradicated with penicillins. Graft failure is the major complication that is observed occasionally with these bacteria, especially β -hemolytic streptococci. Of these, Group A (*S. pyogenes*) is the most problematic, followed by Group B (*S. agalactiae*) [12].

Enterococcus. The importance of enterococci has been brought to the fore with the emergence of vancomycin-resistant *Enterococcus* (VRE). In a recent review comparing the cause of death from sepsis between consecutive decades (1989–1999 and 1999–2009), a steep decline in the rate of infection with enterococci (25% to 2%) was found [2]. This may be attributable, in part, to the more liberal use of vancomycin during recent years. However, the emergence of VRE should encourage vigilance for this organism, as mortality rates now are greater than that for MRSA (58% vs. 33%) [13]. Usually, VRE is treated with linezolid; however, the organism also may be susceptible to a combination of ampicillin and an aminoglycoside or Synercid[®] (quinupristin-dalfopristin).

Gram-negative bacteria

Pseudomonas. *Pseudomonas* is not only the most ubiquitous burn wound pathogen, but also the most likely to be responsible for sepsis leading to burn-linked death [2,14]. Both the local environment and the gastrointestinal tract (via translocation of endogenous gastrointestinal flora) are believed to be the main sources of this problematic species of gram-negative bacteria. *Pseudomonas aeruginosa* is the chief pathogen responsible for respiratory tract infections in the hospital; however, it also may cause invasive burn wound infection because of its preference for moist environments. A superficial wound infection caused by *P. aeruginosa* typically will have a characteristic yellow/green color and a malodorous fruity smell [15]. This may become an invasive infection or ecthyma gangrenosum, causing blue-purple “punched-out” lesions in the skin. This picture indicates local thrombosis of vessels and requires urgent debridement to remove the newly necrotic tissues.

The treatment of choice for *P. aeruginosa* infection has changed over the years from aminoglycosides to piperacillin-tazobactam because of developing resistance patterns [16]. The increasing prevalence of multiply drug-resistant *P. aeruginosa* has caused many problems for clinicians looking

after the severely burned. This has led to the resurgence of the use of polymyxins, in particular colistin (polymyxin E). Colistin has a substantial side-effect profile, with significant accumulation in important tissues such as the kidney, brain, liver, muscle, and lung (in descending order of frequency) [17,18]. Therefore, prolonged use is not recommended, particularly in patients with renal impairment of any kind (the drug is excreted by the kidneys). During administration, patients must be monitored closely for signs of nephrotoxicity and neurotoxicity.

Acinetobacter. Observed with increasing frequency, this organism may lead to numerous opportunistic infections, including pneumonia and those of the surgical site and urinary tract [19]. Second only to *P. aeruginosa* in frequency [20,21], this organism has an enhanced capacity for transfer between patients because of its ability to survive in both dry and wet conditions as well as on both animate and inanimate objects, whether metal or plastic [22]. Although traditionally susceptible to ceftazidime and ciprofloxacin, *Acinetobacter* has developed resistance to such an extent that only the carbapenems (e.g., imipenem and meropenem) can be relied now on to treat these infections. In cases of pan-resistant *Acinetobacter*, colistin has become the fallback treatment, as for *Pseudomonas* infections [23].

Enterobacteriaceae (*Escherichia coli*, *Klebsiella*, *Enterobacter*, *Serratia*, *Proteus*). Although less problematic than the organisms already discussed, Enterobacteriaceae are associated with infections in burn patients, most often causing pneumonia and urinary tract infections [24]. Although these pathogens have greater sensitivity to antibiotics than do other gram-negative organisms, resistance patterns have been changing over recent years such that carbapenems and fourth-generation cephalosporins are used increasingly for problematic infections because of the new sensitivity patterns [25].

Anaerobes. Anaerobic bacteria now are rarely a cause of invasive infection in burns. The most common anaerobic organisms isolated are the *Bacteroides* and *Fusobacterium* spp. These are sometimes observed in myonecrosis secondary to electrical or crush injury when devascularized muscle is retained in a compartment. In these cases, broad-spectrum antibiotics should be given until sensitivities are available so that an appropriate drug can be given [26,27].

Fungi/yeasts. Colonization with fungi has become an increasing problem because the introduction of topical antimicrobials and liberal use of broad-spectrum antibiotics. This has resulted in a surge in invasive fungal infection, which has been linked to higher death rates regardless of the extent of the burn, coincident inhalation injury, or patient age [28]. In a recent review of 15 burn units, fungi were isolated at least once from 6.3% of 6,918 patients [29], with positive cultures being obtained most commonly from the wound itself followed by (in order of decreasing frequency) respiratory, urine, and blood specimens.

Candida albicans is the fourth most frequently found pathogen in blood cultures from ICU patients [30]. However, invasive infection with molds such as *Aspergillus* is correlated more closely with death [30]. Non-*albicans* *Candida* spp. are becoming an increasingly frequent cause of invasive

candidiasis, with their incumbent resistance to conventional antifungal agents such as fluconazole [31]. Recent guidelines list caspofungin (an echinocandin) as the treatment of choice in these cases [32]. The trend away from *C. albicans* also is worrying, as deep fungal infection associated with a higher mortality rate is associated with *C. tropicalis* and *C. krusei* [33,34]. *Aspergillus*, *Fusarium*, and zygomycetes (*Rhizopus* and *Mucor*) are isolated less often but have a far greater propensity for aggressive, invasive infection than do yeasts [35].

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 non-candidal infection, voriconazole is the first-line treatment followed by amphotericin B (lipid formulation). An echinocandin such as caspofungin can be considered for combination treatment of *Aspergillus* and *Fusarium* [23].

Viruses. Primary viral burn wound infection, although rare, certainly is possible. The most common cause is reactivation of latent infection because of the debilitated immunosuppressed state of the patient after a substantial injury. Herpes viruses, especially herpes simplex and varicella-zoster, have by far the greatest occurrence. The viral infections arising most frequently in healing burn wounds are caused by herpes simplex virus. These also can occur in donor sites. Typical patterns of vesicles are found at the edge of the wound, and these vesicles coalesce into a confluent raw area. Prompt treatment with both oral and topical antiviral therapies such as acyclovir should be continued for a minimum of 10 days.

Special considerations

In addition to obvious sources and areas of infection, there are other vulnerable tissues and organ systems in the burn patient that require special consideration. Those associated with indwelling catheters such as intravenous and intra-arterial lines and urinary catheters are paramount. These will be discussed, along with the respiratory and gastrointestinal systems.

Intravenous and intra-arterial catheters. Intravenous and intra-arterial catheters provide access to the blood, an essential route for delivery of resuscitative and pharmacologic therapy, which are crucial for treating burn patients. Regardless of aseptic technique practice, rates of catheter-associated infection and septic thrombophlebitis in the burn patient are as high as 57% [36–38].

Franchesi et al. [39] described a 50% correlation between the organisms cultured from the tip and the connectors of the catheter within 2 d of placement, and they found that a negative correlation existed between the frequency of catheter infection and the distance separating the point of catheter insertion and the burn wound. These data support the hypothesis that catheter infections arise primarily from burn wound contamination migrating to the catheter tip.

Serious complications often can be avoided by following strict aseptic techniques. General guidelines for protecting against catheter-related infections are as follows [40]:

1. Training healthcare staff on the correct procedures for inserting and maintaining catheters, including indications and suitable infection control practices;

2. Use of a mask, hat, gown, and sterile gloves and drapes during placement of central venous catheters (CVCs);
3. Use of 2% chlorhexidine to prevent infection;
4. Avoiding routine CVC changes;
5. In the event that infection continues while adhering to guidelines 1–3, use short-term CVCs coated with an antibiotic, antiseptic, or both.

Serial positive blood cultures without a sign of local infection should alert clinicians to suspect suppurative thrombophlebitis. In this case, it is necessary to remove the catheter promptly, and, if the diagnosis is confirmed, to perform urgent operative excision of the cannulated vessel to avoid progressive sepsis.

Genitourinary system. Hematogenous dissemination of bacteria and fungi can lead to urinary tract infections in the susceptible burn patient, but these organisms often are introduced via prolonged or unnecessary use of urinary catheters. If catheters are used under strict guidelines (e.g., aseptic techniques, catheter care, routine urine monitoring, and early removal), urinary tract infections can be avoided. When infection does occur, patients should be treated with appropriate systemic antibiotics and antifungal agents.

Respiratory tract. Respiratory tract infections are a major trigger of septic deaths after burns, second only to infection of burn wounds leading to septicemia. Pneumonia has two basic etiologies: Organisms can enter either through direct contamination of the airway or hematogenously. The organisms cultured usually are reflective of burn wound flora. The diagnosis of pneumonia is a clinical one and requires a chest radiograph showing two of the following: A new and enduring infiltrate, consolidation, or capitation [13]. In burn patients, sepsis is defined as a clinical deterioration in status and a change or purulence in the sputum. In the mechanically ventilated burn patient, close attention should be paid to ventilator-associated pneumonia, which is pneumonia appearing greater than two d after intubation in patients who showed no signs of pneumonia before this time.

Pneumonia should be diagnosed on the basis of the clinical picture in combination with two of these three criteria: A radiograph of the chest showing a new, persistent infiltrate, consolidation, or capitation; sepsis (as defined for burns); or a change or purulence in expectorated or aspirated sputum [1]. Sputum examination should include observations of the color, amount, consistency, odor, and gram staining.

Gastrointestinal system. Placement of a central venous catheter may be necessary for proper alimentary support. Placement through the burned tissue should be avoided. If unavoidable, the area should be cleansed daily and topical antibiotics applied. The catheter should be cultured routinely to identify any micro-organisms gaining entry via the surgical puncture wound.

The gastrointestinal tract also can serve as the chief source of infection after burn injury. In large burns, the abdomen often is involved, and this can lead to the perception of limitation during the clinical examination. The affected skin should not be allowed to interfere with a proper physical examination. Burn patients, like all patients, can suffer from,

and should be evaluated for, appendicitis, intussusception, and bowel obstruction. Intra-peritoneal dialysis may be necessary to aid compromised renal function and may also serve as a source of infection.

Clostridium difficile is a well-known opportunistic pathogen in severely ill individuals with a history of antibiotic use and in immunocompromised patients. Surveillance for the organism remains necessary, although its clinical observance may wane in the wake of the emergence of methicillin-resistant *Staphylococcus* and the use of intravenous vancomycin.

Burn patients also should be evaluated for necrotizing enterocolitis, with the classic presentation of high-spiking fevers accompanied by left upper-quadrant pain, referred pain in the left shoulder from the adjacent diaphragm, splenic hypertrophy, and tenderness. Diagnostic imaging should be performed, and broad-spectrum antibiotics with activity against streptococci and both aerobic and anaerobic gram-negative bacilli should be administered on confirmation of the infection.

Surveillance, sampling, and prevention

Burn wound cultures. Identifying and treating infections after burn injury has relied routinely on clinical impression and qualitative findings from surface swabs, although analysis of burn wound biopsies through quantitative bacteriology is needed to confirm burn wound infection and improves patient management and outcomes [41].

Historically, quantitative wound cultures have been utilized to monitor healing. Culturing the surface of burn wounds can help in determining whether pathogens are present; however, the results do not indicate wound status. It has been reported that death after burn injury correlates with the presence of $>10^5$ organisms/g of tissue or histologic signs of invasive infection [42].

Histologic analysis of burn wound biopsies is the only means by which microbial invasion can be identified definitively and invasive disease can be diagnosed. Quantitative culture is inadequate for detecting invasive infection. Therefore, histologic determinations of invasive infection should be paired with non-quantitative culture to identify pathogens and determine their sensitivity to antimicrobial agents. This approach will aid in diagnosis and guide choices for suitable interventions. One should keep the following points in mind:

- Early cultures should be negative or have low counts of sensitive gram-positive organisms. Positive cultures or high counts suggest early contamination of the burn wound.
- If invasive burn wound infection is suspected, wound culture and histologic analysis can aid in confirmation of the diagnosis.
- Routine culturing and identification of colonization may aid in empiric antimicrobial agent coverage if the patient subsequently becomes ill.
- Increasing colony counts may indicate a need to change topical antimicrobial agents.
- Not all organisms are created equal. Wound colonization with particularly virulent or resistant organisms may be a predictor of impending invasive burn wound infection.

- Operative wound colony counts $>10^6$ suggest a high risk of infectious complications and graft failure.
- Burn wound culture results may aid in the evaluation of nosocomial spread of organisms and guide infection control practice.
- Regular catheter changes—every 5 to 6 d for central catheters—can decrease the likelihood of catheter-related infections. The Nosocomial Infection Surveillance System of the U.S. Centers for Disease Control and Prevention has shown that CVC-derived primary infections of the blood stream occur at elevated rates in burn ICUs.

Summary

Developments in critical care and surgical approaches to treating burn wounds together with antimicrobial treatments have reduced significantly the morbidity and mortality rates associated with this injury. However, several resistant organisms have emerged as the maleficent cause of invasive infection, including MRSA, VRE, *Pseudomonas*, *Acinetobacter*, non-*albicans Candida* species, and *Aspergillus*. Advances in antimicrobial therapies and the release of new classes of antibiotics have certainly added to the armamentarium of resources for the clinician. Nevertheless, strict infection control measures, constant wound surveillance with regular sampling of tissues for quantitative culture, and early excision and wound closure remain the principal adjuncts to control invasive infection in burn patients.

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