Prevention and Management of Infections Associated With Burns in the Combat Casualty

Laurie C. D’Avignon, MD, Jeffrey R. Saffle, MD, Kevin K. Chung, MD, and Leopoldo C. Cancio, MD

Burns complicate 5% to 10% of combat associated injuries with infections being the leading cause of mortality. Given the long term complications and rehabilitation needs after initial recovery from the acute burns, these patients are often cared for in dedicated burn units such as the Army Surgical Research Unit (SRU). The initial focus of the microbiologist who later became the first Director of the US monograph was written by Dr. Champ Lyons, a surgeon and disease service (MCHE-MD), San Antonio Military Medical Center, 3851 Roger Brooke Drive, Fort Sames Healthcare beneficiaries, including Army, Navy, Air Force, and Marine personnel, arrive in the United States for definitive care on average 4 to 6 days after injury. During the course of an evacuation from Iraq or Afghanistan, patients transition through several medical facilities before arriving at a major US medical center.

The military uses a level-based evacuation system, in which injured personnel initially receive basic resuscitation and hemorrhage control by organic military medics (Level I). Some patients undergo initial medical therapy at facilities staffed by physicians or physician assistants (Level IIa). Casualties who require further care are transported to a facility that can provide initial surgical stabilization such as a forward surgical team (Level IIb) or more often a Combat Support Hospital (Level III) that contains surgical subspecialists and intensive care capabilities. Personnel who require ongoing care are transported to Landstuhl Regional Medical Center in Germany (Level IV) and from there are triaged to a major military medical center in the United States (Level V). In the case of thermal injury, patients are transferred to the United States Army Institute of Surgical Research (USAISR, the U.S. Army Burn Center). The criteria for evacuation of burn casualties. Areas of emphasis include antimicrobial prophylaxis, debridement of devitalized tissue, topical antimicrobial therapy, and optimal time to wound coverage.

Key Words: Combat, Trauma, Burns, Infection.

involving the hands, face, or perineum, evacuation to the USAISR burn center is crucial. In addition to surgical and nursing expertise, the USAISR provides the intensive physical, occupational therapy, and psychological support necessary for these patients.

Historically, burn wound infection has been the most common cause of death in the thermally injured patient. Fortunately, advances in care have led to a decline in the occurrence of burn wound infection. Complications such as ventilator-associated pneumonia and sepsis associated with the hands of health care workers. Microorganisms may also be transferred to the burn wound from contaminated surfaces, equipment, or on the hands of health care workers. Of the many bacterial microorganisms that colonize the burn wound surface shortly after injury, Staphylococcus aureus, Psuedomonas aeruginosa, Klebsiella pneumoniae, and Escherichia coli, colonize the wound within the first 24 to 48 hours after injury. Endogenous gram-negative bacteria from the patients’ respiratory and gastrointestinal tract, such as Pseudomonas aeruginosa, Klebsiella pneumoniae, and Escherichia coli, colonize the wound within the first 48 to 72 hours after injury. Microorganisms may also be transferred to the burn wound from contaminated surfaces, equipment, or on the hands of healthcare workers. Of the many bacterial microorganisms that colonize the burn wound surface shortly after injury, Staphylococcus aureus and Pseudomonas aeruginosa are the most likely to result in an invasive infection. This finding is in part a result of the array of virulence factors possessed by these organisms. In addition to these pathogens, the US military health care system has experienced an increased rate of multidrug-resistant Acinetobacter calcoaceticus-baumannii complex (Acb) infections in military personnel injured in Iraq and Afghanistan. A recent retrospective cohort study by Albrecht et al. found multidrug-resistant Acb to be a frequent cause of infection in burn patients. However, this infection was not found to independently affect mortality in this population.

Patients with burns are also subject to tetanus if inadequately immunized. Minor burn wounds have been associated with fatal tetanus in at least one case report. Therefore, tetanus immunization status of all burn patients should be determined. Tetanus immunization should be administered if the last booster was over 5 years ago (AII) (grading outlined in this supplement of Journal of Trauma—Guidelines for the

### Microbiology and Epidemiology of Burn Wound Infections

The microbial epidemiology of burn wound infections has evolved during the past 20 years, as use of topical antimicrobials, early burn wound excision, and definitive coverage with autograft have become standard practice. There is evidence to suggest that the incidence of bacterial burn wound infection has declined because of the practice of early excision and grafting, but data are inconclusive in the setting of large burns. A recent meta-analysis of all available randomized controlled studies found a reduction in mortality with early excision for all burn patients without an inhalation injury.

Although data are inconclusive, early excision and grafting has become standard practice in most US burn centers. This level of care is typically not available for military personnel injured in forward operating areas until they arrive at the USAISR. The transit time for seriously injured burn patients from time of injury to the USAISR averages 4 days and often includes stops at 2 to 3 medical facilities depending on the origin of the patient (unpublished data, LTC Evan Renz, October 2007). Therefore, knowledge of pre-excision burn wound flora is important to our understanding of the risks for burn wound infection in military personnel.

Most of the available data on the bacteriology of burn wound infections have been taken from studies performed before the practice of early excision and grafting. Although the incidence of infection has decreased, the list of offending microorganisms has not changed significantly. In the absence of topical antimicrobials, the immediate postburn period is characterized by rapid colonization of the injured tissue by resident microbial flora. Endogenous gram-negative bacteria from the patients’ respiratory and gastrointestinal tract, such as Staphylococcus aureus, Klebsiella pneumoniae, and Escherichia coli, colonize the wound within the first 24 to 48 hours after injury. Endogenous gram-negative bacteria from the patients’ respiratory and gastrointestinal tract, such as Pseudomonas aeruginosa, Klebsiella pneumoniae, and Escherichia coli, colonize the wound within the first 48 to 72 hours after injury. Microorganisms may also be transferred to the burn wound from contaminated surfaces, equipment, or on the hands of healthcare workers. Of the many bacterial microorganisms that colonize the burn wound surface shortly after injury, Staphylococcus aureus and Pseudomonas aeruginosa are the most likely to result in an invasive infection. This finding is in part a result of the array of virulence factors possessed by these organisms. In addition to these pathogens, the US military health care system has experienced an increased rate of multidrug-resistant Acinetobacter calcoaceticus-baumannii complex (Acb) infections in military personnel injured in Iraq and Afghanistan. A recent retrospective cohort study by Albrecht et al. found multidrug-resistant Acb to be a frequent cause of infection in burn patients. However, this infection was not found to independently affect mortality in this population.

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Prevention of Infection After Combat-Related Injuries). Tetanus vaccination plus anti-tetanus immunoglobulin should be administered to patients who have no history of vaccination (AII). Booster vaccination should be administered at 4 weeks and 6 months for the later group.

Yeasts, such as Candida species, and filamentous fungi, such as Aspergillus species, have far outpaced bacterial pathogens as the most common cause of invasive burn wound infection since the introduction of topical antimicrobial agents.16,20 Candidal colonization of burn wounds is more common than invasive disease and may arise from an endogenous or exogenous source.28–30 The filamentous fungi are uniformly acquired from an exogenous environmental source and are much more likely to cause invasive disease than the Candida species.28–32 The filamentous fungi commonly associated with burn wound sepsis include Aspergillus sp., Fusarium sp., and members of the Mucorales order of the Zygomycetes.33 There have also been case reports of invasive wound infection because of a variety of dematiaceous fungi such as Curvularia sp.34 Infections caused by the filamentous fungi prove difficult to diagnose in the absence of a biopsy with interpretation by a skilled pathologist. A recent retrospective analysis of patients with thermal burns admitted to the USAISR found that fungal burn wound infection is an independent predictor of mortality in patients with total body surface area (TBSA) 30% to 60%.30 Fungal pathogens typically become a concern later in the treatment course after patients have undergone surgery and received broad spectrum antibacterials, and should not be a frequent cause of infection in the first few days after injury.20,28

Viral infection of burn wounds is rarely reported but does occur. Members of the herpes virus family, including herpes simplex virus and varicella zoster virus, are the most common culprits.32,35 Cutaneous disease typically occurs in healing partial thickness burns and donor sites.36 Cutaneous infection follows a benign course if recognized and treated early with topical therapy. Fortunately, invasive disseminated herpes simplex virus or varicella zoster virus is a rare occurrence in the burn patient, but should be considered in the patient with cutaneous disease and findings of concomitant pneumonitis, hepatitis, or meningitis as these patients will require systemic therapy.32,35

**Prevention of Infection**

The primary measures employed to prevent infection in the thermally injured patient are topical antimicrobials, early excision with coverage and good infection control measures. It should be noted that the availability of these measures will vary depending upon the location of the patient within the military hierarchical system.

Wound care, in the form of topical antibiotics and early excision with coverage, has been associated with a significant decline in the incidence of invasive burn wound infection.14,37–39 The use of topical antimicrobials across all levels of care is feasible, whereas excision and coverage is typically available only at Levels III to V. First degree and superficial partial thickness burns may also be treated with topical antimicrobials and daily dressing changes (AII).37–39 The use of temporary bio-synthetic materials such as Biobrane is also an option for superficial partial thickness burns (BII).40–42 Deep partial thickness and full thickness burns should be treated with topical antibiotics and twice daily dressing changes followed by excision and grafting (AII).10–14,37–39 Ideally, excision and autografting should be performed at a burn center; however, if definitive surgical care must be accomplished in theater, it should be performed at a Level III facility by experienced personnel (CIII). Management recommendations based on burn severity are summarized in Table 2.

The importance of wound care—both at the time of initial debridement and thereafter—cannot be overemphasized. Wound care should be directed at thoroughly removing devitalized tissue, debris, and previously placed antimicrobials. A broad-spectrum surgical detergent such as chlorhexidine gluconate should be used (CIII). Adequate analgesia (e.g., with frequent small doses of intravenous narcotics or ketamine), along with preemptive anxiolysis (e.g., with a preprocedure oral benzodiazepine), are necessary to permit adequate wound care. Except when silver dressings or Biobrane are used, wound care should be repeated twice daily (CIII). However, we recognize that in the deployed environment, it may be possible to do thorough wound care only once daily.

The most commonly employed topical antimicrobials for the prevention and treatment of burn wound infection are mafenide acetate, silver sulfadiazine, silver nitrate solution, and silver-impregnated dressings.37–39,43

**Mafenide Acetate**

Mafenide acetate (Sulfamylon) was first introduced in 1964.37 A retrospective study comparing USAISR patients treated in the pre-mafenide era (1962–1963) with those

<table>
<thead>
<tr>
<th>Wound</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree</td>
<td>Symptomatic care</td>
</tr>
<tr>
<td>Superficial partial thickness</td>
<td>Topical antibiotics with twice daily dressing change</td>
</tr>
<tr>
<td>Deep partial thickness</td>
<td>Topical antibiotics with twice daily dressing change</td>
</tr>
<tr>
<td>Full thickness</td>
<td>Topical antibiotics with twice daily dressing change</td>
</tr>
</tbody>
</table>

### Table 2 Management of Burn Wounds Based Upon Depth

<table>
<thead>
<tr>
<th>Wound</th>
<th>Interventions</th>
</tr>
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<tbody>
<tr>
<td>First degree</td>
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treated after the introduction of mafenide found a decrease in overall burn mortality from 38% to 20%, and a reduction in the rate of invasive burn wound infection from 22% of admissions to 2%.37

Mafenide acetate is available as an 11% water-soluble cream composed of α-amino-p-toluenesulfonamide monooctate. Despite the name, it is functionally a non-sulfonamide antibiotic. It rapidly penetrates full thickness eschar and exerts a broad antibacterial effect.44 In vitro and animal studies have demonstrated mafenide acetate to have efficacy against Staphylococcus and Pseudomonas species.45,46 Although resistant strains of Providencia and Enterobacter developed at the USAISR in the late 1960s, none of the nearly 8,500 strains of P. aeruginosa isolated from USAISR burn patients during the period 1967 to 1992 were resistant to clinically relevant concentrations of the drug.47

There are some drawbacks to the use of mafenide acetate. It has no efficacy against filamentous fungi. It is painful on application, a consequence of its otherwise desirable ability to penetrate eschar and reach viable tissue. The drug and its primary metabolite (p-carboxybenzenesulfonamide) are inhibitors of carbonic anhydrase and metabolic acidosis has been reported in patients with extensive burns treated twice daily.48 Patients with inhalation injury are at greater risk of this if their pulmonary dysfunction limits respiratory compensation.48 This may pose a problem given that concentrations of the drug in eschar drop below therapeutic levels approximately 10 hours after application, necessitating twice daily dosing unless a second agent is also used.44 One common practice at USAISR is to apply mafenide acetate in the morning and silver sulfadiazine 12 hours later to realize the benefits of both drugs while limiting the toxicities.47

Mafenide acetate is also available in powder form for reconstitution as a 5% aqueous solution. This solution is used to moisten gauze dressings and is indicated for topical treatment of wounds after skin grafting. In addition, we often use this solution, along with twice daily gauze dressing changes, for the topical treatment of deep partial thickness burns of limited extent. However, it was less effective than mafenide acetate cream in prevention of death in a murine model of Pseudomonas burn wound infection.49

Silver Sulfadiazine

Silver sulfadiazine (Silvadene, Thermazine, Flamazine, SSD, Burnazone) is available as a 1% water soluble cream. It was developed in 1968 by complexing silver nitrate and sulfadiazine.46,50 Previously, sulfadiazine alone had been used as a topical agent but the development of resistance became an issue. Complexing sulfadiazine with silver nitrate has largely overcome the resistance problem, and the agents appear to act synergistically. In essence, the complex acts as a slow-release formulation of silver cation.51,52 Much like mafenide acetate, silver sulfadiazine exhibits activity against gram-negative and gram-positive organisms; however, unlike mafenide it has poor eschar penetration.46,51,52 The advantages of silver sulfadiazine are that it is relatively painless on application and it has some activity against Candida species, but not against filamentous fungi. Rarely, a decrease in the neutrophil count has been observed with initiation of therapy, and has been attributed to depression of granulocyte-macrophage progenitor cells in the marrow.50 This effect typically resolves even when the agent is continued and rarely necessitates discontinuation of therapy.50

Silver Nitrate Solution

Silver nitrate (AgNO3) solution was first introduced in 1964 as topical prophylaxis against burn wound infection. It had been previously used as a 10% solution that was found to be tissue toxic.52 It is now used as a 0.5% aqueous solution, a concentration at which it is not toxic to regenerating epithelium.43,52 Burn wounds are dressed with multiple, thick layers of coarse mesh gauze, to which the silver nitrate solution is frequently reapplied to keep the gauze continuously moist.47 Much like silver sulfadiazine, it exhibits activity against gram-positive bacteria, gram-negative bacteria, and Candida. The major drawbacks to silver nitrate solution is that it has poor penetration of eschar, requires the use of occlusive dressings, and turns black upon contact with tissues.52 Dressings must be changed twice daily to prevent buildup of exudate or of tissue-toxic levels of the silver nitrate. The need for continuously moist dressings means that patients with large wounds are at risk of hypothermia, particularly during transport or in general hospital rooms. Another drawback to this drug is the depletion of cations caused by leeching across the open wound into the hypotonic solution. This phenomenon may result in hypotension, hypocalcemia, hypokalemia, and hypomagnesemia; therefore, close monitoring of electrolytes is necessary.43

Silver-Impregnated Dressings

A variety of dressings impregnated with elemental silver have been recently approved by the Food and Drug Administration (FDA) as topical therapy for burns. Numerous formulations of these dressings are now available, but it is unknown if they are equivalent in silver delivery and antimicrobial efficacy. Some examples of available silver dressings include Silverlon (Argentum LLC, Willowbrook, IL) and Acticoat (Smith and Nephew, Hull, United Kingdom). Silverlon is a knitted fabric composed of pure nylon-base fibers, covered uniformly and circumferentially with a thin coat of metallic silver. Alone and in combination with weak direct current, silver nylon has been shown to be effective in a lethal Pseudomonas murine model.53 Acticoat is a rayon/polyester core encased in a dense polyethylene mesh coated with nanocrystalline silver. Tredget et al. have reported Acticoat to be more effective then silver nitrate solution with respect to preventing heavy burn wound colonization (105 organisms per gram of tissue).54 Both Acticoat and Silverlon are approved for use in superficial and partial thickness burns and can be left in place for several days (at least 3, and possibly
which Biobrane is appropriate for clean partial thickness burns. This, and similar products, act as a wound barrier and prevent evaporative losses but have no intrinsic antimicrobial properties. \(^46\) Integra, a bilaminar product (inner dermal analog of chondroitin-6-sulfate and collagen; outer temporary epidermal analog of silicone) should only be used by experienced surgeons in a burn center.

As previously noted, surgical excision is normally not performed in the combat zone because it is labor and supply intensive, and because optimal outcomes require the multidisciplinary capabilities present only in a burn center. However, definitive surgical care for local nationals may be required in the combat zone. This should be performed by qualified individuals at Level III facilities, \(^61\) recognizing that the situation is far from ideal.

### Excision and Grafting

Early excision of burned tissue and coverage with skin grafts or skin substitutes has been associated with a decrease in mortality in several studies. \(^13,14,18\) The beneficial effect of this practice on mortality is likely multi-factorial, with a decreased incidence of wound infection \(^16\) and with the removal of devitalized tissue as a stimulus for the inflammatory process both likely playing a role. The definition of “early” has not been definitively established. Studies have variably defined early excision as that performed either at admission or up to 5 days after injury. \(^13,14,18,59\)

Excision and grafting is indicated for deep partial thickness burns and for full-thickness burns. The accurate assessment of burn depth is challenging, and it is often difficult to predict the ultimate fate of a burn within hours to days of injury. In fact, some burns may progress from partial to full thickness during a period of days. \(^60\)

If excision is performed, the entire burn wound may be excised in a single procedure or in serial procedures performed during the course of several days. \(^46\) Definitive coverage requires the application and successful integration of autograft. If sufficient autograft is not available, options for temporary wound coverage after excision include biological and synthetic coverings. Temporary biological dressings consist of allografts and xenografts. Allografts may be used to protect an excised wound, or as an overlay to protect an excised wound after application of widely meshed (e.g., 3:1, 4:1) autograft. Fresh allograft may be available in the United States, but more often is frozen. A shelf-stable allograft product, GammaGraft, has been used in the combat zone during OIF. \(^9\) Xenografts (such as pig skin) are typically used as temporary coverage of wounds expected to heal. \(^60\) Temporary synthetic skin substitutes are also commonly used. There are several brands of synthetic coverings available, of which Biobrane is appropriate for clean partial thickness

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### Table 3 Topical Antimicrobial Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Application</th>
<th>Penetration</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mafenide Acetate</td>
<td>Apply 1/16” layer twice daily*</td>
<td>Penetrates eschar</td>
<td>Painful on application</td>
</tr>
<tr>
<td>Silver Sulfadiazine</td>
<td>Apply 1/16” layer twice daily*</td>
<td>Poor eschar penetration</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Silver Nitrate Solution</td>
<td>Dress wounds with multiple layers of coarse gauze and apply solution to keep gauze continuously moist</td>
<td>Poor eschar penetration</td>
<td>Transient leukopenia</td>
</tr>
<tr>
<td>Acticoat † or Silverlon †</td>
<td>Moisten dressing with sterile water (not saline), cut to size, secure to wound with secondary dressing, change in 3–7 d</td>
<td>Poor eschar penetration</td>
<td>Discolors wound bed Electrolyte disorders</td>
</tr>
</tbody>
</table>

* Commonly, alternate mafenide in the morning with silver sulfadiazine in the evening.
† Application information obtained from package insert.

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as many as 7 days) (BII). This offers significant advantages, particularly for the treatment of wounds sufficiently small that outpatient or ward care are reasonable option (AII). \(^35\) The method of application for each of the topical agents is summarized in Table 3.

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### Systemic Antibiotic Prophylaxis

Use of prophylactic systemic antibiotics is now well accepted in a wide variety of settings, including the performance of many surgical procedures. But in the treatment of burns, use of systemic antibiotics for prophylaxis of subsequent burn wound infection has not been proved effective. Early use of antibiotics such as penicillin and erythromycin aimed at controlling outbreaks of Streptococcus have been anecdotally observed to be associated with an increase in infections caused by multiply-resistant Staphylococci, \(^62\) though this has not been found uniformly. \(^56\) However, no study has demonstrated a reduction in burn wound infections with the use of prophylactic antibiotics, and at least one has shown an increased incidence of infections from gram-negatives, including Pseudomonas. \(^63\) The only exception to this might be found in the use of antibiotic prophylaxis against Staphylococcal toxic shock, which can be a problem in pediatric burn care, \(^64\) although this remains controversial. Therefore, routine systemic antimicrobial prophylaxis in the burned patient is not indicated for rapid or delayed evacuation (EII) and there are insufficient data to recommend for or against its use in patients with concomitant inhalation injury (CII). In the event that a burn patient suffers from concomitant traumatic penetrating injury or fracture, antibiotic prophylaxis should be administered as recommended for that injury.
Antibiotic prophylaxis has also been examined in burn surgery. Few studies have supported the use of systemic antibiotics during acute burn surgery. Antibiotics appear to be of no value in the prophylaxis of wound infections accompanying surgery for small to moderate burns. Early studies documented a significant incidence of transient bacteremia associated with wound manipulation, but a more recent evaluation showed this incidence to be much reduced. Antibiotic administration may reduce the incidence of this transient bacteremia, but this does not affect outcomes. Antibiotic prophylaxis was of some benefit in one early study of reconstructive surgery, but this has not been replicated. Despite fairly clear evidence on this topic, units continue to vary widely in their practices of providing perioperative antibiotic prophylaxis, and a number of centers continue to administer antibiotics for every procedure which involves wound manipulation. Given the lack of benefit, routine predebridement antibiotic prophylaxis of burns <40% TBSA is not recommended. It is important to note that few data have been compiled on surgical prophylaxis of patients with massive (≥40% TBSA) burns. Therefore, preoperative prophylaxis with a single dose of an intravenous antibiotic effective against resident flora can be considered pending further data.

It is crucial to note that systemic antibiotic therapy is clearly indicated in the surgical treatment of infected burn wounds, and this may necessitate empiric treatment of many patients with large open wounds and evidence of infection. Many patients with large burns develop symptoms such as fever and elevated white blood cell count—as a consequence of the systemic response to injury, rather than infection—further complicating decisions regarding the use of antibiotics.

**Infection Control**

Burn patients are highly susceptible to wound infection, pneumonia, and bacteremia because of the loss of the barrier function of skin, the immune dysregulation that accompanies severe burn injury, and the requirement for invasive procedures such as endotracheal intubation and central venous catheter placement. Endogenous organisms account for early colonization of burn wounds but later colonization with drug-resistant bacteria is primarily the result of nosocomial transmission via contaminated equipment or on the hands of health care workers.

As a means of detecting these organisms, some centers strongly advocate obtaining routine surveillance cultures of burn wounds, sputum, urine, and even stool as often as three times weekly. These techniques are widely used in the United States, but little data exist to support this labor-intensive and expensive practice. The likelihood of obtaining positive cultures from biopsy is dependent on burn wound size, but no burn size-specific criteria for surveillance cultures have been developed. An aggressive surveillance regimen may be indicated in cases of epidemics of specific infections, sometimes even including staff members, to detect "carriers" of such organisms as methicillin-resistant *S. aureus* (MRSA) and drug-resistant gram-negatives.

The environment surrounding the burn patient is an important factor in the risk for infection. Several studies in burn units have demonstrated that hand hygiene compliance, isolation rooms, and environmental cleaning reduced outbreaks with drug-resistant organisms (AII). A particular problem faced by the US military has been outbreaks of wound infections caused by drug-resistant **Acb** in personnel injured in OIF/OEF. Data form OIF indicate that soldiers became colonized with the organism after entry into a Level III facility and not at time of initial injury, thus suggesting that a breakdown of infection control measures played a significant role. The Centers for Disease Control and Prevention and the Society for Health Care Epidemiology have released general infection-control guidelines for the hospital setting; however, there are currently no guidelines that specifically address infection control practices in the burn unit. Until further data are available we must rely on general infection-control guidelines.

**Diagnosis of Infection**

Although burn treatment methods have greatly reduced the incidence of invasive burn wound infections, these still occur, and can represent life-threatening problems for the burn patient. Clearly, the most important method of detecting burn wound infection is the routine (at least daily) close inspection of all burn wounds by experienced personnel. Several types of infection, including cellulitis, invasive infection, impetigo, and others, can be distinguished by routine examination, and used as an indication to obtain cultures and/or begin empiric antibiotic therapy.

On the other hand, major thermal injury epitomizes the systemic inflammatory response syndrome. Consequently, systemic signs of infection such as fever and elevated white blood cell count are notoriously unreliable in burn patients. In burn patients, occurrence of hyperglycemia, or worsening of previously-stable blood sugar control, have been shown to correlate with increased incidence of severe infection, and may be considered an indication to search for an infectious source.

**Culture Technique**

A variety of techniques for both surveillance and directed burn wound cultures have been advocated. Surface swab cultures frequently demonstrate bacterial growth, but this often reflects colonization without invasive infection, and correlation with more definitive methods is poor. For these reasons, surface swab cultures should not be performed for diagnosis of infection (DII). For many years, quantitative cultures of burn wound biopsies have been used to diagnose burn wound infections, with cultures growing greater than or equal to 10⁵ organisms/gram considered "positive". Quantitative cultures of wound biopsies are somewhat more specific than swab cultures, but have a number of limitations. Among them is the finding that clinically septic patients often have far higher density of bacterial counts, sometimes as much as
10^{11} organisms/gram. In addition, quantitative cultures are costly and time-consuming, with low rates of positive cultures in many patients. Because such cultures represent a random “sample” from a single site, they may miss significant infection in adjacent wounds. Both false-positive and false-negative results are possible, further limiting their correlation with systemic infection.

In addition, quantitative cultures have not been shown to correlate well with histopathologic examination of wounds, nor do they predict outcome of grafting or other procedures. As a result, quantitative cultures are advocated largely to detect and identify the sensitivities of predominant wound microflora. Therefore, quantitative cultures can be considered for this purpose in Levels III–V facilities with microbiology capabilities in an attempt to guide antibiotic therapy (CIII).

The use of burn wound histopathology to detect microorganisms penetrating beneath burn eschar into viable tissue has long been considered the “gold standard” for diagnosis of invasive burn wound infection/sepsis. This method differentiates colonization from invasion based upon the location of the microorganisms within the wound (Table 4) and is the diagnostic modality of choice for burn centers. However, this technique requires technology and unique expertise and therefore, cannot be recommended for use in theater (CIII). Experimental techniques such as rapid polymerase chain reaction assays may be promising, but await clinical confirmation.

There seems to be little disagreement that cultures are indicated in cases of specific infections. Indications for obtaining surveillance blood cultures seem to be less clear. Burns have been identified as a high-risk group for bacteremia. Positive blood cultures have been detected during routine surveillance programs in burn patients after burn wound excision; in this circumstance, bacteremia is more commonly found in patients with large (>40% TBSA injuries), and in procedures performed more than 10 days after injury. However, routine blood culture surveillance in the absence of systemic signs of sepsis has had poor yield and is not recommended.

Even in patients with positive wound cultures, indications for treatment are not entirely clear. For example, the recovery of Candida sp from burn wounds is specifically mentioned as an indication for systemic anti-fungal therapy by some. Other authors state that invasive Candida infections are rare, whereas wound cultures showing filamentous fungi more frequently indicate invasive infection, and should be treated. It should be noted that cultures alone are inadequate for diagnosis of wound infections because of filamentous fungi, as many of the causative organisms are more likely to be seen on histopathology and correlation between the two methods is inconsistent. Recommendations for diagnosis of burn wound infection across the levels of care are summarized in Table 5.

### Treatment of Infection

Burn wound infection is highly lethal, and urgent surgical excision of infected tissue, as soon as possible after resuscitation and institution of appropriate antimicrobials, is the most effective method of controlling burn wound infection. Such excision should be sufficiently radical to extirpate all involved tissue; thus, excision to fascia is frequently required. When infection is suspected, samples of the debrided tissue should be sent for histopathologic examination (if available) as well as for bacterial and fungal culture. Initial systemic antimicrobial therapy should be broad with tailoring of therapy based upon results of histology and culture of infected tissue and blood. Given that S. aureus, P. aeruginosa are the most common bacterial cause of burn wound infections, empiric treatment regimens should cover these organisms. Level III to V facilities report antibiotic resistance profiles in quarterly antibiograms, which enables the local resistance profiles, to include the presence of extended beta-lactamase producing isolates, to be taken into consideration when choosing empiric antibiotic therapy. Appropriate agents for empiric therapy include piperillin-tazobactam.

### Table 4 Histopathologic Classification of Burn Wound Infection

<table>
<thead>
<tr>
<th>Stage</th>
<th>Grade</th>
<th>A. Superficial colonization: microbes present on burn wound surface</th>
<th>B. Microbial penetration: microbes present throughout eschar</th>
<th>C. Subeschar proliferation: microbes multiplying beneath eschar</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Colonization of nonviable tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II: Invasion of viable tissue</td>
<td>A. Microinvasion: foci of microbes in viable tissue immediately beneath eschar</td>
<td>B. Generalized invasion: multifocal or diffuse penetration of microbes into viable tissue</td>
<td>C. Microvascular invasion: microbes present in unburned blood vessels and lymphatics</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5 Diagnosis Procedures of Burn Wound Infection Based Upon Evidence-Based Recommendations and Level of Medical Care

<table>
<thead>
<tr>
<th>Diagnostic Measure</th>
<th>Level I/IIA</th>
<th>Level I/IB/II</th>
<th>Level IV</th>
<th>Level V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily wound inspection</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>All</td>
</tr>
<tr>
<td>Surface swab culture</td>
<td>NA</td>
<td>DII</td>
<td>DII</td>
<td>DII</td>
</tr>
<tr>
<td>Biopsy and quantitative culture</td>
<td>NA</td>
<td>CII</td>
<td>CII</td>
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<td>Biopsy and histology</td>
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NA, not applicable.
or anti-pseudomonal cephalosporin, plus or minus an aminoglycoside. If extended beta-lactamase-producing organisms are a concern, anti-pseudomonal carbapenem plus or minus an aminoglycoside is the treatment of choice. Antibiotic therapy should be narrowed once histology and culture results are available to avoid overuse of broad-spectrum agents.

Prompt excision of infected tissues, administration of systemic antimicrobials, and topical antimicrobials are clearly the mainstays of therapy. In the event that surgical intervention is delayed, subeschar clysis with an antipseudomonal penicillin can be considered, though data are limited (CIII). The procedure described by McManus et al. consists of suspending one-half of the total daily dose of a semisynthetic penicillin (such as piperacillin) in a sufficient volume of crystalloid solution to treat the entire infected area. The solution is injected into the sub-eschar tissue using a No. 20 spinal needle. This procedure is repeated twice daily. Other authors have recommended sub-eschar injection of the full daily dose once a day. There are no data to suggest superiority of one approach over another at this time. Recommendations for initial management of wound infections are summarized in Table 6.

Fungal pathogens are also a concern, and therapy of fungal infections has become more interesting with the introduction during the past decade of several new anti-fungal agents, such as voriconazole, posaconazole, and the echinocandins. Given that Aspergillus sp are the most common cause of invasive fungal burn wound infections, it is reasonable to direct anti-fungal therapy at this organism pending definitive identification.

It is important that aggressive attempts be made to identify the fungal pathogen to the species level as not all species of Aspergillus are sensitive to amphotericin formulations. For example, A. terreus is inherently resistant to amphotericin. In addition, less common but potential pathogens such as the Zygomycetes are resistant to voriconazole.

CONCLUSIONS

The occurrence of invasive burn wound infection has decreased with the widespread use of early excision and grafting, topical antimicrobials, and the implementation of strict infection control measures in most centers. However, the unique and often austere environment encountered in the combat zone raises the issue of how best to prevent infection in injured military personnel. Wound care and the use of prophylactic, topical antimicrobials should occur as soon as possible in the evacuation process. The use of systemic antimicrobials should be avoided during the evacuation process to minimize selective pressure for resistant organisms. The recommendations offered by this article will certainly evolve, along with our knowledge of the unique risks posed to the burn patient receiving initial care in the combat environment.

REFERENCES


