Infections in Burns

4

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4.1 Burn Wound Infections

4.1.1 Diagnosis and Treatment of Burn Wound Infections

4.1.1.1 Introduction

Infections remain a leading cause of death in burn patients. This is as a result of loss of the environmental barrier function of the skin predisposing these patients to microbial colonization leading to invasion. Therefore, reconstitution of the environmental barrier by debriding the devitalized tissue and wound closure with application of allograft versus autograft is of optimal importance.

Given that infections are a common complication of the thermally injured patient, early diagnosis and treatment are of paramount importance. The pathophysiological progression of burn wound infection runs the spectrum from bacterial wound colonization to infection to invasive wound infection. The characteristics of each are as follows:

- *Bacterial colonization*
  - Bacterial levels $<10^5$
  - Does not necessarily prevent wound healing
- *Bacterial infection*
  - Bacterial levels $>10^5$
  - Can result in impaired wound healing and graft failure
  - Can lead to systemic infection
- *Invasive wound infection*
  - Clinically can have separation of the eschar from wound bed
  - Appearance of focal dark brown, black, or violaceous discoloration of the wound [1]

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Table 4.1 Common pathogens of burn wound infection

Organism	Common species
Gram-positive bacteria	*Staph* and *Strep* species
Gram-negative bacteria	*Pseudomonas aeruginosa, Acinetobacter baumannii, E. coli, Klebsiella pneumoniae, Enterobacter cloacae*
Yeast	*Candida sp*.
Fungi	*Aspergillus, Penicillium, Rhizopus, Mucor, Rhizomucor, Fusarium,* and *Curvularia*—have greater invasive potential
Virus	HSV, CMV
Multiresistant bacteria	MRSA, VRE, MDR *Pseudomonal* and *Acinetobacter* species

- Presence of pyocyanin (green pigment) in subcutaneous fat
- Erythema, edema, pain, and warmth of the surrounding skin
- Associated with signs of systemic infection/sepsis and positive blood cultures

Of note there are particular clinical signs unique to fungal and viral infections. An unexpected and rapid separation of the eschar is characteristic of fungal infection [2], while vesicular lesions caused by HSV-1 can be found in healed or healing burn wounds [3].

4.1.2 Common Pathogens and Diagnosis

In general the organisms causing burn wound infection/invasion have a chronological appearance. Initially, Gram-positive organisms are commonplace, while Gram-negative organisms become predominant after 5 days post-burn injury. Yeast and fungal colonization/infection follow, and finally multiresistant organisms appear typically as result of broad-spectrum antibiotics or inadequate burn excision or patient response to therapy [4].

As part of infection surveillance of burn patients, clinicians need to pay close attention to clinical signs of wound infection and rapidly confirm their diagnosis. There is some controversy as to the exact method of diagnosis, with some advocating for quantitative cultures—with $>10^5$ organisms per gram tissue being diagnostic of invasive infection [5]—and others arguing for histological examination as the only reliable method of determining invasive infection [6–9] since quantitative cultures are only positive in 50 % of histological invasive wound infections [9]. The most common pathogens of burn wound invasion are MSSA, MRSA, and *Pseudomonas aeruginosa* species (Table 4.1).

In order to provide the thermally injured patient with adequate treatment, it is important to have knowledge of each institution's bacterial flora as they vary with geography and over time [10, 11].

Fungal infections have increased in frequency with the use of topical agents, and the incidence of mycotic invasions has doubled. Even though the burn wound is the

Table 4.2 Topical agents and the antimicrobial activity

Agent	Affective against
Silver sulfadiazine	Gram-positives, gram-negatives, yeast
Mafenide acetate (5 %)	Gram-positives, gram-negatives
Silver nitrate (0.5 %)	Gram-positives, gram-negatives, yeast, fungi
Acetic acid (0.5 %, 2 %)	Gram-positives, gram-negatives, pseudomonas at higher concentration
Dakin's solution (0.25 % or 0.5 % sodium hypochlorite)	Gram-positives, gram-negatives, yeast, fungi
Acticoat	Gram-positives, gram-negatives, yeast, fungi, MRSA, VRE

most commonly infected site, there is an increasing trend toward systemic and organ-specific fungal infections [12].

The diagnosis of fungal infection is complicated by delay in their identification as cultures typically require 7–14 days [13], and their clinical presentation is similar to low-grade bacterial infections. Diagnosis can be aided by arterial blood samples as well retinal examination.

4.1.3 Clinical Management

Early excision and wound coverage is the mainstay of modern burn care and best method of minimizing burn wound infection. Any delay in the surgical treatment of burn wounds leads to increased bacterial loads, and any wound with bacterial counts exceeding 10^5 organisms per gram of tissue can develop burn wound sepsis even after burn wound excision [9].

The treatment of burn wound infections involves both local and systemic therapy.

4.1.3.1 Local

- Early excision of burn eschar (for un-excised burns)
- Aggressive excision of necrotic/infected tissue
- Topical agents (Table 4.2) to minimize bacterial colonization [14]

The use of any particular topical agent should be based on suspected organism in the wound but is at times guided by the availability of the agent on hospital formulary. These are not substitute for aggressive surgical management of wound infections.

4.1.3.2 Systemic

- Use of antibiotics and antifungals should be reserved for patients demonstrating systemic signs of sepsis (see ABA criteria for definition of sepsis (Box 4.1)).
- Use of systemic prophylaxis can reduce the rate of surgical wound infections but can increase bacterial antimicrobial resistance [15].
- The choice of antimicrobials needs to be based on each institution's antibiogram and tailored specifically to the organism (Table 4.3), i.e., narrow the coverage as soon as sensitivities become available.

Table 4.3 Ross Tilley Burn Centre guidelines for empiric antibiotic therapy

Early phase (*<5 days*)
The most common pathogens (from any source) in the *early* phase of a patient's admission are:
Gram-positive
Staphylococcus aureus (~90 % susceptible to cloxacillin)
Gram-negatives (95 % susceptibility to ceftriaxone)
H. influenza
E. coli
Klebsiella spp.
Based on this data, septic patients admitted within the past 5 days should be started on an empiric regimen of:
Ceftriaxone 1 g IV q24 h
+/− Cloxacilliin 1–2 g IV q4–6 h (renal dosing required)
Penicillin allergy
Levofloxacin 750 mg IV/PO q24 h
Late phase (*>5 days*)
The most common pathogens (from any source) in the *late* phase of a patient's admission are:
Gram-positive
Staphylococcus aureus (only ~60 % susceptible to cloxacillin)
Gram-negative (generally more predominant in the late phase)
Pseudomonas aeruginosa (>80 % susceptible to piperacillin/tazobactam)
Based on this data, septic patients admitted 5 days or more should be started on an empiric regimen of:
Piperacillin/tazobactam 4.5 g IV q6 h (renal dosing required)
+ Vancomycin 1 g IV q12 h (with pre- and post-levels around the third dose)
Or
Meropenem 500 mg IV q6 h (renal dosing required)

- Yeast species (*Candida*) are typically sensitive to fluconazole, while fungal infections would most likely require treatment with amphotericin or caspofungin (the use is for systemic infection, as wound infections require surgical debridement).
- Viral infections (typically HSV) require treatment with acyclovir.

Box 4.1 ABA Criteria for Definition of Sepsis [16]

Includes at least three of the following:

Temperature >39° or <36.5 °C

Progressive tachycardia

- Adults >110 bpm
- Children >2 SD above age-specific norms (85 % age-adjusted max heart rate)

Progressive tachypnea
- Adults >25 bpm not ventilated. Minute ventilation >12 L/min ventilated
- Children >2 SD above age-specific norms (85 % age-adjusted max respiratory rate)

Thrombocytopenia (will not apply until 3 days after initial resuscitation)
- Adults <100,000/mcl
- Children >2 SD below age-specific norms

Hyperglycemia (in the absence of preexisting diabetes mellitus)
- Untreated plasma glucose >200 mg/dL or equivalent mM/L
- Insulin resistance—examples include:
  - >7 units of insulin/h intravenous drip (adults)
  - Significant resistance to insulin (>25 % increase in insulin requirements over 24 h)

Inability to continue enteral feedings >24 h
- Abdominal distension
- Enteral feeding intolerance (residual >150 mL/h in children or two times feeding rate in adults)
- Uncontrollable diarrhea (>2,500 mL/day for adults or >400 mL/day in children)

In addition, it is *required* that a documented infection (defined below) is identified:
- Culture-positive infection
- Pathologic tissue source identified
- Clinical response to antimicrobials

Infections of burn wounds are typically found in patients with burns exceeding 20 % TBSA and most commonly in the lower extremities [17]. However, there are no specific organisms associated with the site of infection [17]. Moreover, these infections can have dire consequences:
- Conversion of superficial to deeper burn wounds
- Systemic infection and sepsis
- Graft loss requiring further surgery for regrafting
- Increased hospital length of stay
- Conversion of donor sites requiring surgical debridement and grafting
- Increased mortality, more so with yeast and fungal infection

4.1.4 Conclusion

Burn wound infection is an all too common complication of the thermally injured patient. These infections tend to have a chronological appearance and depend on burn size, depth, length of hospital stay, and geographical location. The common organisms remain *Staphylococcus* and *Pseudomonas*; however, more resistant

strains are becoming prevalent. The clinician needs to be vigilant with surveillance of burn wounds and institute aggressive treatment of wound infection once clinical signs appear before systemic illness sets in. It is of utmost importance to have ongoing assessment of the unique flora of each institution in order to better utilize systemic therapy.

4.2 Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) as defined by CDC (Center for Diseases Control) is an infection that occurs in a mechanically ventilated patient with an endotracheal or tracheostomy tube (traditionally >48 h after hospital admission) [18, 19]. The diagnosis of VAP in the thermally injured patient can be challenging, as fever, leukocytosis, tachycardia, and tachypnea can be present in these patients without infection. The sources of bacteria are typically the oropharynx and upper gastrointestinal tract [20–24]. The organisms also have a temporal pattern, community-acquired organisms (*Streptococcus pneumoniae and Haemophilus influenza*) are dominant in the early-phase VAP and Gram-negative and multiresistant organisms (i.e., MRSA) are the common pathogens in late-stage VAP.

Regardless of the organisms, early antimicrobial treatment guided toward the likely organism based on the onset of VAP (early vs. late) is beneficial in the overall outcome of the patients [25–30]. These broad-spectrum antimicrobials would need to be de-escalated as culture and sensitivities become available [31–33].

As VAP is an increasing common complication with significant consequences, VAP prevention strategies need to be implemented and ABA guidelines (Box 4.2) utilized to improve overall patient outcome.

Box 4.2 American Burn Association Practice Guidelines for Prevention, Diagnosis, and Treatment of Ventilator-Associated Pneumonia (VAP) in Burn Patients [34]

- Mechanically ventilated burn patients are at high risk for developing VAP, with the presence of inhalation injury as a unique risk factor in this patient group.
- VAP prevention strategies should be used in mechanically ventilated burn patients.
- Clinical diagnosis of VAP can be challenging in mechanically ventilated burn patients where systemic inflammation and acute lung injury are prevalent. Therefore, a quantitative strategy, when available, is the preferable method to confirm the diagnosis of VAP.
- An 8-day course of targeted antibiotic therapy is generally sufficient to treat VAP; however, resistant *Staphylococcus aureus* and Gram-negative bacilli may require longer treatment duration.

4.3 Central Line-Associated Infections

Central catheters inserted into veins and arteries are common practice in the management of the critically ill thermally injured patient and can be associated with infection rates from 1.5 to 20 % [35–37]. The introduction of central line insertion bundles by CDC has dramatically reduced these infections [38, 39]. These measures include:

- Hand washing
- Full-barrier precautions during line insertion
- Cleaning the skin with chlorhexidine
- Avoiding the femoral site if possible
- Removing unnecessary catheters

In burn patients some unique features complicate the use of the central catheters. Typically there are associated burn wounds in close proximity, and it has been shown that catheters within 25 cm^2 of an open wound are at an increased risk of colonization and infection [40]. Other risk factors associated with increased rate of infection are [41]:

- Age (extremes of age have more infection)
- Sex (female)
- %TBSA burned
- % full-thickness burns
- Presence of smoke inhalation
- Type of burn (flame)
- Number of surgical procedures performed
- Larger number of CVCs
- Longer insertion of the catheter
- Wound burn infection or colonization
- Insertion of the venous catheter in emergency situation
- Longer stay in hospital
- More operations
- Insertion site near the burns wound

The diagnosis of catheter-related infection (CRI) is based on clinical and microbiological criteria (see Table 4.4). Following the diagnosis of CRI prompt treatment is essential as delay in catheter removal or in the start of appropriate antimicrobial therapy can result in increased morbidity and mortality [43].

Currently there is no clear evidence that routine exchange of lines decreases the rate of catheter-related blood stream infections (CRBSI) [44]; however, all catheters need to be removed once a CRBSI is diagnosed or once they are no longer needed.

As with all severe infections empiric antimicrobial treatment should be initiated immediately and should take into account the severity of the illness, the site of catheter insertion, and the institutions' antibiogram [45]. These broad-spectrum antimicrobials need to be de-escalated after identification and susceptibility testing of the microorganism.

Table 4.4 Catheter-related infection [42]

Type of infection	Criteria
Catheter colonization	A significant growth of a microorganism from the catheter tip, subcutaneous segment, or catheter hub in the absence of clinical signs of infection
Exit-site infection	Microbiologically documented exudates at catheter exit site yield a microorganism with or without concomitant bloodstream infection. Clinically documented erythema or induration within 2 cm of the catheter exit site in the absence of associated bloodstream infection and without concomitant purulence
Positive blood culture	Microorganism, potentially pathogenic, cultured from one or more blood culture
Bloodstream infection	Positive blood culture with a clinical sepsis (see below)
Clinical sepsis	Requires one of the following with no other recognized cause: fever (>38 °C), hypotension (SBP <90 mmHg), oliguria, paired quantitative blood cultures with a >5:1 ratio catheter versus peripheral, differential time to positivity (blood culture obtained from a CVC is positive at least 2 h earlier than a peripheral blood culture)

4.4 Guidelines for Sepsis Resuscitation

As described in the previous segments of this chapter, infections in the thermally injured patient have dire consequences. Sepsis occurs at a rate of 8–42.5 % in burn patients with a mortality of 28–65 % [46]. Much research has been conducted in the optimal management of the septic patient. The following Table 4.5 summarizes the guidelines as recommended by the surviving sepsis campaign committee [47]. Only the strong recommendations with high level of evidence are included. This is to be used as a tool to guide the delivery of optimal clinical care for patients with sepsis and septic shock. The ABA criteria for definition of sepsis (see Box 4.1) in the burn patients have been established. However, Mann-Salinas and colleagues have challenged the predictive ability of ABA criteria demonstrating that their multivariable model (heart rate >130, MAP <60 mmHg, base deficit <−6 mEq/L, temperature <36 °C, use of vasoactive medications, and glucose >150 mg/dL) is capable of outperforming the ABA model [48].

Table 4.5 Guidelines for management of sepsis and septic shock [47][a]

Initial resuscitation (first 6 h)	Begin resuscitation immediately in patients with hypotension or elevated serum lactate >4 mmol/L; do not delay pending ICU admission
	Resuscitation goals:
	CVP 8–12 mmHg
	Mean arterial pressure ≥65 mmHg
	Urine output ≥0.5 mL/kg/h
	Central venous (superior vena cava) oxygen saturation ≥70 % or mixed venous ≥65 %
Diagnosis	Obtain appropriate cultures before starting antibiotics provided this does not significantly delay antimicrobial administration
	Obtain two or more BCs
	One or more BCs should be percutaneous
	One BC from each vascular access device in place >48 h
	Culture other sites as clinically indicated
	Perform imaging studies promptly to confirm and sample any source of infection, if safe to do so
Antibiotic therapy	Begin intravenous antibiotics as early as possible and always within the first hour of recognizing severe sepsis and septic shock
	Broad-spectrum: one or more agents active against likely bacterial/fungal pathogens and with good penetration into presumed source
	Reassess antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity, and minimize costs
	Consider combination therapy in Pseudomonas infections
	Consider combination empiric therapy in neutropenic patients
	Combination therapy ≤3–5 days and de-escalation following susceptibilities
	Duration of therapy typically limited to 7–10 days; longer if response is slow or there are undrainable foci of infection or immunologic deficiencies
	Stop antimicrobial therapy if cause is found to be noninfectious
Source identification and control	A specific anatomic site of infection should be established as rapidly as possible and within first 6 h of presentation
	Formally evaluate patient for a focus of infection amenable to source control measures (e.g., abscess drainage, tissue debridement)
	Implement source control measures as soon as possible following successful initial resuscitation (exception: infected pancreatic necrosis, where surgical intervention is best delayed)
	Choose source control measure with maximum efficacy and minimal physiologic upset. Remove intravascular access devices if potentially infected

(continued)

Table 4.5 (continued)

Fluid therapy	Fluid-resuscitate using crystalloids or colloids
	Target a CVP of ≥8 mmHg (≥12 mmHg if mechanically ventilated)
	Use a fluid challenge technique while associated with a hemodynamic improvement
	Give fluid challenges of 1,000 mL of crystalloids or 300–500 mL of colloids over 30 min. More rapid and larger volumes may be required in sepsis-induced tissue hypoperfusion
	Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent hemodynamic improvement
Vasopressors	Maintain MAP ≥65 mmHg
	Norepinephrine and dopamine centrally administered are the initial vasopressors of choice
	Do not use low-dose dopamine for renal protection
	In patients requiring vasopressors, insert an arterial catheter as soon as practical
Inotropic therapy	Use dobutamine in patients with myocardial dysfunction as supported by elevated cardiac filling pressures and low cardiac output
	Do not increase cardiac index to predetermined supernormal levels
Steroids	Do not use corticosteroids to treat sepsis in the absence of shock unless the patient's endocrine or corticosteroid history warrants it
Recombinant human activated protein C	Adult patients with severe sepsis and low risk of death (typically, APACHE II <20 or one organ failure) should not receive rhAPC
Blood product administration	Give red blood cells when hemoglobin decreases to <7.0 g/dL (<70 g/L) to target hemoglobin of 7.0–9.0 g/dL in adults. A higher hemoglobin level may be required in special circumstances (e.g., myocardial ischemia, severe hypoxemia, acute hemorrhage, cyanotic heart disease, or lactic acidosis)
	Do not use antithrombin therapy
Mechanical ventilation of sepsis-induced ALI/ARDS	Target a tidal volume of 6 mL/kg (predicted) body weight in patients with ALI/ARDS
	Target an initial upper limit plateau pressure ≤30 cm H_2O. Consider chest wall compliance when assessing plateau pressure
	Allow $PaCO_2$ to increase above normal, if needed, to minimize plateau pressures and tidal volumes
	Set PEEP to avoid extensive lung collapse at end expiration
	Maintain mechanically ventilated patients in a semi-recumbent position (head of the bed raised to 45°) unless contraindicated
	Use a weaning protocol and an SBT regularly to evaluate the potential for discontinuing mechanical ventilation
	SBT options include a low level of pressure support with continuous positive airway pressure 5 cm H_2O or a T piece
	Do not use a pulmonary artery catheter for the routine monitoring of patients with ALI/ARDS
	Use a conservative fluid strategy for patients with established ALI who do not have evidence of tissue hypoperfusion

Sedation, analgesia, and neuromuscular blockade in sepsis	Use sedation protocols with a sedation goal for critically ill mechanically ventilated patients Use either intermittent bolus sedation or continuous infusion sedation to predetermined end points (sedation scales), with daily interruption/lightening to produce awakening Avoid neuromuscular blockers where possible. Monitor depth of block with train-of-four when using continuous infusions
Glucose control	Use intravenous insulin to control hyperglycemia in patients with severe sepsis following stabilization in the ICU Aim to keep blood glucose <150 mg/dL (8.3 mmol/L) using a validated protocol for insulin dose adjustment Provide a glucose calorie source and monitor blood glucose values every 1–2 h (4 h when stable) in patients receiving intravenous insulin Interpret with caution low glucose levels obtained with point of care testing, as these techniques may overestimate arterial blood or plasma glucose values
Bicarbonate therapy	Do not use bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements when treating hypoperfusion-induced lactic acidemia with pH ≥7.15
DVT prophylaxis	Use a mechanical prophylactic device, such as compression stockings or an intermittent compression device, when heparin is contraindicated Use either low-dose UFH or LMWH, unless contraindicated
Stress ulcer prophylaxis	Provide stress ulcer prophylaxis using H2 blocker or proton pump inhibitor
Consideration for limitation of support	Discuss advance care planning with patients and families. Describe likely outcomes and set realistic expectations

[a]Adapted from Dellinger et al. [47]

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