Infections in Burns

Shahriar Shahrokhi

1 Burn Wound Infections

1.1 Diagnosis and Treatment of Burn Wound Infections

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].
  - 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 and high mortality.

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].

1.2 Common Pathogens and Diagnosis

In general, the organisms causing burn wound infection/invasion have a chronological appearance. Initially, Gram-positive organisms are com-

S. Shahrokhi (✉)
Division of Plastic and Reconstructive Surgery, Sunnybrook Health Sciences Centre, Toronto, ON, Canada
e-mail: shar.shahrokhi@sunnybrook.ca

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monplace, while Gram-negative organisms become predominant after 5 days post-burn injury. Yeast and fungal colonization/infection follow, and finally multi-resistant organisms appear typically as a 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 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 change 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 most commonly infected site, there is an increasing trend towards 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 and duration of treatment can be aided by arterial blood samples as well as retinal examination.

1.3 Clinical Management

Early excision and wound coverage is the mainstay of modern burn care and the 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.

1.3.1 Local

- Early excision of burn eschar (for unexcised burns).
- Aggressive excision of necrotic/infected tissue.
- Use of topical agents (Table 2) to minimize bacterial colonization [14].

Table 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
Multi-resistant bacteria	MRSA, VRE, MDR *Pseudomonal* and *Acinetobacter* species

Table 2 Common topical agents and their antimicrobial activity

Agent	Effective 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 (0.5–5%)	Gram-positives, Gram-negatives, pseudomonas at higher concentration
Sodium hypochlorite (0.005–0.5%)	Gram-positives, Gram-negatives, yeast, fungi
Acticoat™ (Nanocrystalline silver)	Gram-positives, Gram-negatives, yeast, fungi, MRSA, VRE

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 a substitute for aggressive surgical management of wound infections.

1.3.2 Systemic

- Use of systemic antibiotics and antifungals should be reserved for patients demonstrating systemic signs of sepsis (see ABA criteria for definition of sepsis (Box 1)).
- Use of systemic prophylaxis can reduce the rate of surgical wound infections but can increase bacterial antimicrobial resistance [15].

Box 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 pre-existing 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 (>2500 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.

- 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.

Table 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 q24h +/− Cloxacillin 1–2 g IV q4–6h (renal dosing required)
If penicillin allergy: Levofloxacin 750 mg IV/PO q24h
***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 for 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)

- The choice of antimicrobials needs to be based on each institution's antibiogram and tailored specifically to the organism (Table 3), i.e., narrow the coverage as soon as sensitivities become available.

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.

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 multi-resistant organisms (i.e., MRSA) are the common pathogens in late-stage VAP.

Regardless of the organisms, early antimicrobial treatment, guided towards 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 cultures 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

Box 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.

guidelines (Box 2) utilized to improve overall patient outcome.

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 25cm^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). 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 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 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 5 summarizes the guidelines as recommended by the surviving sepsis campaign committee originally published in 2008 [47] and later revised in 2016 [48]. 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.

Table 5 Guidelines for management of sepsis and septic shock [48][a]

Initial resuscitation
• Sepsis and septic shock are emergencies—Treatment should start immediately
• Give 30 ml/kg IV crystalloid within 3 h for hypoperfusion
• Ongoing fluid resuscitation depends on reassessment of hemodynamic status
• If clinical exam not helpful, assess cardiac function
• Use dynamic variables to assess hemodynamic status
• Aim for MAP ε65mmHg when using pressors
• Aim to lower lactate to normal levels
Diagnosis
• Cultures should be obtained before starting antimicrobial therapy
Antimicrobial therapy
• Start IV antimicrobials within one hour of diagnosis of sepsis and septic shock
• Empiric broad-spectrum therapy should cover likely pathogens
• Narrow coverage once pathogens are identified and sensitivities are established, or clinical improvement
• Recommend against sustained antimicrobial prophylaxis in patients with severe inflammatory states (burns, pancreatitis)
• Optimize dosing based on pharmacokinetic and pharmacodynamic principles
• Start empiric combination therapy (at least two of different classes) aimed at likely organisms for septic shock
• Do not use combination therapy for other serious infections (sepsis, bacteremia)
• Do not use combination therapy for neutropenic sepsis
• De-escalate combination therapy within first few days in response to improvement for septic shock
• Treatment for 7–10 days is adequate for most infections causing sepsis/septic shock
• Longer courses are appropriate in patients with slow response, undrainable foci of infection, bacteremia with *S. aureus*, some fungi or viruses, or immunologic deficiencies
• Shorter courses are appropriate for patients with rapid resolution following source control
• Daily assessment for de-escalation
• Procalcitonin can be used to shorten therapy
• Procalcitonin can be used to support discontinuation of antibiotics
Source control
• Search for a diagnosis that can be treated with source control (i.e., abscess, infected wound)
• Remove intravascular access devices that could be a cause of sepsis as soon as possible (change lines)

Vasoactive medications
- Norepinephrine is the first choice for vasopressor
- Add vasopressin (up to 0.03 units/min) or epinephrine to norepinephrine next
- Use dopamine only in highly selected patients (low risk for tachyarrhythmias and bradycardia)
- Do not use dopamine for renal protection
- Use dobutamine in patients with persistent hypoperfusion despite adequate volume status and use of vasopressors
- Arterial lines should be placed if on vasopressors

Fluid therapy
- Continue fluid challenges as long as hemodynamic factors improve
- Use crystalloids as fluid of choice for initial resuscitation and subsequent volume replacement
- Use balanced crystalloids or saline for fluids
- Add albumin to crystalloids when patients require large volumes
- Do not use hydroxyethyl starches
- Crystalloids are preferred over gelatins

Corticosteroids
- Do not use steroids if fluids and vasopressors are effective. If not, IV hydrocortisone at 200 mg/day

Blood products
- Transfuse blood only when hemoglobin <7.0 mg/dL (except in extenuating circumstances—Myocardial ischemia, severe hypoxemia, acute hemorrhage)
- Do not use erythropoietin for anemia
- Do not use fresh frozen plasma to correct clotting abnormalities in the absence of bleeding or planned invasive procedure
- Transfuse platelets when <10,000/mm^3, and when <20,000 mm^3 if at risk for bleeding, ≥50,000mm^3 for active bleeding, surgery, or invasive procedures

Immunoglobulins
- Do not use IV immunoglobulins for sepsis/septic shock

Anticoagulants
- Do not use antithrombin for sepsis/septic shock

Mechanical ventilation (for sepsis-induced ARDS in adults)
- Target tidal volume of 6 mL/kg predicted body weight (not 12 mL/kg) 2. Use upper limit goal for plateau pressures of 30 cm H_2O
- Use higher PEEP over lower PEEP
- Use recruitment maneuvers
- Use prone position over supine if P/F < 150
- Do not use high-frequency oscillatory ventilation
- No recommendation about noninvasive ventilation
- Use neuromuscular blocking agents for ≤48 h if P/F < 150
- Use a conservative fluid strategy if no hypoperfusion
- Do not use β-2agonists if no bronchospasm
- Do not use a pulmonary artery catheter for sepsis-induced ARDS in adults
- Use lower tidal volumes in sepsis-induced respiratory failure without ARDS
- Elevate the head of bed to 30°–45° in ventilated patients
- Use spontaneous breathing trials in ventilated patients
- Use weaning protocols in patients who can tolerate weaning

Sedation and analgesia
- Minimize continuous or intermittent sedation in ventilated patients

Glucose control
- Use a protocol for glucose control when two consecutive glucose >180 mg/dL
- Monitor glucose every 1–2 h until stable, then every 4 h if on insulin infusion
- Interpret point-of-care glucose with caution
- Use arterial over capillary blood if arterial line present

Renal replacement therapy
- Use either continuous or intermittent renal replacement therapy
- Use continuous renal replacement therapy if hemodynamically unstable
- Do not use renal replacement therapy just for increased creatinine or oliguria without other definitive indications for dialysis

Bicarbonate therapy
- Do not use sodium bicarbonate with lactic acidemia with pH ≥ 7.15

Venous thromboembolism prophylaxis
- Use pharmacologic prophylaxis (UFH or LMWH) in the absence of contraindications
- Use LMWH rather than UFH
- Combine pharmacologic prophylaxis and mechanical prophylaxis whenever possible
- Use mechanical prophylaxis when pharmacologic prophylaxis is contraindicated

Stress ulcer prophylaxis
- Give stress ulcer prophylaxis to patients at risk for GI bleeding
- Use either proton pump inhibitors or histamine-2 receptor antagonists
- Do not use stress ulcer prophylaxis in patients without risk factors for GI bleeding

Nutrition
- Do not use parenteral feedings if enteral feedings possible
- Do not provide parenteral nutrition for the first 7 days if enteral feedings not possible (advance enteral feedings as tolerated)
- Start early enteral feedings if possible
- Start early trophic/hypocaloric or early full feedings (advance as tolerated)
- Do not use omega-3 fatty acids
- Do not check routine gastric residual volumes (but check if feeding intolerance or high risk for aspiration—applies to nonsurgical patients)

[a]Adapted from Rhodes et al. [48]

The ABA criteria for definition of sepsis (see Box 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 [49]. In addition, the new Sepsis-3 clinical criteria for identification of sepsis and septic shock [50–52] have been developed, which defines sepsis and septic shock as follows:

- **Sepsis—**Suspected or documented infection and an acute increase of >2 SOFA points.
- **Septic Shock—**Sepsis and vasopressor therapy needed to elevate MAP >65 mmHg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation.

More recently, the publication by Stanojcic and colleagues as well as Yan and colleagues demonstrated that the Sepsis-3 had superior sensitivity in predicting sepsis in comparison to Mann-Salinas and ABA criteria for sepsis; however, none of the aforementioned had the accuracy to be a stand-alone diagnostic tool within the burn population [53, 54].

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