Rational Selection and Use of Antimicrobials in Patients with Burn Injuries

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KEYWORDS

• Burn • Antimicrobials • Sepsis • Infections • Biomarkers • Pharmacokinetics • Pharmacodynamics • Dosing

KEY POINTS

- Caring for patients with burn injuries is challenging secondary to the acute disease process, chronic comorbidities, and underrepresentation in evidence-based literature.
- Much of current practice relies on extrapolation of guidance from different patient populations and wide variations in universal practices.
- Identifying infections or sepsis in this hypermetabolic population is imperfect and often leads to overprescribing of antimicrobials, suboptimal dosing, and multidrug resistance.
- An understanding of pharmacokinetics and pharmacodynamics may aid optimization of dosing regimens to better attain treatment targets.

INTRODUCTION

Over the past century, the armamentarium available to the burn practitioner has dramatically increased.[1] Mortality from a burn injury has been dramatically reduced with the discovery of new technology and medications, development of new surgical philosophies, and the continual expansion of burn-specific literature. Parallel to the expanding repertoire of available antimicrobials is the occurrence of multidrug-resistant (MDR) organisms.[2] The increasing prevalence of MDR organisms is unfortunate, as they are associated with increased morbidity and mortality.[3] Proper selection and use of antimicrobials is imperative for reducing unneeded exposure, cost, resistance, and mortality.[4] Knowledge of existing literature and an understanding of pharmacokinetics and pharmacodynamics will aid appropriate antimicrobial prescribing and optimize patient outcomes.

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DEFINING INFECTION AND SEPSIS

Defining infection in a patient with burn injuries can be challenging in light of the hyperdynamic, hypermetabolic, and proinflammatory presentation. As a result, burn injury is often an exclusion criteria for studies of sepsis identification, treatment, and outcomes. Unfortunately, infection is a frequent accompaniment to acute illness and even more so in patients with burn injuries with a compromised primary immunologic barrier. However, the identification of early signs that distinguish infection from acute burn injury physiology is key for prompt and appropriately targeted intervention.[5]

The diagnosis of pneumonia in a patient in the intensive care unit is controversial.[6,7] Patients with acute burn injury are uniquely challenging in that they are prone to pulmonary dysfunction due to multiple noninfectious mechanisms, such as inhalational injury, pulmonary edema, dysregulated systemic inflammation, and the acute respiratory distress syndrome. Because of these and other noninfectious sources of pulmonary dysfunction, patients with burn injuries often exhibit the clinical signs and symptoms associated with infectious pneumonia. Even in the absence of bacterial pneumonia, many patients with burn injuries will have fever, purulent sputum, leukocytosis (or leukopenia), abnormal gas exchange, and infiltrates on chest imaging. There have been numerous clinical scoring systems created to aid in the diagnosis of pneumonia, such as the clinical pulmonary infection score. Such tools have not been adopted or validated in patients with burn injuries because they use many of the same clinical signs seen in patients with burn injuries without pneumonia.[8] Most burn centers depend on bronchoscopic sampling (protected specimen brush or bronchoalveolar lavage [BAL]) or nonbronchoscopic BAL and quantitative cultures of the samples obtained to make a diagnosis of pneumonia.[6,9–11] Pneumonia should be diagnosed if clinically suspected and BAL results in quantitative culture of $\geq 10^4$ colony-forming units/mL.[12]

Burn wound infections do not occur with the frequency that they did several years ago because of a more aggressive surgical approach, topical antimicrobials, and the appropriate use of systemic antibiotics. The appearance of the burn wound often holds the key to early diagnosis of the infection and thus optimal care. Therefore, it is imperative that constant wound surveillance be performed. It is stated that early eschar separation is indicative of burn wound infections, but this is rarely seen today due to early wound excision.[12] Color changes within the wound are often the first subtle signs of infection. Conversion of partial-thickness wounds to full thickness and the loss of grafts are indicative of localized wound infections. *Pseudomonas* colonization may be a yellow/green exudate in the wound bed, whereas black violent areas suggest invasive infection. Typically, fungal infections are insidious. *Candida* infections may be more purulent in appearance, whereas *Aspergillus* may be gray-brown and *Mucor* appear as black-staining growths on the wound bed itself.[12] Herpetic infections will appear more like punched-out lesions and often occur in healed second-degree burns. With changes occurring subtly, vigilant visual surveillance is vital for survival of tissue and sometimes the person. As Krizek and Robson[13] have noted: "Having preceded man on earth, bacteria continue to exert a 'territorial imperative' and the interaction between man, his environment and his defense system is either a symbiotic relationship or one that is leading to the path of infection."

Systemic Inflammatory Response Syndrome (SIRS) criteria have been repeatedly documented as having poor correlation with infection in patients with burn injuries, with up to 98% of patients fulfilling criteria regardless of clinical stability or infection status.[14–17] Burn injury is traditionally classified in 2 phases: "ebb" and "flow." The first 24 to 48 hours after burn injury is termed the ebb phase and is characterized by the initiation of the inflammatory process. Inflammatory mediators surge to produce local vasodilation and augment vascular permeability. The resulting albumin and fluid shifts into the interstitial space transiently produce a low cardiac output, increase systemic vascular resistance, and potential for reduced organ perfusion.[18] After adequate resuscitation, the flow phase is characterized by the hyperdynamic response to the insult with increased cardiac contractility and output plus a reduced systemic vascular resistance.

SIRS has traditionally been considered a trigger for the initial suspicion of an infectious process in patients without burn injuries. Danger exists when extrapolating definitions and treatment protocols for sepsis validated only in patients without burn injuries, as they can lead to overtreatment with resuscitation volumes and antimicrobials. Early goal-directed therapy has improved outcomes in nonburn septic patients; however, use of recommended resuscitation volumes to reach end hemodynamic targets may lead to new unwanted issues in a fragile and often overresuscitated population.[19–22] To be discussed later, overexposure to antimicrobials also must be avoided in a population with an expected prolonged hospital stay and heightened risk for MDR and fungal pathogens.

Recognizing the irrelevance in application of sepsis criteria to patients with burn injuries,