Review Article

Intravenous Antibiotic and Antifungal Agent Pharmacokinetic-Pharmacodynamic Dosing in Adults with Severe Burn Injury

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ABSTRACT

Purpose: Despite advances in the care of patients with severe burn injury, infection-related morbidity and mortality remain high and can potentially be reduced with antimicrobial dosing optimized for the infecting pathogen. However, anti-infective dose selection is difficult because of the highly abnormal physiologic features of burn patients, which can greatly affect the pharmacokinetic (PK) disposition of these agents. We review published PK data from burn patients and offer evidence-based dosing recommendations for antimicrobial agents in burn-injured patients.

Methods: Because most infections occur at least 48 hours after initial burn injury and anti-infective therapy often lasts ≥10 days, we reviewed published data informing PK-pharmacodynamic (PD) dosing of anti-infectives administered during the second, hypermetabolic stage of burn injury, in those with >20% total body surface area burns, and in those with normal or augmented renal clearance (estimated creatinine clearance ≥130 mL/min). Analyses were performed using 10,000-patient Monte Carlo simulations, which uses PK variability observed in burn patients and MIC data to determine the probability of reaching predefined PK-PD targets. The probability of target attainment, defined as the likelihood that an anti-infective dosing regimen would achieve a specific PK-PD target at the single highest susceptible MIC, and the cumulative fraction of response, defined as the population probability of target attainment given a specific dose and a distribution of MICs, were calculated for each recommended anti-infective dosing regimen.

Findings: Evidence-based doses were derived for burn-injured patients for 15 antibiotics and 2 antifungal agents. Published data were unavailable or insufficient for several agents important to the care of burn patients, including newer antifungal and antipseudomonal agents. Furthermore, available data suggest that antimicrobial PK properties in burned patients is highly variable. We recommend that, where possible, therapeutic drug monitoring be performed to optimize PK-PD parameter achievement in individual patients.

Implications: Given the high variability in PK disposition observed in burn patients, doses recommended in the package insert may not achieve PK-PD parameters associated with optimal infectious outcomes. Our study is limited by the necessity for fixed assumptions in depicting this highly variable patient population. New rapid-turnaround analytical technology is needed to expand the menu of antimicrobial agents for which therapeutic drug

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monitoring is available to guide dose modification within a clinically actionable time frame. (*Clin Ther*. 2016;38:2016–2031) Published by Elsevier HS Journals, Inc.

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BURN INFECTION EPIDEMIOLOGY

Infection Risk in Patients With Burn Injury

Despite advances in the care of patients with severe burn injury, infection-related morbidity and mortality remain high.[1] Damage to the skin barrier disrupts the innate immune system and increases systemic exposure to infectious pathogens. The US Army Burn Center serves both the military population, including burn-injured combat casualties, and the surrounding civilian population as a major burn care referral center in the south Texas region. Data collected from 2003 to 2008 in the US Army Burn Center suggested that pneumonia was the leading infectious complication overall, with a respiratory tract culture source representing 39% of recovered isolates.[2] Pneumonia was followed by bacteremia, with blood cultures representing 25% of recovered isolates. The burn wound was the source of 7% of recovered isolates, likely reflecting standard-of-care practices at our burn center. Burn wound infection rates may have decreased because of early excision of the burn eschar coupled with early skin grafting and the use of topical antibiotics to prevent infection. These data are inferential because these conclusions are derived from a retrospective survey of bacterial cultures rather than from patients meeting predefined criteria for infection.

In contrast to our experience, a multicenter study of 573 patients from civilian burn centers in the United States found that burn wound infection occurred in 54% of patients $\geq$16 years old, pneumonia in 43%, and sepsis in 11% of these patients.[3] Less frequent infectious complications observed in our burn center include infective endocarditis, which was observed in 0.4% of burn unit admissions and 9% of patients with bacteremia that persisted for $>$24 hours.[4] Central nervous system infections were exceedingly rare, with an incidence of 0.1%.[5] According to data from the American Burn Association National Burn Repository, the most prevalent complications of patients hospitalized with burn injury in the past decade include pneumonia, cellulitis, and urinary tract infections.[1] Given the high infection risk, rapid diagnosis and prompt empiric anti-infective therapy initiation are important. In selecting empiric anti-infectives, clinicians caring for patients with burns should account for the bacteriology of these infections.

Bacteriology of Infections in Patients With Burn Injury

The bacteriologic mechanism of infections in the burned patient consists of human pathogenic bacteria similar to nonburned patients. In the above-mentioned review of isolates from the US Army Burn Center, *Acinetobacter baumannii* was the most frequent isolate from respiratory cultures among military combat casualties, although this may not currently be the case given the decrease in burn admissions from Iraq and Afghanistan. *Staphylococcus aureus* was the most frequently isolated pathogen from civilian patients.[6] *Pseudomonas aeruginosa* was the second most frequent respiratory isolate in both groups. Among bacteremia isolates, *P aeruginosa* and *Klebsiella pneumoniae* were the most commonly isolate organisms. These organisms have been associated with mortality among burn patients, and their treatment is complicated by the potential for antimicrobial resistance among these organisms.[7]

Organisms resistant to multiple antimicrobials (termed multidrug-resistant organisms [MDROs]) are a growing concern globally, including in the care of burn patients. Among patients in our burn center between 2003 and 2008, 53% of the initial isolates of *A baumannii* met MDRO criteria (resistant to at least 3 of the following 4 drug classes: penicillins/cephalosporins, carbapenems, aminoglycosides, fluoroquinolones). In addition, 59% of the MDRO *A baumannii* were resistant to all 4 classes.[6] Rates of MDR were much lower for *P aeruginosa* (15%) and *K pneumoniae* (17%). Interestingly, the frequency of MDRO isolation increased along with stratified total body surface area (TBSA) burned: 23% for $<$30% TBSA, 33% for 30% to 60% TBSA, and 33% for TBSA $>$60%. This finding was driven by increasing MDR *A baumannii* isolation. Notably, 95% of initial, single-patient isolates of *A baumannii* were nonsusceptible to imipenem. Despite such concerning statistics, recovery of *A baumannii*, even from blood cultures, does not appear to adversely affect mortality overall in our burn-injured population.[8] In contrast,