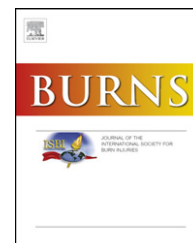


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# Prevalence of multidrug-resistant organisms recovered at a military burn center<sup>☆</sup>

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## ABSTRACT

Infections caused by multidrug-resistant (MDR) pathogens are associated with significant morbidity and mortality in patients with burn injuries. We performed a 6-year antibiotic susceptibility records review from January 2003 to December 2008 to assess the prevalence of MDR isolates by pathogen at the US Army Institute of Surgical Research Burn Center. During the study period *Acinetobacter baumannii* (780 isolates [22%]) was the most prevalent organism recovered, followed by *Pseudomonas aeruginosa* (703 isolates [20%]), *Klebsiella pneumoniae* (695 isolates [20%]), and *Staphylococcus aureus* (469 isolates [13%]). MDR prevalence rates among these isolates were *A. baumannii* 53%, methicillin-resistant *S. aureus* (MRSA) 34%, *K. pneumoniae* 17% and *P. aeruginosa* 15%. Two isolates, 1 *A. baumannii* and 1 *P. aeruginosa*, were identified as resistant to all 4 classes of antibiotics tested plus colistin. *A. baumannii* isolates recovered from patients with burns greater than 30% of total body surface area (TBSA) were more likely to be MDR (61%) with no significant difference for *P. aeruginosa* and *K. pneumoniae*. A higher proportion of MDR *P. aeruginosa* isolates were recovered from respiratory specimens compared to blood specimens (24% vs. 9%) while the opposite was true for MRSA (35% vs. 54%). A comparison of *A. baumannii* recovered during hospitalization days 1–5 and 15–30 revealed higher MDR levels as length of stay increased (48% vs. 75%) while no significant trends were observed for *P. aeruginosa* and *K. pneumoniae*. A similar pattern was observed for MDR *A. baumannii* levels for the facility between 2003 and 2005 and 2006–2008 (39% vs. 70%), with no significant increase in MDR *P. aeruginosa* and MDR *K. pneumoniae*. Increasing antibiotic resistance patterns of the most prevalent isolates recovered during extended hospitalization, impact of % TBSA and other clinical parameters may affect empirical antimicrobial therapy and patient management decisions during treatment.

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## 1. Introduction

Many of the organisms commonly recovered from infected patients in the burn ICU are members of the ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) group of pathogens recognized by the Infectious Disease Society of America as the most challenging bacteria facing clinicians today [1]. ESKAPE pathogens are of particular concern because they are responsible for a majority of US hospital infections and often “escape” the effects of traditional antimicrobials through broad-spectrum resistance [2]. Over time these microorganisms have developed resistance to several classes of antibiotics and represent a significant challenge to clinicians. The term “multidrug-resistant” (MDR) is commonly used in the biomedical literature to describe antimicrobial resistance levels among bacteria. While the exact definition of what constitutes an MDR organism can vary, it is frequently used to indicate resistance to representatives of three or more classes of antimicrobial agents [3]. Bacteria resistant to all but one or two classes of antibiotics are being isolated with greater frequency and are commonly referred to as “extensively drug-resistant” (XDR) to highlight the limited treatment options available to patients infected with these organisms.

Very few antibiotics directed against MDR Gram-negatives are in development. As a result, several MDR Gram-negative pathogens, primarily *A. baumannii*, *P. aeruginosa* and *Klebsiella* species, have emerged as significant pathogens worldwide [4,5]. Infections caused by these organisms are associated with higher morbidity and considered a significant risk factor for mortality in patients with burns [6]. Another important consideration is increasing antimicrobial resistance among burn patient isolates recovered during prolonged stays in the ICU. A previous study demonstrated that isolates recovered after 7, 14 and 21 days of hospitalization were considerably more resistant to the antibiotics tested compared to admission day isolates [7]. Changing resistance patterns throughout hospitalization can have a significant impact on empirical therapy choices for patients that develop infection weeks after arriving in the hospital. Inadequate initial antimicrobial therapy to treat infections with MDR bacteria can result in higher mortality [8].

In this study in conjunction with its companion paper looking at the incidence and bacteriology of burn infections, we review 6 years of antibiotic susceptibility results in a single institution burn ICU to assess MDR and XDR isolate frequency and antimicrobial resistance patterns by pathogens, total body surface area (TBSA) burns, hospital length of stay and effect of burns sustained during military operations in Iraq and Afghanistan which are reflective of later presentations to our burn center.

## 2. Methods

This is a 6-year retrospective review of all bacteriology culture and antibiotic susceptibility testing results and clinical data from patients admitted to the US Army Institute of Surgical Research (USAISR) Burn Center ICU at Brooke Army Medical

Center, Fort Sam Houston, TX from January 1, 2003 to December 31, 2008. Management strategies for patients with burns along with data collection were described in the accompanying article [9]. The overall patient demographics and bacteriology were presented in the companion paper.

Bacterial cultures were processed in the clinical microbiology laboratory using standard microbiology techniques; organism identification and antimicrobial susceptibility profiles were performed using Vitek1 or 2 (bioMérieux Vitek, Durham, NC). Susceptibility profiles of *A. baumannii*, *K. pneumoniae*, *P. aeruginosa*, and *S. aureus* were determined for the entire burn center ICU inpatient population and further compared in subgroups including Operation Iraqi Freedom and Operation Enduring Freedom versus local civilian admissions, percent TBSA, and specimen type/source of the bacterial isolate. Specimen types were categorized based on their origination—respiratory tract, bloodstream, wounds, or urinary tract. Isolates were considered MDR if resistant to at least 3 out of 4 classes of antimicrobial agents (penicillins/cephalosporins, carbapenems, aminoglycosides, and quinolones), not including tetracyclines or colistin [3]. Isolates were further characterized as MDR-4 if resistant to all 4 classes of antimicrobial agents and susceptible to colistin, and XDR if resistant to all 4 classes as well as colistin. Susceptibility testing of colistin during the study period was performed by disk diffusion and Etest. To determine the effect of extended hospitalization of burn patients on antimicrobial resistance, susceptibility profiles for combat-injured patients and local civilian admissions, grouped by hospitalization days 1–5 and days 15–30 were compared. Hospitalization days 1–5 were chosen to examine patient isolates before or immediately following early excision and debridement procedures, which are typically performed during a patient's first week (5–7 days) in the burn ICU, and best reflective of community acquired pathogens or very early nosocomial acquisition of pathogens. Admission days 15–30 were selected to examine pathogens recovered when clinically indicated after extended hospitalization [7,10].

Categorical values were compared using Pearson  $\chi^2$  analysis. All statistical operations were performed using SISA (<http://home.clara.net/sisa/>; accessed 7 July 2009). P value less than 0.05 were considered significant, and all reported p values were two-tailed. This study was approved by the Institutional Review Board of Brooke Army Medical Center.

## 3. Results

### 3.1. Antibiotic susceptibility

We identified 97 (53%) first isolate *A. baumannii* that met the criteria for classification as MDR. Of the MDR *A. baumannii* isolates, 92 (95%) were not susceptible to imipenem. Fifty-seven of the 96 (59%) MDR *A. baumannii* isolates were found to be MDR-4. In contrast, fewer MDR isolates of *P. aeruginosa* and *K. pneumoniae* were identified, with only 20 (15%) MDR *P. aeruginosa* and 25 (17%) MDR *K. pneumoniae* recovered. Of these isolates, 3 (0.03%) *P. aeruginosa* and 6 (0.04%) *K. pneumoniae* were classified as MDR-4. Among all isolates only 2 XDR organisms were identified; 1 *A. baumannii* (respiratory) and 1 *P. aeruginosa*

(blood). The resistance profiles of *A. baumannii*, *P. aeruginosa*, *K. pneumoniae* and *S. aureus* were determined for the entire burn ICU population. Analysis of agents most active against first isolates revealed that *A. baumannii* were most susceptible to imipenem (42%) and amikacin (31%), *P. aeruginosa* were most susceptible to piperacillin/tazobactam (pip/tazo) (76%) and gentamicin (58%), *K. pneumoniae* were most susceptible to imipenem (82%) and pip/tazo (68%). Thirty-four percent of *S. aureus* isolates were resistant to methicillin. Statistically significant differences in antibiotic susceptibility by population were identified in *P. aeruginosa* isolates from combat-injured patients; these bacteria were less susceptible to gentamicin than isolates from local patients ( $p < 0.05$ ). *K. pneumoniae* from combat-injured patients were less susceptible to gentamicin, aztreonam and ampicillin/sulbactam ( $p < 0.05$ ).

A review of susceptibility data by specimen collection site revealed that a higher percentage of MDR *P. aeruginosa* isolates were recovered from respiratory specimens compared to blood specimens (24% vs. 9%;  $p < 0.05$ ). Prevalence of MDR *A. baumannii* isolates recovered from blood specimens was slightly higher than those from respiratory specimens (54 [67%] vs. 67 [57%]); however the differences were not statistically significant. *A. baumannii* blood isolates were more likely to be resistant to all 4 classes of antibiotics than those from respiratory specimens (48% vs. 34%;  $p < 0.05$ ). There did not appear to be a difference in *K. pneumoniae* MDR rates by specimen type. *S. aureus* isolates obtained from bloodstream infections were more resistant to antimicrobials than those from respiratory tract infections. MRSA isolates were recovered with greater frequency from blood specimens compared to respiratory specimens (54% vs. 35%;  $p < 0.05$ ). Direct comparison of *P. aeruginosa* and *K. pneumoniae* respiratory isolates showed higher levels of resistance compared to same species blood isolates. Compared to *P. aeruginosa* blood isolates, respiratory isolates were 28% more resistant to amikacin and *K. pneumoniae* respiratory isolates were 17% more resistant to imipenem ( $p < 0.05$ ).

Analysis of isolates by percentage TBSA burns revealed that the percentage of MDR and MDR-4 isolates was higher in patients with 30–60% and greater than 60% TBSA burns when each group was compared to patients with burns less than 30% TBSA ( $p < 0.05$ ). Patients with less than 30% TBSA burns produced 38 (23%) MDR and 15 (9%) MDR-4 isolates; 30–60% TBSA produced 63 (33%) MDR and 36 (19%) MDR-4 isolates and patients with greater than 60% TBSA burns produced 39 (39%) MDR, 15 (15%) MDR-4 and 2 (2%) XDR isolates. The MDR differences between 30% and 60% TBSA and greater than 60% TBSA were not considered significant although resistance levels appeared to be higher for the greater than 60% TBSA cohort compared to the 30–60% TBSA group but fewer isolates were available for analysis among patients with more severe burns. Further analysis of the antibiotic susceptibility data for isolates recovered from patients with burns greater than 30% TBSA revealed the increase in MDR rates associated with more severe burns is due to higher prevalence of MDR *A. baumannii* (61% vs. 40%;  $p < 0.05$ ). MDR rates for *A. baumannii*, *P. aeruginosa* and *K. pneumoniae* for combat burn patients were slightly higher than local patients but the differences were not statistically significant. A total of 70 (38%) MDR, 38 (21%)

MDR-4 and 1 (0.5%) XDR isolates were recovered from combat injured patients while 34 (28%) MDR, 19 (15%) MDR-4 and 1 (0.8%) XDR strains came from local civilian burn patients. An analysis of cultures obtained from patients with less than 30% TBSA, 30–60% TBSA and greater than 60% TBSA demonstrated increasing levels of resistance to certain antibiotics as burn severity increased. Specifically, a comparison of less than 30% to 30–60% and greater than 60% TBSA antibiotic susceptibilities revealed increasing resistance of *A. baumannii* to imipenem, *P. aeruginosa* to imipenem and tobramycin, *K. pneumoniae* to amikacin and gentamicin, and *S. aureus* to clindamycin and erythromycin ( $p < 0.05$ ).

The overall frequency of MDR and MDR-4 isolate recovery appeared comparable with 65 (30%) MDR and 35 (16%) MDR-4 admission day 1–5 isolates and 44 (31%) MDR and 21 (15%) MDR-4 admission day 16–45 isolates being recovered. A closer examination of *A. baumannii* susceptibility data during hospitalization days 1–5 and 15–30 revealed a higher percentage of MDR isolates recovered later into a patient's stay in the hospital (48% vs. 75%;  $p < 0.05$ ). No significant difference in recovery was observed for *P. aeruginosa* and *K. pneumoniae*. Both XDR isolates were recovered during admission days 16–45—*A. baumannii* on day 44 and *P. aeruginosa* on day 27. Culture isolates recovered within the first 5 days of admission are more susceptible to antibiotics compared to isolates recovered after 15 days of hospitalization. Analysis of total cultures obtained from admission through hospital day 5 versus hospital days 15–30 revealed that resistance of *A. baumannii* isolates increased 15% for imipenem and 17% for amikacin, *K. pneumoniae* 15% for imipenem and 28% for amikacin, for *P. aeruginosa* 21% for pip/tazo and 27% for ciprofloxacin, and for *S. aureus* 51% for clindamycin and 40% for oxacillin ( $p < 0.05$ ) (Fig. 1). Analyzing the susceptibility data by patient population (deployed versus local civilian) demonstrated the same trends with susceptibility of combat-injured *A. baumannii* decreasing 12% for imipenem and 17% for tobramycin, *P. aeruginosa* decreasing 29% for pip/tazo and 24% for cefepime, *K. pneumoniae* decreasing 28% for amikacin and 15% for imipenem and *S. aureus* 65% for clindamycin and 42% for oxacillin ( $p < 0.05$ ) (Fig. 2). After 15 days of hospitalization susceptibility of local civilian *A. baumannii* decreasing 56% for tobramycin and 43% for amikacin, *P. aeruginosa* decreasing 37% for pip/tazo and 45% for cefepime, *K. pneumoniae* decreasing 48% for ciprofloxacin and 51% for gentamicin and *S. aureus* decreasing 42% for clindamycin and oxacillin ( $p < 0.05$ ). Comparison of % TBSA by day group was not possible due to the small number of isolates available for evaluation.

Culture isolates from 2003 to 2005 were directly compared to isolates from 2006 to 2008 to determine global changes in MDR prevalence in the burn ICU over time. The most prevalent Gram-negative isolates as a whole demonstrated higher MDR levels in the 2006–2008 group compared to 2003–2005 (43% vs. 28%;  $p < 0.05$ ). Further analysis of each pathogen individually revealed that the increase was due to higher levels of MDR *A. baumannii* ( $p < 0.05$ ). Of the 94 *A. baumannii* first isolates recovered from 2003 to 2005, 37 (39%) were considered MDR and 17 (18%) were MDR-4 while 66 of the 94 (70%) from 2006 to 2008 were MDR and 46 (49%) were MDR-4. The increase in MDR and MDR-4 *A. baumannii* during this time period is largely due to decreasing susceptibility to imipenem (51% vs. 31%;

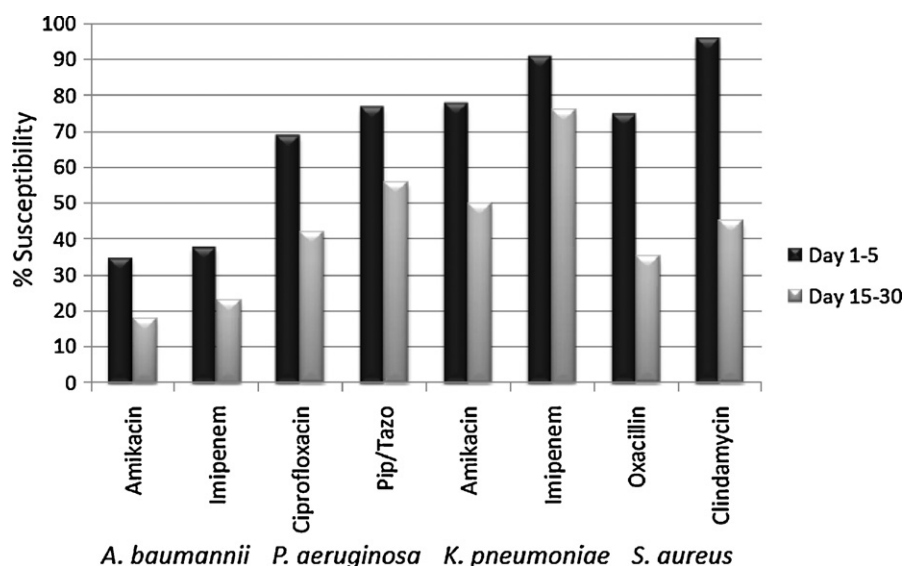


Fig. 1 – Antibiotic susceptibility by days of hospitalization for the 2 most active agents for the 4 most common bacteria—total isolates ( $p < 0.05$ ). Piperacillin/tazobactam (Pip/Tazo).

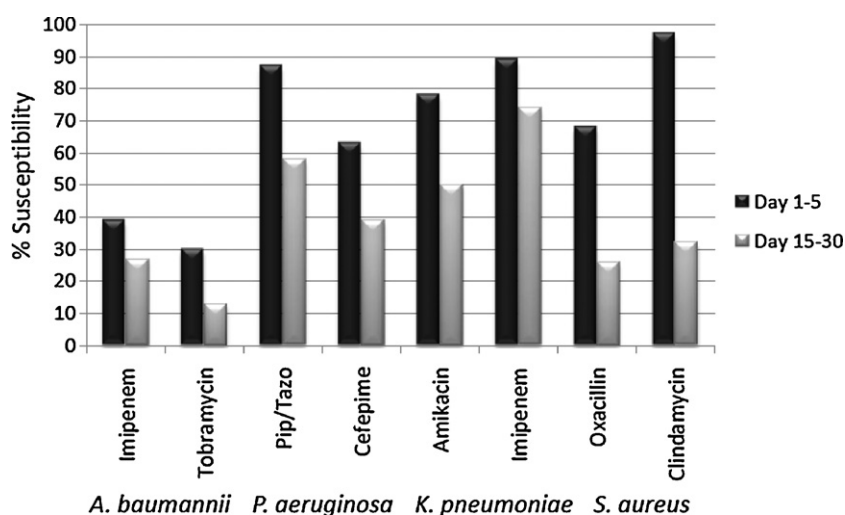


Fig. 2 – Antibiotic susceptibility by days of hospitalization for the 2 most active agents for the 4 most common bacteria—total isolates: A deployed; B local civilian ( $p < 0.05$ ). Piperacillin/tazobactam (Pip/Tazo).

$p < 0.05$ ). From 2003 to 2005 to 2006 to 2008 the number of MDR *P. aeruginosa* increased from 9 (13%) to 12 (18%) and MDR *K. pneumoniae* increased from 10 (14%) to 15 (18%); however the MDR differences and antibiotic susceptibility comparisons were not considered significant.

#### 4. Discussion

Antimicrobial resistance of the pathogens responsible for a majority of nosocomial infections continue to increase throughout the healthcare system [11]. Patients with burn wounds are frequently exposed to antimicrobial agents

throughout their hospitalization, increasing the likelihood of colonization or infection with drug-resistant organisms. Infection with MDR pathogens is associated with higher morbidity and mortality; making it imperative to rapidly identify any recovered isolates and assess their susceptibility patterns to help guide proper treatment. In this study, we evaluated the MDR prevalence and antibiotic susceptibility profiles of the most commonly recovered pathogens from military and civilian burn patients at a single institution over a 6-year period.

During the study period the most commonly recovered isolates in the burn ICU from were *A. baumannii*, *P. aeruginosa*, *K. pneumoniae* and *S. aureus*. More than half of the recovered *A.*



*baumannii* isolates were classified as MDR while the number of MDR *P. aeruginosa* and *K. pneumoniae* was much lower (15% and 17%, respectively). The ability to compare MDR rates between institutions is often limited because criteria for what constitutes a MDR organism can vary from hospital to hospital. A review of surveillance data collected from 1994 to 2002 using a similar MDR definition (resistance to 3 or more classes of antibiotics) revealed that consensus national rates of MDR *P. aeruginosa* (1% to 16%) and MDR *K. pneumoniae* (0.5% to 17%) were comparable to our observed rates [12]. Conversely, MDR *A. baumannii* prevalence in our burn ICU exceeded ICU and non-ICU cumulative rate results (24.2% to 32.5%), although the study evaluated an earlier time period from 1998 to 2001 [13]. Increasing incidence of *A. baumannii* has been occurring in the US military healthcare system since the onset of OIF/OEF and the higher incidence of MDR isolates most likely represents the importation of resistant strains from Iraq and Afghanistan [14–17]. Analysis of cultures recovered from patients with burns greater than 30% TBSA revealed higher prevalence of MDR *A. baumannii* compared to patients with less severe burns. The contribution of *A. baumannii* to increased burn-related mortality and morbidity may be due in part to its association with large burns and multidrug resistance. Not surprisingly, culture isolates recovered from patients with greater than 60% TBSA burns were less susceptible to commonly-prescribed antibiotics than isolates from the less than 30% TBSA and 30–60% TBSA burn categories.

Pulmonary complications are common in burn patients and can occur with or without concomitant inhalation injury [18]. Aspirations and mechanical ventilation are important risk factors for developing hospital-acquired and ventilator-associated pneumonia. Rates of hospital-acquired pneumonia due to MDR pathogens, especially MDR *P. aeruginosa*, have increased dramatically among intensive care patients [19,20]. Our data revealed MDR *P. aeruginosa* isolated from respiratory specimens was more prevalent than strains recovered from blood specimens. This is concerning because resistant *P. aeruginosa* strains are associated with higher mortality, hospital length of stay and ventilator days in burn patients [21]. The exact role of biofilm formation and elevated *P. aeruginosa* resistance in respiratory infections is unknown and warrants further investigation. In contrast to *P. aeruginosa*, MDR *A. baumannii* was more commonly recovered from blood cultures. *S. aureus* was identified as the second most common isolate recovered from patients with bloodstream infections in US hospitals and the surveillance data indicated 41% of tested isolates were methicillin-resistant [22]. The MRSA rate in our burn ICU was 13% higher in comparison to the surveillance data ( $p < 0.05$ ). Burn wound infections are the most common source of bacteremia due to destruction of the skin's protective barrier. Colonization of burn wounds by MRSA and MDR *A. baumannii*, which can be ubiquitous in the ICU environment, and subsequent seeding of the bloodstream may explain its increased prevalence in blood cultures [23].

Although there was only a difference in MDR rates for *A. baumannii* between the first 5 days of admission and days 15–30, we demonstrated that a majority of isolates recovered from burn ICU patients during the first 5 days of hospitalization were less antibiotic resistant than those recovered after day 15. Two possibilities exist to explain the increasing resistance

over time: selection of bacterial mutations that enable the pathogen to survive or cross-transmission from the environment. Exposure to an antibiotic during therapy can lead to resistance to that drug and others with similar targets or mechanisms of action. Our data revealed increasing resistance to 1 or 2 drugs within a given class of antibiotic; however, any drugs within the class remaining susceptible would render its MDR status unchanged. The data suggest that patient hospitalization days should be considered when making individual antimicrobial therapy decisions for patients presenting with signs of infection during prolonged stays although it is encouraging that antibiotics remain available for treatment of infections with these pathogens.

The emergence of MDR Gram-negative bacteria as a source of nosocomial infections presents a significant challenge to clinicians caring for critically ill and immunocompromised patients. Our data suggest that except for *A. baumannii*, pathogens recovered in the burn ICU are rarely MDR-4. Despite increasing resistance to individual antibiotics during hospitalization MDR levels did not increase; indicating treatment options were still available. In many healthcare facilities with MDR Gram-negative pathogens, colistin (polymyxin E) has emerged as a viable treatment option for these infections [24]. Alarming, *A. baumannii* and *P. aeruginosa* isolates resistant to colistin are being isolated in ICUs with greater frequency [25]. Despite these patterns, increasing colistin resistance was not observed; being detected in only two clinical isolates among the total cultures tested at this facility.

The main limitations of our study are the retrospective design and use of only a single burn center's data. Culture isolates were unavailable for additional antibiotic susceptibility testing or molecular analysis to determine if isolates were acquired through nosocomial transmission. Detailed treatment regimens were unavailable and it is unknown what impact antibiotic use had on culture data. Data obtained from electronic patient records for certain specimen types make it difficult to distinguish infection from colonization; however, the database contained a sizable number of test results and specimens were systematically collected based upon clinical indications. Records describing initial burn wound management and empirical antimicrobial therapy for combat-injured burn patients treated throughout the evacuation chain were unavailable for analysis.

Our study reviewed antibiotic susceptibility data from a single institution burn ICU to assess MDR and XDR isolate levels and evaluate antimicrobial resistance patterns by pathogens, TBSA burned, hospital length of stay and effect of burns sustained during combat operations. Over half of the *A. baumannii* isolates recovered during the study period were MDR and an alarming number were resistant to all 4 classes of antibiotics tested. The frequency of MDR *A. baumannii* recovery in the burn ICU increased over time and this was most likely due to the continued influx of combat-injured patients from Iraq and Afghanistan. National surveillance networks have shown significant increases in MDR *P. aeruginosa* and MDR *K. pneumoniae* over the past decade; however, rates at this facility have not followed this trend [17]. It is possible that infection control strategies and antibiotic use policies are effective in keeping these rates stable over time. MDR *A. baumannii* rates

were higher in patients with more severe burns while MDR *P. aeruginosa* rates were higher in respiratory infections. Overall, there was no significant change in MDR levels for the duration of hospitalization except for *A. baumannii*, but resistance to specific antimicrobial agents does increase over the course of admission. Although there are differences between patients admitted immediately after burn injury (local patients vs. deployed), there was no significant difference in resistance rates.

Timely and accurate epidemiological and susceptibility information is needed to guide appropriate empirical therapy. Initial empirical antimicrobial therapy should be tailored to each individual burn ICU and based on current prevalence and resistance data. Aggressive infection control methods should be enforced to limit the cross-transmission of antibiotic resistant pathogens and continued development of new antibiotics against MDR Gram-negatives and focus on alternative treatment regimens is imperative. Increasing resistance to antimicrobial agents during the course of hospitalization is a concern and determining whether patients are acquiring new pathogens or present pathogens are developing resistance through drug pressure represents an area of future research.

## Conflict of interest

The authors have no conflict of interest to report.

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