Acinetobacter baumannii Skin and Soft-Tissue Infection Associated with War Trauma

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(See the article by Whitman et al. on pages 439–43)

Background. Acinetobacter baumannii is usually associated with nosocomial pneumonia or bacteremia. Reports of A. baumannii skin and soft-tissue infection (SSTI) are uncommon.

Methods. We performed a retrospective review of 57 inpatients admitted to a naval hospital ship and identified 8 patients with A. baumannii–associated SSTI. Demographic and clinical characteristics were compared between these patients and 49 patients with A. baumannii infections that were not SSTIs. We also reviewed 18 cases of A. baumannii–associated SSTI from the literature.

Results. Our 8 cases of A. baumannii–associated SSTI were associated with combat trauma wounds. The median age of the patients was 26 years. Although not statistically significant, A. baumannii–associated SSTIs were more likely to be associated with gunshot wounds (75% vs. 55%) or external fixators (63% vs. 29%), compared with A. baumannii infections that were not SSTIs. Use of a central venous catheter and total parenteral nutrition was also more common for patients with SSTI. Our cases of A. baumannii–associated SSTI presented as cellulitis with a “peau d’orange” appearance with overlying vesicles and, when untreated, progressed to necrotizing infection with bullae (hemorrhagic and nonhemorrhagic). In our case series, all isolates were multidrug resistant, and clinical success was achieved for 7 of 8 patients with debridement and carbapenem therapy.

Conclusions. A. baumannii–associated SSTI is an emerging infection in patients who experience trauma. Clinicians should be aware of the potential role of A. baumannii as a multidrug-resistant pathogen causing hospital-acquired SSTI, particularly when associated with previous trauma or use of invasive devices. It should be suspected in patients who experience trauma and have edematous cellulitis with overlying vesicles. Early empirical coverage for drug-resistant species (e.g., with carbapenem therapy), combined with debridement, is usually curative.

Acinetobacter species are nonfermentative, gram-negative rods distributed widely in the environment. Acinetobacter species can form part of the endogenous bacterial flora of humans, particularly in the skin, oral cavity, and respiratory tract. Humidity is a common environmental factor associated with skin colonization (the toe webs, axilla, and groin are the sites with the highest rates of colonization) [1]. The skin colonization rate was initially reported to be 25% [2]; however, taxonomic changes make current interpretation of these data difficult. Skin carriage rates in a more recent study [3] were 75% among inpatients and 43% among non-hospitalized control subjects, although the majority (99%) of organisms isolated were not the Acinetobacter species that commonly cause nosocomial infections. Colonization rates among the general public may actually be lower, because control subjects included microbiology laboratory employees. Despite these colonization rates, A. baumannii–associated skin and soft-tissue infection (SSTI) is fairly uncommon; a 4-year review of >1700 microbiological isolates from Latin American medical centers revealed that Acinetobacter species were isolated from 4.1% of all SSTIs [4].

Among military members, a recent study of healthy soldiers found that 17% of these soldiers were colonized with Acinetobacter species; however, isolates had antibiotic susceptibility and ribotyping findings different from those for nosocomial comparators associated with infection [5]. Since 2003, the incidence of A. baumannii infection in US military hospitals has increased, pri-
marily among wounded troops from Southwest Asia [6]. One of our investigators noted an association between unusual skin infections contiguous to trauma wounds and Acinetobacter bacteremia during a 2003 outbreak of infection on a US Navy hospital ship [7]. Here, we report all of the cases of war wound–associated SSTI in which A. baumannii was recovered and present evidence to establish and confirm the pathogenic role of A. baumannii in a unique infectious disease syndrome.

METHODS

Fifty-seven Acinetobacter infections occurring in 211 inpatients admitted to hospital ship USNS Comfort from March through May 2003 were reviewed for identification of A. baumannii–associated SSTIs. Patients included wounded US service members and Iraqi civilian adults and children injured in the conflict. Individual charts were reviewed, and SSTIs were identified on the basis of definitions of the Infectious Diseases Society of America [8]. In addition to these SSTI criteria, we also required isolation of A. baumannii from sterile body fluid (e.g., blood) or a wound with dehiscence, purulence, or foul smell and at least 1 side of the following findings: fever (temperature, >38°C), hypotension (systolic blood pressure, ≤10,000 cells/µL). A total of 8 cases were identified. Microbiological isolates were identified in debrided tissue specimens obtained in the operating room under sterile conditions and in blood culture specimens obtained under sterile conditions; culture of fluid aspirated under sterile conditions from a bulla was performed for 1 patient (patient 8). Histopathologic analysis of tissue specimens was not available on USNS Comfort. Wound material underwent Gram staining and culture on blood, chocolate, and MacConkey agars and in thioglycollate broth. Blood specimens were cultured aerobically and anaerobically with use of BBL Septi-Chek Blood Culture System (Becton Dickinson). Identification was performed with use of API 20E strips (bioMérieux). Susceptibility testing was performed by the Kirby Bauer disk method [9], with use of criteria established by the Clinical Laboratory and Standards Institute (formerly the NCCLS) [10]. A composite trauma injury severity score was calculated at the time of culture [11]. The demographic, wound pattern, and clinical characteristics of the 8 patients were compared with those of 49 other patients with A. baumannii infections that were not trauma-associated SSTIs (e.g., pneumonia); the infections were defined according to the respective Centers for Disease Control and Prevention definitions [12]. Dimensional differences between groups were tested with use of the nonparametric Kruskal-Wallis test, and categorical variables were tested with use of Fisher’s exact test. P < .05 was considered to be statistically significant. Analysis was conducted with use of Stata, version 9 (StataCorp). A search of the Medline database for the period 1966–2007 was performed with use of the search terms “cellulitis” or “soft-tissue infection” and “Acinetobacter.” All studies identified were reviewed, as were references cited in the articles but not found in the original search. This study was reviewed and approved by the Institutional Review Board of the National Naval Medical Center.

RESULTS

We noted 8 cases of A. baumannii SSTI (table 1). All patients were male; 7 were Iraqi nationals, and 1 was an American soldier. The median age of the patients was 25.5 years (range, 13–55 years). Five patients had gunshot wounds, 2 had shrapnel wounds, and 1 had a blunt force injury (from a motor vehicle accident). Patients were moderately injured overall. The median injury severity score was 11 (range, 4–25), and 3 patients (37.5%) met the criteria for sepsis. Mortality was 12.5%. The median time from injury to hospital admission was 5 days (range, 2–13 days). All of the patients were evacuated from forward field hospitals after undergoing emergent stabilizing surgical procedures. With the exception of patient 2, all of the patients received perioperative antibiotic therapy before the diagnosis of Acinetobacter SSTI was determined; most of the patients received cephalosporins (6 received cefazolin, and 1 received ceftriaxone). One-half of the patients also received antibiotics, including fluoroquinolones and/or aminoglycosides, for other indications (e.g., sepsis) before the diagnosis of SSTI was determined. The median time from injury to the clinical diagnosis of culture-proven A. baumannii SSTI was 15 days (range, 5–17 days).

All 8 patients had a similar clinical presentation of SSTI. Cellulitis (figure 1, left) was initially well demarcated, erythematous, mildly edematous ("peau d’orange" appearance), and slightly warm to the touch. It arose from the margins of the infected wound (figure 2) in all of the patients except 1 bacteremic patient (patient 3); this patient’s cellulitis was remote from the wound and was in an area with no skin breaks (figure 1, right). Cellulitis progressed to a sandpaper-like appearance from a distance, and on close inspection (figure 3, left), numerous overlying small (1-mm) vesicles containing clear fluid were seen. Two patients (patients 3 and 8) with initially unrecognized A. baumannii–associated SSTI became bacteremic and developed hemorrhagic bullae, suggesting necrotizing infection at all areas with skin breaks (e.g., old sites of intravenous catheter use or blood sample obtention) (figure 3, right).

All A. baumannii isolates were multidrug resistant. All were susceptible to imipenem; 7 were susceptible to imipenem only, and 1 was also susceptible to amikacin. Susceptibility testing for polymyxin E (colistin) and tigecycline was not performed. Copathogens were isolated in samples from 5 of the 8 patients. Enterobacter cloacae was the most common copathogen (3 of 8 patients). Proteus species were present in 2 patients (1 had Proteus mirabilis isolated, and 1 had Proteus vulgaris isolated) and were always isolated with Enterobacter species. Pseudomonas aeruginosa and Streptococcus species (Lancefield group B) were also each isolated once.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Sex</th>
<th>Comorbidities</th>
<th>Copathogen(s)</th>
<th>Location</th>
<th>Devices present</th>
<th>Sepsis</th>
<th>ISS score</th>
<th>Previous antibiotic therapy</th>
<th>Test used to determine pathogen</th>
<th>Final treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>M</td>
<td>Shrapnel injury on right upper extremity, bilateral lower extremities</td>
<td>Proteus vulgaris, Enterobacter cloacae</td>
<td>Left foot</td>
<td>External fixator, wound drain, CVC</td>
<td>No</td>
<td>No</td>
<td>OR culture</td>
<td>13 Cefoxitin, tobramycin</td>
<td>Debridement (3 times), imipenem plus clasin (12 days)</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>M</td>
<td>Motor vehicle accident with right femur fracture</td>
<td>E. cloacae</td>
<td>Right ankle</td>
<td>External fixator, wound drain, CVC, Foley</td>
<td>No</td>
<td>No</td>
<td>OR culture</td>
<td>9 None</td>
<td>Debridement (2 times), imipenem plus clasin (21 days), tobramycin (17 days)</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>M</td>
<td>Gunshot wound on pelvis</td>
<td>E. cloacae, Proteus mirabilis</td>
<td>Abdomen, neck, chest, perineum</td>
<td>ET tube, NG tube, wound drain, CVC, Foley</td>
<td>Yes</td>
<td>Yes</td>
<td>Blood, OR culture</td>
<td>25 Cefazolin, ceftriaxone, clindamycin, vancomycin</td>
<td>Debridement (once), imipenem plus clasin (1 day)</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>M</td>
<td>Gunshot wound on right thigh, left leg</td>
<td>Pseudomonas aeruginosa</td>
<td>Left leg</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>OR culture</td>
<td>4 Cefazolin</td>
<td>Debridement (once), imipenem plus clasin (7 days)</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>M</td>
<td>Shrapnel injury on neck, jaw, head, frontal head injury with dural tear, open fracture of mandible</td>
<td>None</td>
<td>Left face</td>
<td>ET tube, NG tube, wound drain, CVC, Foley</td>
<td>No</td>
<td>No</td>
<td>OR culture</td>
<td>18 Cefazolin</td>
<td>Debridement (once), oesophagojejunostomy (7 days)</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>M</td>
<td>Gunshot wound on left shoulder; open humerus fracture</td>
<td>Group B Streptococcus species</td>
<td>Left shoulder</td>
<td>NG tube, external fixator, CVC, Foley</td>
<td>No</td>
<td>No</td>
<td>OR culture</td>
<td>9 Cefazolin, gentamicin</td>
<td>Debridement (4 times), imipenem plus clasin (16 days), tobramycin (17 days)</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>M</td>
<td>Gunshot wound on right buttock; femur fracture, sciatic nerve injury</td>
<td>None</td>
<td>Hip, abdomen</td>
<td>External fixator, NG tube, ET tube</td>
<td>Yes</td>
<td>No</td>
<td>Blood, OR culture</td>
<td>14 Ampicillin, clindamycin, levofloxacin, tetracycline</td>
<td>Debridement (6 times), imipenem plus clasin (19 days)</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>M</td>
<td>Gunshot wound on abdomen</td>
<td>None</td>
<td>Abdomen, right flank</td>
<td>ET tube, NG tube, wound drain, CVC, Foley</td>
<td>Yes</td>
<td>No</td>
<td>Blood, bullae culture</td>
<td>25 Cefoxitin, nafcilin, clindamycin, vancomycin, ciprofloxacin</td>
<td>Debridement (6 times), imipenem plus clasin (9 days), vancomycin (10 days), fluconazole (9 days), doxycycline (3 days)</td>
</tr>
</tbody>
</table>

**NOTE.** CVC, central venous catheter; ET, endotracheal; ISS, infection severity score; NG, nasogastric; OR, operating room.

* Blood culture for *A. baumannii* alone; wound culture for *A. baumannii, E. cloacae, and P. mirabilis.*
All 8 patients underwent 1–6 wound debridements. Seven surviving patients clinically improved with debridement and antibiotic therapy (figure 2). Of these 7 patients, 1 patient recovered with debridement and oral cephalexin therapy alone, and the remaining 6 received intravenous imipenem plus cilastatin (500 mg every 6 h) for a median duration of 14 days (range, 7–21 days). Patient 3 died of overwhelming sepsis after receiving 2 doses of imipenem.

Our search of the Medline database revealed 12 articles and 1 abstract that reported 18 cases of A. baumannii SSTI. Only 1 case was related to combat trauma [13], and the majority were dissimilar to our cases. Among our patients, no statistically significant differences were found between the patients with SSTIs and the patients with other Acinetobacter infections, except that the patients with SSTIs more frequently received total parenteral nutrition (25% vs. 2%; \( P = 0.049 \)). Gunshot wounds (75.0% vs. 55.1%; \( P = 0.3 \)) and external fixators (62.5% vs. 29.2%; \( P = 0.1 \)) were found in the majority of patients with SSTI but were also common among patients with A. baumannii infections that were not war trauma–associated SSTIs.

**DISCUSSION**

Historically, A. baumannii–associated SSTIs have been rare. Of 18 reviewed cases, only 7 (39%) were associated with cellulitis, and 7 (39%) were associated with necrotizing fasciitis. Mortality associated with A. baumannii–associated SSTI is high; 15% of reviewed patients died, which is consistent with the 12.5% observed mortality among our patients. We identified some trends related to combat trauma–related A. baumannii–associated SSTI versus other Acinetobacter infections, but our numbers were small, and the trends could have been a result of chance. In our case series, gunshot wounds and placement of an external orthopedic fixator were common in the majority of patients with SSTI (but to a lesser extent in patients with other trauma–associated Acinetobacter infections). Historically, 35% of A. baumannii–associated SSTIs have involved invasive medical devices. Both fixators, because of their foreign nature and multiple skin penetrations, and gunshot exit wounds, which have been shown to quickly become colonized with environmental flora in animal models [14], might be sites of development of SSTI in a hospital area that is highly contaminated with Acinetobacter species. Our significant positive correlation between SSTI and total parenteral nutrition is likely to be a surrogate marker for more severe injury that predisposes to infection.

We identified some clinical features that we believe to be indicative of A. baumannii–associated SSTI. In our cases, SSTI evolved from an edematous “peau d’orange” appearance to a sandpaper appearance with overlying clear vesicles, followed by a necrotizing process with hemorrhagic bullae at areas of previous skin disruption, with accompanying bacteremia. Although histopathologic examination was not available, the clinical appearance in patients 3 and 8 (figures 2 and 3, right) was sufficient to diagnose necrotizing infection and was identical to that in a recent histopathologically proven case of war–associated necrotizing fasciitis [13]. In our literature review, we found other rare reports of necrotizing A. baumannii SSTIs featuring both “peau d’orange” cellulitis developing vesicles [15] (also progressing to sepsis and death) and bacteremia concurrent with bullae [16]; these findings provide further evidence that this is a unique infectious syndrome with recognizable features. Both of our patients who developed bullae (patients 3 and 8) had bacteremia; this shows the usefulness of blood cultures for identifying organisms causing bullous cellulitis when wound cultures are not available.

Acinetobacter virulence factors and the role of copathogens clearly require further study. Recently, a role for copathogens in the development of necrotizing war trauma–related Acinetobacter infection was suggested [13]. Five wounds in our case series contained copathogens, 1 of which was associated with a necrotizing infection. Copathogens were noted in 6 patients with necrotizing fasciitis in the literature and included Klebsiella pneumoniae [13], Enterococcus faecalis, Candida albicans [17], and group A Streptococcus species [18]. In the largest series that we reviewed, all Acinetobacter species–associated necrotizing SSTIs involved copathogens, but details regarding those organ-

**Figure 1.** Cellulitis caused by Acinetobacter baumannii on the abdomen (left) and neck (right) of a 16-year-old male patient (patient 3). Cellulitis was associated with a gunshot to the pelvic area, later progressed to bacteremia, and was fatal.
isms are lacking [19]. Although Enterobacter [20] and Klebsiella [21] species are rarely reported to cause hemorrhagic bullae and could be considered to have caused infection in our patients and in those in the study by Perez et al. [13], clearly, the isolation of A. baumannii alone in blood and/or bulla fluid specimens from 3 of our patients argues for A. baumannii as the causative agent of the observed syndrome. In addition, the dearth of copathogens, such as Streptococcus pyogenes, Aeromonas hydrophila, and Vibrio vulnificans— which classically cause “peau d’orange” cellulitis or necrotizing infection with hemorrhagic bullae—both in our observations and in the literature adds weight to this argument. However, necrotizing fasciitis caused by A. baumannii without copathogens has only been reported once in the previous literature [15] and occurred in a minority (3 of 8 cases; 1 necrotizing infection) of our cases. Most likely, copathogens synergistically cause necrotizing infection and might create a nidus of entry into the bloodstream for Acinetobacter species. Additional research is needed.

Surgical debridement remains paramount to the management of SSTI. The effectiveness of debridement was demonstrated by the patient who recovered after facial wound debridement (the antibiotics used would not have been effective). This might have been attributable to the face having a more abundant vascular supply than other areas and to facial wounds healing differently than other war wounds [24]. Another unique aspect of these infections was that none of the patients required fasciotomy. Carbapenems were effective for antimicrobial adjunctive therapy and should be favored for treatment of SSTI presenting as bullous or necrotizing cellulitis in the context of war injury. However, providers should be aware that carbapenem resistance is increasing in Acinetobacter species [25].

Military hospitals have recently seen an increase in the number of nosocomial A. baumannii infections; studies suggest a nosocomial transmission source in field hospitals [6]. Seven of 8 patients in our case series were Iraqi nationals treated in these field hospitals. After stabilization, such patients are currently transferred to civilian hospitals in Iraq, but at the time of this study, they were kept in field hospitals for prolonged periods; these patients might have served as a reservoir of colonization in these hospitals. A. baumannii infection still occurs in soldiers returning from Iraq and Afghanistan, but only 1 additional A. baumannii–associated SSTI [13] has been reported since our cases from 2003. This may be attributable to successful infec-
tion-control efforts, to frequent carbapenem use for empirical treatment of wound or serious infections, to increased transfer of potentially colonized Iraqi source patients to nonmilitary facilities in Iraq, or in part, to US soldiers having *A. baumannii* immune response or colonization rates that differ from those of Iraqi nationals.

Because few case reports of *A. baumannii*-associated SSTI have been reported, it is difficult to determine whether antecedent colonization with *A. baumannii* predisposes a person to *Acinetobacter* SSTI. Previous studies reported low rates of both colonized military outpatients [5] and colonized wounds at initial injury [26] and a lack of nosocomial *Acinetobacter* infections [3, 5]. Our mean time to SSTI diagnosis of 12.8 days is more consistent with nosocomial acquisition than with infection as a result of previous colonization as an outpatient. Antibiotic treatment before diagnosis of *A. baumannii*-associated SSTI was received by 7 of our 8 patients and by 13 of 18 patients with SSTI in the literature, suggesting that antibiotics (primarily cephalosporins) may place patients at risk of SSTI infection with multidrug-resistant pathogens such as *A. baumannii*.

Cellulitis and other SSTIs associated with *Acinetobacter* species are likely to be underrecognized and may be underreported because of the difficulty of isolation of a causative organism in most patients with cellulitis. Certainly, the potential for development of this unique SSTI exists in members of the military with polytrauma and in other patients, such as immunocompromised patients. Sources of colonization and infection and their interrelationship in military hospitals require further study. Clinicians who work in areas where *A. baumannii* colonizes the skin or is part of the local environmental flora should be aware of its potential as a multidrug-resistant pathogen causing hospital-acquired SSTI, particularly when associated with antecedent trauma or use of invasive devices.

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**References**