Impact of *Acinetobacter* Infection on the Mortality of Burn Patients

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BACKGROUND: *Acinetobacter calcoaceticus-baumannii* complex (Acb) is recognized as an important cause of nosocomial infections. Although Acb can be associated with multidrug resistance, its impact on mortality in burn patients has not been fully elucidated.

STUDY DESIGN: In a retrospective cohort study assessing medical records and microbiology laboratory data at a US military tertiary care burn center, we evaluated all patients admitted to the burn center between January 2003 and November 2005. Data collected included age, severity of burn, comorbidities, length of stay, and survival to hospital discharge. In addition, microbiology data were reviewed to determine which patients were infected with Acb during this time frame. These data were then used to compare patients infected with Acb to patients not infected. Multivariate analysis using logistic regression was performed to determine which patient characteristics were associated with increased mortality.

RESULTS: There were 802 patients included in the study. Fifty-nine patients met the case definition for infection. An additional 52 patients were found to be colonized with Acb. Patients with Acb infection had more severe burns and comorbidities, and had longer lengths of stay compared with patients without Acb or those with Acb colonization. Mortality in infected patients was higher compared with those without infection (relative risk = 2.86, p = 0.001). On multivariate analysis, infection with Acb was not statistically associated with mortality.

CONCLUSIONS: Multidrug-resistant Acb is a common cause of nosocomial infection in the burn patient population. Despite this, it does not independently affect mortality. (J Am Coll Surg 2006;203: 546–550. © 2006 by the American College of Surgeons)

The US military health-care system has recently witnessed an increased rate of infections caused by the *Acinetobacter calcoaceticus-baumannii* complex (Acb), primarily in soldiers injured while deployed to Iraq or Afghanistan.[1] This also appears to be an increasing problem in burn patients worldwide.[2-5] These infections have had an impact on soldiers evacuated to the burn center of the US Army Institute of Surgical Research (Fort Sam Houston, TX). Although Acb infections seem to be associated with a high mortality, it is unclear whether this increased mortality is a result of the infection itself or the underlying characteristics of the infected patients. To date, other studies that have examined the mortality attributable to Acb have reported mixed results.[3,6-10] Further characterizing the effect of Acb infection on burn patient mortality will direct development of proper treatment strategies. We performed a retrospective cohort study of all patients admitted to the US Army Institute of Surgical Research Burn Center to determine the effect of Acb infection on mortality.

METHODS

The US Army Institute of Surgical Research Burn Center is the only tertiary care burn center in the US military health-care system. It provides definitive burn treatment

Competing Interests Declared: None.

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to military beneficiaries, to include service members burned in combat. In addition, in its role as part of a regional burn center, it also serves civilian burn patients from south Texas. On average, the center operates 44 beds, including 16 in the ICU.

The electronic medical records database of the burn center was searched to identify all patients admitted from January 2003 through November 2005. For each admission, the following information was extracted: age, total body surface area burned, Injury Severity Score, length of stay in hospital, length of stay in the ICU, days requiring mechanical ventilation, presence of inhalation injury, and survival to hospital discharge. In addition, the microbiology records were searched to determine which patients had cultures growing Acb.

For patients with Acb recovered on culture, charts were further reviewed to determine whether the cultures represented infection or colonization. All patients with Acb isolated from normally sterile sites, to include blood, were considered infected. Respiratory infections included pneumonia, which was defined as a positive respiratory culture if accompanied by a new infiltrate on chest x-ray; a change in the consistency or an increase in amount of sputum; and two of the following: worsening oxygenation (by either PaO_2 or O_2 saturation), new fever (>101°F), or new leukocytosis (WBC >11,000 cells/μL). In addition, patients with inhalational injury who had a positive respiratory culture and new fever associated with obvious purulence noted on fiberoptic bronchoscopy were also considered to have a respiratory infection. Isolates from other nonsterile sites, such as urine or wounds, were considered infections if they were associated with signs and symptoms of infection both systemically and at the site of isolation. Patients who had positive cultures, but who did not meet these definitions for infection, were considered to be colonized. Patients were deemed colonized on admission if cultures drawn during the first 24 hours of their hospitalization grew Acb.

For patients with Acb, the following information was additionally extracted: length of time before development of colonization and time to infection. The records of patients found to be colonized on admission were further examined to study the impact of colonization on subsequent development of infection. Infected patients were reviewed to determine whether effective antimicrobial therapy was given. Effective therapy was defined as use of at least one antimicrobial with in vitro activity against the first isolate associated with a given infection. Antimicrobial susceptibilities of each isolate were determined using the VITEK2 automated system (bioMerieux VITEK Inc). Kirby-Bauer disk diffusion testing was performed as confirmation in multidrug-resistant isolates.

Table 1. Types of *Acinetobacter* Infections Seen in the US Army Institute of Surgical Research Burn Center from January 2003 to November 2005

Type of infection	n
Bacteremia	31
Respiratory source	8
Primary	23
Respiratory infection	22
Pneumonia	17
Other	5
Burn wound infection	4
Urinary tract infection	1
Peritonitis	1

Statistical comparison between Acb groups (infected, colonized, or neither) was performed using Kruskal-Wallis ANOVA and Mann-Whitney tests for continuous variables and Pearson chi-square tests for proportions. The impact of colonization on admission on the further development of infection was described using Pearson's chi-square test. The comparison of time to development of infection between those colonized and those not colonized was done using an independent sample *t*-test. Fisher's exact test was used to describe the impact of appropriate therapy on mortality. The univariate analysis of risk factors for mortality was performed using Spearman's rank correlation. Multivariate analysis was performed using stepwise logistic regression. For all tests, differences were considered statistically significant if the p values were <0.05.

RESULTS

From January 2003 through November 2005, 821 patients were admitted to the burn center. Nineteen patients still in the hospital at the end of the study period were excluded, leaving 802 patients for inclusion in the analysis.

One hundred eleven patients had cultures growing Acb, of which 59 met the case definition for infection (Table 1). Bacteremia was the most common type of infection, accounting for 31 of 59 infections. Eight bacteremias were from a respiratory source. The remaining 23 did not have an obvious source. Although it was presumed that the source was translocation

Table 2. Comparison of Study Groups with Respect to *Acinetobacter* Culture Status

	***Acinetobacter* culture status**		
	Positive		
Characteristic	**Infected (n = 59)**	**Colonized (n = 52)**	**Negative (n = 691)**
Mean age, y (range)	32.2 (19–81)	29.8 (17–79)	35.9 (11–100)
Mean % TBSA burned (range)	29.1 (<1*–80)[†‡]	23.8 (2–81.5)	14.2 (<1*–97.9)
Mean Injury Severity Score (range)	20.7 (1–51)[†‡]	16.9 (1–38)	6.3 (0–75)
% with inhalational injury	37.3[‡]	26.9[‡]	9.6
Mean length of stay, d (range)	56.3 (2–266)[†‡]	44.0 (1–207)[‡]	14.5 (<1–285)
Average in ICU, d (range)	31.3 (0–126)[†‡]	15.4 (0–102)[‡]	4.6 (0–206)
Average on ventilator, d (range)	20.4 (0–121)[†‡]	6.3 (0–69)[‡]	2.7 (0–206)

*Includes patients with electrical burns.
[†]Statistically different compared with colonized patients ($p < 0.05$).
[‡]Statistically different compared with patients with negative cultures ($p < 0.05$).
TBSA, total body surface area.

through a burn wound, other sources such as catheters, gut translocation, or other unknown source could not be ruled out. Pneumonia without bacteremia was the second most common infection seen, with 17 patients. Burn wound infections, urinary tract infections, peritonitis, and other respiratory infections made up the remainder of patients. In general, patients with Acb infection had more severe burns, more comorbidities, and longer lengths of stay than those patients with colonization or no Acb recovered (Table 2).

Fifty-one patients were colonized with Acb within 24 hours of admission. These patients were at increased risk of Acb infection later in their hospital stay compared with those not colonized within 24 hours (45.8% risk versus 4.3% risk, $p < 0.001$). Infection developed in those individuals with colonization on admission, on average, 4.0 (±4.5 SD) days after admission, compared with 16.9 (±19.7 SD) days for those not colonized on admission ($p < 0.002$). Patients colonized within 24 hours of admission were assumed to have acquired colonization at other health-care facilities during initial treatment. For this group, it was not possible to adequately determine earlier treatment or length of evacuation time. In an attempt to prevent spread of Acb from these patients to others in the burn unit, special precautions are used on all patients admitted to the burn unit. This includes use of single room, cohort nursing; and the required wearing of sterile gown, gloves, and mask for all patient contact. Despite this, 50 patients (6% of all admissions during the study period) acquired Acb colonization or infection later in their hospital stay, suggesting nosocomial spread.

There were 70 deaths during the study period, of which 13 occurred in patients with Acb infection. Mortality with infection was 22%, compared with 7.7% in those without infection (relative risk = 2.86, $p = 0.001$). On univariate analysis, the following factors were also found to be associated with mortality: infection with Acb, age, percent total body surface area burned, Injury Severity Score, length of ICU stay, time spent on the ventilator, and presence of inhalational injury. On multivariate analysis, only age, percent total body surface area burned, Injury Severity Score, and time spent on the ventilator were associated with increased mortality (Table 3).

Most of the Acb isolates seen were resistant to a broad range of antimicrobials (Table 4). Imipenem had the greatest activity, with 61% of isolates being susceptible. Five isolates were resistant to all tested antimicrobials. Forty-nine (83%) of the infected patients received effective therapy, as defined previously. The majority of these patients (32) received imipenem-cilastatin. Other antimicrobials administered included amikacin, tobramycin, ampicillin/sulbactam, pipericillin/tazobactam, ciprofloxacin, tigecycline, colistin, and trimethoprim-sulfamethoxazole. Seventeen patients received combination therapy with two agents. There was no statistical difference in mortality between those treated with effective agents and those who were not (24.5% versus 10%, respectively, $p = 0.432$).

DISCUSSION

In this large series of burn patients, we examined the mortality attributable to Acb. We found that Acb infection occurred in 7.4% of burned patients admitted to

Table 3. Analysis of Factors Associated with Mortality in Burn Patients

Risk factor	p Value Univariate*	p Value Multivariate†
Infection with Acb	<0.01	0.651
Age	<0.01	<0.01
% TBSA burned	<0.01	<0.01
Injury Severity Score	<0.01	0.044
Presence of inhalational injury	<0.01	0.061
Increasing length of stay	0.114	—
Increasing length of stay in ICU	<0.01	0.882
Increasing time on the ventilator	<0.01	<0.01
Colonization with Acb on admission	0.267	—
Appropriate therapy for Acb infection	0.322	—

*Spearman's rank correlation.
†Step-wise logistic regression.
Acb, *Acinetobacter*; TBSA, total body surface area.

Table 4. In Vitro Susceptibilities of Infection-Associated *Acinetobacter* Isolates*

Antimicrobial	% of isolates susceptible
Imipenem	61
Amikacin	36
Ampicillin-sulbactam (n = 58)	24
Tobramycin	22
Piperacillin-tazobactam	14
Trimethoprim-sulfamethoxazole	12
Gentamicin	10
Ciprofloxacin	8
Levofloxacin	8
Cefepime (n = 49)	6
Ceftriaxone	3
Aztreonam (n = 48)	2

*n = 59 unless otherwise specified.

our center. Infection was more common in those with larger burns, higher Injury Severity Scores, and increased length of time on the ventilator or in the ICU. Infection occurred, on average, 4 days after admission in those colonized with Acb, and 17 days in those who were not. On univariate analysis, Acb infection was associated with burn-related mortality and morbidity, but on multivariate analysis was not independently associated with death. This finding adds additional insight into the role of Acb as a nosocomial pathogen, which so far has not been clearly defined. Our study suggests that although Acb is a marker of increased crude mortality because of its association with larger burns, it does not affect mortality independently.

Earlier studies have attempted to address the attributable mortality of Acb, with mixed results. Some studies have reported an increased attributable mortality secondary to Acb, others have not.[6-10] Data that specifically addresses burn patients are no less clear. Most earlier studies dealing with Acb in burn patients are limited to case series that report on crude mortality rates but do not correct for severity of burn or other underlying diseases. These series tend to report an increase in crude mortality for Acb-infected patients when compared with controls.[4,5,11] In the only earlier study that specifically analyzed attributable mortality, the only predictor of death in patients with Acb was the underlying severity of illness as measured by the APACHE II score.[3] This study did not distinguish between Acb infection and colonization, possibly biasing the results toward a falsely low attributable mortality.[3] In contrast, our study examined the specific role of infection and still found little attributable mortality.

Of note is the fact that in our study, Acb therapy was not associated with a mortality benefit. Although this might have been a result of the small sample size (only 10 patients were not treated with effective agents), it raises an interesting issue. Previous studies have demonstrated that therapy has less correlation to outcomes than severity of underlying illness.[12,13] In a recent report on Acb extremity infections in soldiers returning from Iraq and Afghanistan, all patients had good outcomes, regardless of the therapy chosen.[14] One of the facts complicating Acb therapy is the bacterium's ability to develop broad-spectrum antimicrobial resistance. This often leads to the use of more toxic antimicrobials, such as colistin or the aminoglycosides. Physicians should perhaps reconsider use of these potentially toxic or unproven antimicrobials in the treatment of these infections.

Aside from mortality, we also examined Acb colonization and its role in development of subsequent infection. In our study, colonization with Acb was associated with increased risk of infection with Acb. Colonization at time of admission was associated with a more rapid onset of infection. This suggests that colonization with Acb can also be a marker of increased morbidity in burn patients and that procedures to reduce the rate of colonization can be beneficial.

This study is limited by its retrospective design and use of only a single burn center's data. To the best of our knowledge, this is the largest series of Acb infection in

burn patients to date. As such, it provides new insight into the management of these infections.

Acinetobacter calcoaceticus-baumannii complex infection and colonization appear to be markers of increased mortality, as they typically occur in patients with severe injuries and more extensive burns. Acb infections do not appear to independently affect mortality. Clinicians should consider these data when treating Acb infections in the future.

Author Contributions

Study conception and design: Albrecht, Griffith, Murray, Hospenthal, Holcomb, Wolf

Acquisition of data: Albrecht, Griffith, Murray, Chung, Horvath, Hospenthal, Holcomb, Wolf

Analysis and interpretation of data: Albrecht, Griffith, Murray, Chung, Horvath, Ward, Hospenthal, Holcomb, Wolf

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