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Scientific Research

Bacteremia Caused by *Acinetobacter baumannii*: Epidemiologic Features, Antimicrobial Susceptibility, and Outcomes

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Abstract

Acinetobacter baumannii **bacteremia is becoming more prevalent and is associated with increasing morbidity and mortality. Escalating antibacterial resistance further contributes to therapeutic dilemmas, enhanced infection control support and poorer outcomes in patients infected with these bacteria. A retrospective analysis of patients whose blood cultures produced *A. baumannii* from January 2007 through January 2013 was performed. Data regarding the epidemiologic features, antimicrobial susceptibility and outcomes of patients with *A. baumannii* bacteremia were collected and analyzed. Sixty *A. baumannii* isolates each from a different patient were identified. The Charlson Comorbidity Index (≥3) was the greatest among patients with multi-drug resistance (MDR) compared to intermediate drug resistance (IDR) and pan-sensitive (PS) *A. baumannii*. The mean APACHE II scores for MDR, IDR and PS *A. baumannii* bacteremia were 21, 15 and 11, respectively ($P < 0.05$, MDR v. PS). Seventy-three percent of the isolates were resistant to quinolones, 44% to piperacillin/tazobactam, 45% to amikacin, 22% to imipenem, 0% to ticarcillin/clavulanate, and 0% to polymyxin. Among 28 patients with MDR *A. baumannii* bacteremia, 20 received inadequate empiric treatment, and 16 of these patients died (80%). Of the remaining eight patients with MDR bacteremia who received adequate empiric antibiotics, only two died (25%). The severity of underlying illness, degree of antibiotic resistance and receiving inadequate initial antibiotic therapy are associated with mortality among patients with bacteremia due to *A. baumannii*.**

Keywords

***Acinetobacter baumannii*; Bacteremia**

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1. Introduction

Acinetobacter baumannii bacteremia has become a global problem with a high incidence of resistance and mortality [1] [2]. A recent survey of blood stream infections (BSIs) in the United States ranks *A. baumannii* 10th with an incidence rate of 0.6/10,000 admissions [3]. A study surveying BSIs in US hospitals from 1995-1998 documented a crude mortality rate of 32% caused by Acinetobacter species [4]. In a more recent investigation, crude mortality rates were 34% for all patients, 43% in patients from intensive care units (ICUs), and 16% in non-ICU patients [3]. Decreasing susceptibility to carbapenems, amikacin, sulbactam and the polymyxins can result in the absence of any single effective agent for treatment of infections caused by *A. baumannii* [5]. Escalating antibacterial resistance in *A. baumannii* coupled with institutional transmission continues to overwhelm infection control personnel, infectious disease specialists, pharmacists and microbiologists [5] [6].

Our hospital has coped with multidrug resistant *A. baumannii* over several years [7] [8]. We have described intervention strategies that are necessary to manage patients infected and/or colonized with such bacteria [5]. This communication reports the epidemiologic features, antimicrobial susceptibility and outcomes associated with *A. baumannii* bacteremia at our center with a major emphasis on patient outcomes by administration of appropriate initial empiric treatment.

2. Materials and Methods

2.1. Surveillance Definitions, Patient Characteristics and Outcome Measures

We performed a retrospective analysis of all patients from whom blood cultures yielded *A. baumannii* between January 2007 and January 2013. This retrospective study, which included only deidentified patient information, did not require ethics approval from Rutgers New Jersey Medical School Institutional Review Board. Data regarding the epidemiologic features, antimicrobial susceptibility and outcomes of patients with *A. baumannii* bacteremia were collected and analyzed.

Bacteremia was defined as the presence of *A. baumannii* in one or more blood cultures from a patient during hospitalization. A relapse was defined as regrowth of the original *A. baumannii* isolate after initial clearance. Clinical infection was defined by positive blood culture(s) taken in conjunction with two of the following signs or symptoms: fever, hypothermia, hypotension, tachypnea, tachycardia, or leukocytosis [4].

Acute Physiology and Chronic Health Evaluation (APACHE) II scores were recorded on the day of the bacteremia. Co-morbidities were assessed by the Charlson Comorbidity index. Associated mortality was defined as death within 30 days of a positive *A. baumannii* blood isolate. Patients were admitted either from home or from a long term care facility (LTCF), defined as a nursing home or rehabilitation facility. Pneumonia associated with bacteremia was defined by the production of purulent sputum, microbiologic confirmation of *A. baumannii* from bronchoalveolar lavage specimens, in association with radiographic findings consistent with pneumonia [4].

2.2. Antimicrobial Susceptibility

Blood isolates of *A. baumannii* were tested for susceptibility to amikacin, aztreonam, trimethroprim/sulfamethoxazole, polymyxin, ampicillin/sulbactam, piperacillin/tazobactam, ticarcillin/clavulanate, levofloxacin or ciprofloxacin, ceftazidime, cefepime, and imipenem. Pan-sensitive (PS) organisms were defined as those susceptible to all the above antibiotics. Intermediate-drug resistant (IDR) organisms were resistant to one or two classes of antibiotics. Multi-drug resistant (MDR) organisms were defined as those resistant to ceftazidime and at least two other classes of antibiotics [9].

Adequate empiric antibiotic treatment was defined as treatment started within 24 hours of bacteremia (when the positive blood was drawn) with an antibiotic that had *in vitro* activity against the isolate. We considered empiric antibiotic treatment inadequate if it did not have *in vitro* activity against the isolate or if treatment was started 24 or more hours after the positive blood was drawn.

2.3. Microbiological Identification, Antimicrobial Testing, and Statistics

Blood isolates of *A. baumannii-Acinetobacter calcoaceticus* complex were identified using the Vitek system (bioMerieux, Marcy l'Etoile, France). Species identification was confirmed by amplification of the $bla_{\text{OXA-51-like}}$ gene and by the fact that all isolates were assigned to a group by the trilocus sequencing typing protocol [10].

Antimicrobial testing was performed according to CLSI guidelines (formerly NCCLS) using Kirby-Bauer susceptibility methodology.

The data were processed using MS Excel (Microsoft, Redmond, Washington) and STATA version 8.2 (College Station, Texas). Statistical analyses were performed using Chi-square or Fisher's exact test for categorical data and ANOVA for continuous variables. Data were examined in a two-tailed fashion to estimate the *P* value. *P* values of <0.05 were considered significant.

3. Results

3.1. Patient Characteristics

All patients with clinical symptoms and bacteremia in this study had *A. baumannii* identified in one or more blood cultures during their hospitalization. No patients with non-*A. baumannii* were included in this study. **Table 1** lists the patient characteristics. The Charlson Comorbidity Index (≥3) was greatest among patients with MDR compared to IDR and PS *A. baumannii*. Sixty isolates each from a different patient were identified during the investigation. Of the 60 isolates, 28 were MDR, 17 were IDR, and 15 were PS. Among patients with bacteremia due to MDR *A. baumannii*, 13 of 28 patients (46%) were from long term care facilities (LTCF). Among those with IDR *A. baumannii* bacteremia, 6 of 17 patients (35%) were from LTCF. Of those with PS *A. baumannii* bacteremia, 2 of 15 patients (13%) was admitted from a LTCF. APACHE II scores for MDR, IDR and PS *A. baumannii* bacteremia were 21, 15, and 11 respectively ($P < 0.05$, MDR vs. IDR and IDR vs. PS).

3.2. Initial Antibiotic Usage and Susceptibility

The most frequently used initial antibiotic was pipercillin/tazobactam (27%), followed by a quinolone (18%) and an aminoglycoside (18%). In total, 73% of *A. baumannii* isolates were resistant to quinolones, 44% resistant to pipercillin/tazobactam, 60% resistant to cefepime, 45% resistant to amikacin, and 22% resistant to imipenem. None of the *A. baumannii* isolates was resistant to polymyxin or ticarcillin/clavulanate (**Table 2**).

3.3. Mortality

Overall mortality was 43% (26 of 60 patients). Mortality rates of patients with MDR, IDR, and PS *A. baumannii* bacteremia were 71% (20 of 28 patients), 29% (5 of 17 patients), and 7% (1 of 15 patients) respectively ($P < 0.05$, MDR vs. IDR; $P < 0.05$, IDR vs. PS).

3.4. Treatment and Outcome

Among 28 patients with MDR *A. baumannii* bacteremia, 20 received inadequate empiric treatment and 16 of these patients died. Eight of 17 patients with IDR *A. baumannii* bacteremia did not receive adequate empiric antibiotic treatment. Three of the eight patients that did not receive adequate empiric antibiotic treatment died. Of the fifteen patients with PS *A. baumannii* bacteremia, five received inadequate empiric therapy primarily due to delay in therapy beyond 24 hours. One of the fifteen patients died [$P < 0.05$, MDR vs IDR; $P < 0.05$, MDR vs. PS]. **Table 3** shows the inadequate initial treatment and associated mortality for patients that received inadequate initial therapy for multi-drug resistant, intermediate-resistant, and antibiotic susceptible *A. baumannii* bacteremia.

Among the 60 patients with *A. baumannii* bacteremia, repeat blood cultures were positive in four (4 of 60 [7%]), all in individuals with MDR *A. baumannii* bacteremia and whom received inadequate initial antibiotic treatment before blood cultures were repeated. Two of four patients with persistent bacteremia died. Among those who received adequate empiric treatment, no persistent bacteremia or relapse occurred.

4. Discussion

Acinetobacter is an important pathogen in traditional and nontraditional healthcare settings. Its ability to infect healthy hosts and its propensity to develop antimicrobial drug resistance has caused concern among the infectious diseases community. In our study, the crude mortality rate of *A. baumannii* was 43% which is similar to that of previous studies (16.3% - 52.0%) [3] [4] [11]-[15]. Persistent *A. baumannii* bacteremia was not demonstrated among our patients if adequate empiric antibiotics were used.

Table 1. Patient characteristics with multi-drug resistant, intermediate-resistant, and pan-sensitive *Acinetobacter baumannii* bacteremia.

	MDR *A. baumannii* (*n* = 28)	IDR *A. baumannii* (*n* = 17)	PS *A. baumannii* (*n* = 15)
Median age, y	56	59	54
Male Sex (%)	16 (57)	9 (53)	7 (47)
Mean Charlson Comorbidity Index			
1 - 2, no. (%)	18 (64)	12 (71)	13 (87)
≥3, no. (%)	10 (36)	5 (29)	2 (13)
Admitted from LTCF, no. (%)	13 (46)	6 (35)	2 (13)
Mean APACHE II	21	15	11
Relapse, no. (%)	4 (14)	0 (0)	0 (0)
Concomitant Pneumonia, no. (%)	18 (64)	8 (47)	1 (7)
Death, no. (%)	20 (71)	5 (29)	1 (7)

Abbreviations: MDR, multi-drug resistance; IDR, intermediate-drug resistance; PS, pan-sensitive; y, years; LTCF, long-term care facility; no., number.

Table 2. Antibiotic susceptibility and empiric therapy of 60 blood isolates of *Acinetobacter baumannii*.

Empiric Therapy	Resistant No. (%)	Prescribed No. (%)
Piperacillin/tazobactam	7 (44)	16 (27)
Quinolones	8 (73)	11 (18)
Amikacin	5 (45)	11 (18)
Imipenem	2 (22)	9 (15)
Ticarcillin/clavulanate	0 (0)	7 (12)
Polymyxin	0 (0)	6 (10)
Cefepime	3 (60)	5 (8)
Ampicillin/sulbactam	1 (20)	5 (8)
Trimethoprim/sulfamethoxazole	3 (60)	5 (8)
Ceftazidime	1 (50)	2 (3)
Aztreonam	1(50)	2 (3)

Abbreviations: no., number.

Table 3. Inadequate initial treatment and associated mortality for patients with multi-drug resistant, intermediate-resistant, and pan-sensitive *Acinetobacter baumannii* bacteremia.

	MDR *A. baumannii* (*n* = 28)	IDR *A. baumannii* (*n* = 17)	PS *A. baumannii* (*n* = 15)
Received Inadequate Initial Therapy, no. (%)	20 (71)	8 (47)	5 (33)
Mortality Among Patients that Received Inadequate Initial Therapy, no. (%)	16 (80)	3 (38)	1 (20)

Abbreviations: MDR, multi-drug resistance; IDR, intermediate-drug resistance; PS, pan-sensitive; no., number.

Patients with both MDR and IDR *A. baumannii* bacteremia and pneumonia had a high mortality rate. This finding is consistent with previous reports [10] [16]-[18].

Patients with MDR bacteremic strains had poorer outcomes than those with IDR and PS isolates, possibly reflecting differences in virulence of the *A. baumannii* isolates, receiving inadequate initial antibiotic therapy and/or severity of their underlying illnesses. A disturbing finding in this study was that initial antibiotic therapy, initiated without the benefit of culture and sensitivity results, was inadequate in the majority of patients infected with MDR *A. baumannii*. A novel finding in this study is demonstrated by four of five patients with PS *A. baumannii* bacteremia who survived despite inadequate empiric antibiotic treatment. This group exhibited a relatively low mean APACHE II score (mean APACHE II score of 11). Although an elevated APACHE II score appeared to be an independent risk factor for mortality, the frequent combination of MDR *A. baumannii* bacteremia, receiving inadequate initial therapy, and advanced underlying illness were associated with a higher mortality rate.

Future Recommendations

Initial adequate empiric treatment of MDR *A. baumannii* bacteremia in such patients may reduce the associated high mortality [19]-[21]. Prior studies have suggested that the severity of underlying disease yields an equivalent or greater risk for mortality than inappropriate antibiotic therapy [10] [13]-[15] [22]-[24]. The importance of appropriate antibiotic therapy may be most relevant among bacteremic patients with advanced underlying illness including pneumonia caused by MDR *A. baumannii* [18].

5. Conclusion

The severity of underlying illness, degree of antibiotic resistance and receiving inadequate initial antibiotic therapy are associated with mortality among patients with bacteremia due to *A. baumannii*. Importantly, our study emphasizes the importance of administering adequate initial empiric treatment in the survival among patients with MDR *A. baumannii* bacteremia.

Conflict of Interests and Financial Disclosures

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