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Original Article

Community-acquired bloodstream infections caused by *Acinetobacter baumannii*: A matched case–control study☆

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Abstract *Background: Acinetobacter baumannii* is an important nosocomial pathogen worldwide. Its role in community-acquired infection remains controversial and has rarely been reported.
Methods: Patients with monobacterial bloodstream infections caused by genomic species identified *A. baumannii*, admitted to Taipei Veterans General Hospital between 1999 and 2010, were selected as cases. Controls were defined as patients acquiring infection in a healthcare setting and were matched for age and sex. The clinical, epidemiologic, and microbiological characteristics of cases and controls were compared.
Results: Cases presented with shock more frequently and had higher APACHE II scores (25 vs 19, $p = 0.005$). No significant differences between the two groups were noted in the sources

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of bloodstream infection and underlying diseases. Multidrug resistance rates were higher in nosocomial *A. baumannii* isolates then in those acquired in the community (81.5% vs 38.9%, $p = 0.002$). Patients infected in the community were more likely to receive appropriate antimicrobial therapy than those with hospital-acquired *A. baumannii* (10/18; 55.6% vs 11/54; 20.4%, $p = 0.011$). Acquisition in the community (odds ratio [OR] 5.716, 95% confidence interval [CI] 1.021–32.003, $p = 0.047$), respiratory tract as the infection source (OR 9.514, 95% CI 2.370–38.189, $p = 0.001$), and immunosuppressive therapy (OR 4.331, 95% CI 1.052–17.832, $p = 0.042$) were independently associated with increased 14-day mortality among patients with *A. baumannii* bacteremia in this cohort.

Conclusion: Community-acquired bacteremia caused by *A. baumannii* was rare but associated with a severe outcome. Further investigation of potential virulence factors of community-acquired *A. baumannii* is required.

Introduction

Bloodstream infections (BSIs) are serious clinical events associated with significant morbidity and mortality.[1,2] With progressive changes in the healthcare system, a new classification scheme for BSIs has been proposed. This differentiates between infections acquired (i) in the community, (ii) by outpatients having recurrent contact with the healthcare system, and (iii) by inpatients with hospital-acquired infections. The revised classification was driven by observations of an increased risk of antimicrobial resistance and a higher mortality rate among patients with healthcare-associated BSIs (HCABSIs) than among those with community-acquired BSIs (CABSIs).[3]

Acinetobacter baumannii, *Acinetobacter nosocomialis*, and *Acinetobacter pittii* have emerged as important nosocomial pathogens causing bloodstream infection in critically ill patients. They share similar phenotypic characteristics identified by clinical microbiological laboratories, and are collectively described as the *A. baumannii* complex (Abc).[4] *A. baumannii* is clearly distinct from the latter two species because it is resistant to more classes of antimicrobial agents and it is associated with a worse clinical outcome.[5,6] The inclusion of different *Acinetobacter* species in a study would complicate the interpretation of the results. Therefore, it is reasonable to separate *A. baumannii* from other *Acinetobacter* species in the studies, including those for outcome analysis.

A. baumannii is predominantly a nosocomial pathogen, although sporadic cases of community-acquired pneumonia caused by *A. baumannii* complicated with bacteremia, have been reported.[7,8] The differences in disease epidemiology and impact on clinical outcomes between HCABSIs and CABSIs caused by *A. baumannii* have not been previously examined. Therefore, we performed a retrospective matched case–control study to compare the clinical, epidemiologic, and microbiological characteristics of HCABSIs and CABSIs caused by genomically identified *A. baumannii*.

Methods

Study population

This retrospective matched case–control study was conducted at Taipei Veterans General Hospital, a 2900-bed, tertiary care teaching hospital in Taipei, Taiwan, during a 12-year period between 1999 and 2010. Patients with mono-bacterial bloodstream infections caused by genomic species identified as *A. baumannii* were selected and classified into two groups: the case group included patients who acquired infection in the community and the control group included patients who acquired infection in a healthcare setting, matched for age (within 5 years), sex, and the year of isolation of the causative pathogen. The clinical, epidemiological, and microbiological characteristics of cases and controls were compared.

Data collection and definition

Clinical information was retrospectively extracted from the medical records. The following data were collected at bacteremia onset: demographic profile (age and sex), admission date, initial clinical symptoms, antimicrobial treatment during hospitalization, the sources of bloodstream infection, the usage of immunosuppressive therapy, recent history of trauma, recent surgery, blood analysis, ventilator use, and comorbid illnesses. Immunosuppressive therapy was defined as treatment with corticosteroids at a dosage equivalent to or higher than 15 mg of prednisolone daily for one week within 4 weeks, cytotoxic agents within six weeks, or other immunosuppressive agents within two weeks before bacteremia onset. The severity of patient infection was evaluated using the Acute Physiology and Chronic Health Evaluation (APACHE) II score within 24 h of bacteremia onset.[9] Recent surgery was defined as surgery performed within four weeks of the onset of bacteremia. Renal impairment was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 and neutropenia was determined when an absolute neutrophil count was less

than 0.5 $\times$ 10^9 neutrophils/L. We determined the primary infection source of bacteremia according to the definitions of the Centers for Disease Control and Prevention.[10] Appropriate antimicrobial therapy was defined as the administration of $\geq$1 antimicrobial agent to which the causative pathogen was susceptible *in vitro* within 24 h of the onset of bacteremia, with an approved route and dosage appropriate for end-organ function. Antimicrobial therapy that did not fulfill this definition was deemed inappropriate.

The onset of bacteremia was defined as the day on which the blood culture that eventually yielded *A. baumannii* was obtained. Community-acquired bloodstream infections (CABSIs) were defined as BSIs occurring in patients admitted to hospital from home, with no history of hospitalization within the preceding 30 days and wit no history of undergoing an invasive procedure either just before or at the time of admission.[11] Patients from nursing homes and other healthcare facilities were excluded. Further exclusion criteria were bacteremias occurring in patients on long-term dialysis or in patients admitted with intravascular devices. Patients with bloodstream infections acquired in the intensive care unit were included if the bacteremic episode took place within 48 h of ICU admission in the control group.

We evaluated 14-day mortality as the main outcome. The development of shock, the performance of intubation and tracheostomy, survival on discharge, and iatrogenic instrument use during hospitalization, were also documented.

Microbiological studies

The presumptive identification of the isolates to the level of Abc was determined by the API ID 32 GN system (bioMérieux, Marcy l'Etoile, France) or the Vitek 2 system (bioMérieux, Marcy l'Etoile, France). A multiplex PCR method was used to identify *A. baumannii* to the genomic species level.[12] Isolates identified as non-*A. baumannii* species of *Acinetobacter* were identified to the genomic species level by 16S—23S ribosomal DNA intergenic spacer sequence analysis.[13] The clonal relationships of *A. baumannii* isolates were determined by pulsed-field gel electrophoresis (PFGE).[14] Multilocus sequence typing (MLST) was performed using the Oxford scheme, as previously described.[15] Primers and PCR conditions are listed at http://pubmlst.org/abaumannii/. The MLST sequences were uploaded to http://pubmlst.org/abaumannii/ to identify alleles and sequence types. Antimicrobial susceptibilities to amikacin, gentamicin, ceftazidime, cefepime, piperacillin/tazobactam, ampicillin/sulbactam, ciprofloxacin, imipenem, and colistin were determined by the agar dilution method, according to the Clinical Laboratory Standards Institute (CLSI) criteria.[16] Multidrug resistance was defined as resistance to any one agent in at least three of the following classes of antimicrobials: antipseudomonal cephalosporins, antipseudomonal carbapenems, ampicillin/sulbactam, fluoroquinolones and aminoglycosides.[1]

Statistical analysis

The chi square test with Yate's correction or Fisher's exact test was used to compare discrete variables; the Student's *t*-test or Mann—Whitney rank sum test were used to analyze continuous variables, as appropriate. Logistic regression models were used to explore independent risk factors for 14-day mortality. Univariable analyses were performed separately for each of the risk factor to ascertain the odds ratio (OR) and 95% confidence interval (CI). All biologically plausible variables with a *P* value of $<$0.20 in the univariable analysis exhibited by at least 10% of the patients were considered for inclusion in the logistic regression model in the multivariable analysis. A backward selection process was utilized. Time to mortality was analyzed using the Kaplan—Meier survival analysis. A *P* value $<$0.05 was considered to indicate statistical significance. All of the analyses were processed using the Statistical Package for the Social Sciences (SPSS) software version 18.0 (SPSS, Chicago, IL, USA).

Results

We recruited a total of 825 patients with Abc bloodstream infections in the initial investigation. Of these, 31 patients fulfilled the criterion of community-acquired bloodstream infections caused by Abc isolates. The 31 causative microorganisms (one from each patient) were identified as *A. baumannii* (n = 18), *A. nosocomialis* (n = 7), and *A. pittii* (n = 6). Therefore, there were 18 cases fitting the case group criterion. The control group was obtained by

Table 1 Comparison of sequence types (STs) of community-acquired and hospital-acquired *A. baumannii* isolates.

ST	No. (%)		
	Community-acquired (n = 18)	Hospital-acquired (n = 54)	Total
447	3 (16.7)	0 (0.0)	3 (4.2)
208	2 (11.1)	17 (31.5)	19 (26.4)
455	2 (11.1)	5 (9.3)	7 (9.7)
473	1 (5.6)	5 (9.3)	6 (8.3)
351	1 (5.6)	0 (0.0)	1 (1.4)
684	1 (5.6)	0 (0.0)	1 (1.4)
787	1 (5.6)	0 (0.0)	1 (1.4)
883	1 (5.6)	0 (0.0)	1 (1.4)
1047	1 (5.6)	0 (0.0)	1 (1.4)
1048	1 (5.6)	0 (0.0)	1 (1.4)
449	0 (0.0)	6 (11.1)	6 (8.3)
436	0 (0.0)	5 (9.3)	5 (6.9)
218	0 (0.0)	5 (9.3)	5 (6.9)
626	0 (0.0)	1 (1.9)	1 (1.4)
699	0 (0.0)	1 (1.9)	1 (1.4)
790	0 (0.0)	1 (1.9)	1 (1.4)
856	0 (0.0)	1 (1.9)	1 (1.4)
867	0 (0.0)	1 (1.9)	1 (1.4)
873	0 (0.0)	1 (1.9)	1 (1.4)
875	0 (0.0)	1 (1.9)	1 (1.4)
879	0 (0.0)	1 (1.9)	1 (1.4)
881	0 (0.0)	1 (1.9)	1 (1.4)
882	0 (0.0)	1 (1.9)	1 (1.4)
Unknown	4 (22.2)	1 (1.9)	5 (6.9)

selecting a number of subjects three times greater than the number of cases, matching for age, sex, and the year of isolation.

We identified a seasonal bias of community-acquired bloodstream infections due to *A. baumannii*. The controls were well-distributed throughout the year, with a summer/autumn predominance. Twenty-five (25/54; 46.3%) controls were diagnosed between June and August and fifteen (15/54; 27.8%) controls were diagnosed between September and November. Most of the cases were admitted in the summer. Up to 77.8% (14/18) of cases were diagnosed during June and August and only 11.1% (2/18) of cases were diagnosed between September and November.

The case group (n = 18) comprised 15 different pulsotypes, while the control group (n = 54) comprised 26 different pulsotypes (figure not shown). The sequence types (STs) of the case group and control group were shown in Table 1. The case group and control group belonged to 14 and 17 different STs, respectively. Five isolates in the case group shared the same STs (ST 208, 455, 473) with the control group and the remaining 13 isolates in the case group belonged to STs which were totally different from those of the control group.

No significant differences were detected in the sources of bloodstream infections and underlying diseases between the two groups (Table 2). The 14-day mortality after bacteremia onset was 38.9% and 20.4% among cases and controls, respectively ($p = 0.129$). However, the patients acquiring *A. baumannii* bloodstream infections in the community presented with shock more frequently (50.0% vs 14.8%, $p = 0.008$) and their median APACHE II scores were much higher than the scores of patients acquiring *A. baumannii* bloodstream infection in a healthcare associated environment (25 vs 19, $p = 0.005$).

The multidrug resistance rates were higher in nosocomial *A. baumannii* isolates than in those acquired in the community (81.5% vs 38.9%, $p = 0.002$; Table 3). The patients with community-acquired *A. baumannii* were more likely to receive appropriate antimicrobial therapy than those with hospital-acquired *A. baumannii* (10/18, 55.6% vs 11/54, 20.4%, $p = 0.011$; Table 2).

To investigate whether acquisition in the community was an independent risk factor associated with 14-day mortality, other factors associated with mortality, were assessed by multivariate analysis. Acquisition in the community (odds ratio [OR] 5.716, 95% confidence interval [CI]

Table 2 Demographic and clinical characteristics of patients with community-acquired and hospital-acquired bloodstream infection caused by *A. baumannii*.

Demographic or characteristic	Community-acquired ($n = 18$)	Hospital-acquired ($n = 54$)	p value
Age (years)	79.5 (IQR 62.5—83)	78.5 (IQR 63—82)	0.774
Sex, male	13 (72.2%)	39 (72.2%)	1.000
Comorbidity			
Hypertension	6 (33.3%)	22 (40.7%)	0.780
Coronary artery disease	4 (22.2%)	8 (14.8%)	0.479
Congestive heart failure	1 (5.6%)	9 (16.7%)	0.434
Cerebral vascular disease	3 (16.7%)	14 (25.9%)	0.533
COPD	5 (27.8%)	8 (14.8%)	0.289
Alcoholism	0 (0%)	9 (16.7%)	0.100
Liver cirrhosis	0 (0%)	4 (7.4%)	0.566
Chronic kidney disease	6 (33.3%)	7 (13%)	0.076
Type 2 diabetes mellitus	7 (38.9%)	13 (24.1%)	0.362
Collagen vascular disease	1 (5.6%)	5 (9.3%)	1.000
Use of immunosuppressants			
Cytotoxic chemotherapy	0 (0%)	1 (1.9%)	1.000
Corticosteroids	3 (16.7%)	14 (25.9%)	0.533
Malignancy	4 (22.2%)	13 (24.1%)	1.000
Trauma	0 (0%)	1 (1.9%)	1.000
Infection source			
Respiratory tract	9 (50.0%)	20 (37.0%)	0.488
Urinary tract	2 (11.1%)	8 (14.8%)	1.000
Intravenous device	0 (0%)	9 (16.7%)	0.100
Skin and soft tissue	1 (5.6%)	3 (5.6%)	1.000
Primary bacteremia	4 (22.2%)	11 (20.4%)	1.000
Shock[a]	9 (50%)	8 (14.8%)	0.008
APACHE II score [a]	25 (IQR 21.75—33.25)	19 (IQR 16—23.25)	0.005
Appropriate antimicrobial therapy	10 (55.6%)	11 (20.4%)	0.011
Outcome			
14-day mortality	7 (38.9%)	11 (20.4%)	0.129

[a] At the time the blood culture was obtained.
Data are median values (interquartile range) for continuous variables and number of cases (%) for categorical variables.
ICU, intensive care units; COPD, chronic obstructive pulmonary disease; APACHE, Acute Physiology and Chronic Health Evaluation.

Table 3 Comparison of antimicrobial susceptibilities of community-acquired and hospital-acquired *A. baumannii* isolates.

Antimicrobial agent	Resistance, n (%)		*p* value
	Community-acquired (n = 18)	Hospital-acquired (n = 54)	
Amikacin	4 (22.2)	40 (74.1)	<0.001
Gentamicin	6 (33.3)	41 (75.9)	0.003
Ceftazidime	8 (44.4)	44 (81.5)	0.006
Cefepime	5 (27.8)	34 (63.0)	0.020
Piperacillin/tazobactam	3 (16.7)	35 (64.8)	0.001
Ampicillin/sulbactam	5 (27.8)	28 (51.9)	0.133
Ciprofloxacin	8 (44.4)	44 (81.5)	0.006
Imipenem	2 (11.1)	15 (27.8)	0.207
Colistin	0 (0)	2 (3.7)	1.000
Multidrug resistance	7 (38.9)	44 (81.5)	0.002

1.021—32.003, $p = 0.047$), respiratory tract as the infection source (OR 9.514, 95% CI 2.370—38.189, $p = 0.001$), and immunosuppressive therapy (OR 4.331, 95% CI 1.052—17.832, $p = 0.042$) were independently associated with an increased 14-day mortality among patients with *A. baumannii* bacteremia (Table 4).

Discussion

This retrospective, matched case—control study compared the clinical, epidemiological, and microbiological characteristics of HCABSIs and CABSIs caused by *A. baumannii*. We found that community-acquired bloodstream infection due to *A. baumannii* was prevalent in warm and humid months. No significant differences were detected in the sources of bloodstream infections and underlying diseases between the two groups. The 14-day mortality after bacteremia onset was 38.9% and 20.4% among cases and controls, respectively. However, the patients acquiring *A. baumannii* bloodstream infection in the community presented with shock more frequently and their APACHE II scores were considerably higher. The multidrug resistance rates were lower in community-acquired *A. baumannii* isolates. The patients with community-acquired *A. baumannii* were more likely to receive appropriate antimicrobial therapy than those with hospital-acquired *A. baumannii*. Acquisition in the community was independently associated with an increased 14-day mortality among patients with *A. baumannii* bacteremia.

A. baumannii has emerged as an important nosocomial and healthcare-setting-associated pathogen worldwide during recent years and has evolved, displaying one of the most efficient antibiotic resistance patterns with a relevant all-cause mortality rate of up to 40%.[16—18] The nosocomial outbreaks of *A. baumannii* could be an issue of influence

Table 4 Logistic regression analysis of predictors of 14-day mortality among patients with *Acinetobacter baumannii* bacteremia in this cohort.

Demographic or characteristic	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Community-acquired[a]	2.488 (0.783—7.904)	0.122	5.716 (1.021—32.003)	0.047
Age in year	1.010 (0.973—1.049)	0.607		
Sex, male	0.700 (0.221—2.219)	0.545		
Hypertension	0.518 (0.162—1.660)	0.269		
Coronary artery disease	1.643 (0.430—6.281)	0.468		
Congestive heart failure	0.719 (0.138—3.745)	0.695		
Cerebral vascular disease	0.571 (0.144—2.274)	0.427		
COPD	0.880 (0.213—3.630)	0.860		
Alcoholism	1.600 (0.356—7.187)	0.540		
Liver cirrhosis	1.000 (0.097—10.265)	1.000		
Chronic kidney disease	0.880 (0.213—3.630)	0.860		
Type 2 diabetes mellitus	0.435 (0.111—1.706)	0.233		
Collagen vascular disease[b]	7.429 (1.232—44.807)	0.029		
Immunosuppressive therapy[a]	3.500 (1.136—10.779)	0.029	4.331 (1.052—17.832)	0.042
Respiratory tract as infection source[a]	9.100 (2.579—32.104)	0.001	9.514 (2.370—38.189)	0.001
Appropriate antimicrobial therapy	0.913 (0.279—2.989)	0.881		

[a] Variable included in the logistic regression model in multivariable analysis.
[b] Not included in the multivariable analysis because this condition was present in less than 10% of the cases.
CI, confidence interval; COPD, chronic obstructive pulmonary disease.

because of its long survival characteristics in the inanimate environment and lack of valid infection control practices or judicious antibiotic strategies. *A. baumannii*, particularly the multidrug-resistant isolates, can cause different types of healthcare-associated infection, including bacteremia,[19] resulting in catastrophic consequences, with an overall 14-day mortality rate of up to 29.8%.[20] However, the role of *A. baumannii* in community-acquired bloodstream infections remains controversial. To the best of our knowledge, this study is the first matched case—control surveillance investigating the clinical, epidemiologic, and microbiological characteristics of community-acquired bloodstream infections due to *A. baumannii*. We identified a prevalent trend of community-acquired bacteremia resulting from *A. baumannii* during the warm and humid months of the year in Taiwan; this finding is consistent with previous studies on community-acquired pneumonia due to *A. baumannii*.[7,21]

Although some community acquired isolates shared the same STs as the hospital acquired isolates, the majority had different STs compared with the hospital acquired isolates. Furthermore, the results of PFGE and ST analyses suggested greater diversity of the community acquired isolates compared to those acquired in the hospital setting.

There was no statistically significant difference in 14-day mortality after bacteremia onset between cases and controls; however, patients acquiring *A. baumannii* bloodstream infections in the community presented with shock more frequently and their APACHE II scores were much higher. This suggests that community-acquired *A. baumannii* bloodstream infections are more severe diseases.

We reported inappropriate antimicrobial therapy as an independent risk factor associated with 14-day mortality in patients with *A. baumannii* bloodstream infections, although it is important to note that most patients acquired *A. baumannii* in a healthcare setting. However, because multidrug resistance rates among community-acquired isolates were considerably lower, the number of cases with inappropriate antimicrobial therapy was also lower. In order to remove the effect of appropriate antimicrobial therapy on mortality, multivariate logistic analysis was performed and showed that isolate acquisition in the community was an independent risk factor for 14-day mortality among patients with *A. baumannii* bloodstream infections. This suggests that there are additional virulence factors among community-acquired *A. baumannii*.

One of the main limitations of our study is that it was based on a single-center experience. Although Taipei Veterans General Hospital is a tertiary center, with 2900 beds, the endemic situation may not be representative of the majority of community-acquired bloodstream infections due to *A. baumannii* occurring worldwide. A further limitation is that this was a retrospective study, with small numbers of community-acquired infections, and only 14 day all-cause mortality was used. In addition, the *A. baumannii* complex (Abc) includes at least three different genomic species, including *A. baumannii*, *A. pittii*, and *A. nosocomialis*,[6] and is phenotypically undifferentiated. Further studies are required to investigate the role of other members of Abc in community-acquired bloodstream infections.

In conclusion, our results suggest that community-acquired bloodstream infections caused by *A. baumannii* were rare but severe. Further studies are required to assess potential virulence factors of community-acquired *A. baumannii*.

Conflict of interest statement

The authors declare that they have no conflict of interest related to the research question published here.

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