Risk factors for acquisition and mortality of multidrug-resistant Acinetobacter baumannii bacteremia

A retrospective study from a Chinese hospital

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Abstract

Bloodstream infection caused by Acinetobacter baumannii has become a major clinical concern, especially multidrug-resistant A baumannii (MDRAB). The aim of this study was to identify the risk factors of nosocomial acquired MDRAB bacteremia and determine the risk factors related to the mortality of patients with MDRAB bacteremia. Patients with nosocomial acquired A baumannii bacteremia were enrolled between January, 2013 and December, 2017 at the First Affiliated Hospital, School of Medicine, Zhejiang University. Medical records were reviewed, and the clinical and microbial characteristics were collected. Among the 338 patients suffering from A baumannii bacteremia, 274 patients were infected with MDRAB bacteremia. Bacteremia-related mortality was 46.4% for the overall sample; 56.2% for MDRAB bacteremia patients, 4.7% for non-MDRAB bacteremia patients. The identified risk factors for developing MDRAB bacteremia were previous exposure to carbapenems [odds ratio (OR) 5.78, \( P = .005 \)] and penicillins-\(\beta\)-lactamase inhibitors (OR 4.29, \( P = .009 \)). Primary bacteremia tended to develop non-MDR bacteremia (OR 0.10, \( P = .002 \)). The risk factors for MDRAB bacteremia-related mortality were old age (OR 1.02, \( P = .003 \)), high Pitt bacteremia score (OR 1.32, \( P = .001 \)), bacteremia occurring after severe pneumonia (OR 8.66, \( P < .001 \)), while catheter-related infection (OR 0.47, \( P = .049 \)) and operations for treating infection (OR 0.51, \( P = .043 \)) may have a better outcome. Patients with MDRAB had a higher mortality rate. Patients with previous carbapenems and penicillins-\(\beta\)-lactamase inhibitor exposure are at an increased risk of MDRAB bacteremia, whereas patients with primary bacteremia tended to develop non-MDR bacteremia. The risk factors for MDRAB bacteremia-related mortality were old age, a high Pitt bacteremia score, and bacteremia occurring after severe pneumonia, whereas catheter-related infection and operations for the treatment of infection may have a better outcome.

Abbreviations: CDC = Centers for Disease Control, CRRT = continuous renal replacement therapy, ICU = intensive care unit, MDRAB = multidrug-resistant A baumannii, OR = odds ratio, TNF = tumor necrosis factor.

Keywords: Acinetobacter baumannii, bacteremia, MDRAB, multidrug-resistant, risk factors

1. Introduction

Bloodstream infection caused by Acinetobacter baumannii has become a major concern in the clinic.\(^{[1,2]}\) The propensity for antimicrobial resistance in A baumannii results in the spread of multidrug-resistant (MDR) phenotypes\(^{[3-5]}\) which may lead to a lack of effective therapeutics\(^{[6]}\) long hospital stay\(^{[7]}\) and high rates of mortality.\(^{[8,9]}\) Some studies have reported risk factors associated with MDR acquisition in A baumannii bacteremia,\(^{[8,10,11]}\) including the host’s condition, prior antimicrobial drug exposure (especially broad-spectrum antibiotics), previous colonization with A baumannii, increased Pitt bacteremia score, being in the intensive care unit (ICU), and recent invasive procedures. The risk factors of mortality of A baumannii bacteremia have been reported in different parts of the world in recent years,\(^{[6-10,12,13]}\) including old age, neutropenia, malignancy, surgery before bacteremia, being post-transplantation, severity of illness defined by Pitt bacteremia score or Acute Physiology and Chronic Health Evaluation II score, ICU stay, having a lower level of albumin, respiratory tract as the origin of bacteremia, and inappropriate initial antimicrobial therapy.

For the purpose of prevention and effective treatment of MDR A baumannii (MDRAB) bacteremia, the clinical features, epidemiology, and outcomes of MDRAB bacteremia in our hospital should be reviewed and analyzed. The aim of this study was to identify the risk factors of nosocomial acquired MDRAB bacteremia.
bacteremia and to determine the risk factors related to the mortality of patients with MDRAB bacteremia.

2. Methods

2.1. Study design and patient population

This study retrospectively reviewed consecutive in-patients with *Acinetobacter baumannii* bacteremia between January 1, 2013 and December 31, 2017 at the First Affiliated Hospital, School of Medicine, Zhejiang University, a 2000-bed referral hospital in Hangzhou, China. Adult inpatients hospitalized >3 days with bacteremia due to *A baumannii* and having symptoms and signs of infection were included in the study. For patients with ≥2 positive blood cultures, only the first episode was selected. No patient was included twice in the study. Patients with positive culture results considered to be due to contaminants as recorded in the case notes were excluded.

2.2. Data collection and definition

Medical records were reviewed, and the data on the following parameters were collected: patient characteristics, underlying diseases, primary admission diagnosis, prior exposure to antimicrobial agents, previous immunosuppressant use, previous corticosteroid use, invasive procedure use, source of bacteremia, whether the patient was in the ICU at the time of onset of bacteremia, the patients’ Pitt bacteremia score, treatment after onset of bacteremia, 7-day mortality, 14-day mortality, 28-day mortality, and *A baumannii* bacteremia-related mortality.

The onset of bacteremia was defined as the day when the blood culture that eventually grew *A baumannii* was obtained. Chronic lung diseases included chronic obstructive pulmonary disease, bronchiectasis, pulmonary fibrosis, and old pulmonary tuberculosis. Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m². Prior exposure to antimicrobial agents was defined as antibiotics for at least 72 hours within a 14-day period before the onset of bacteremia. Treatment with other recognized T-cell immunosuppressants, such as cyclosporine, tumor necrosis factor (TNF)-α blockers, specific monoclonal antibodies (such as alemtuzumab), or nucleoside analogs in the 30-day period before the onset of bacteremia was defined as previous immunosuppressant use. Previous corticosteroid use was defined as the use of corticosteroids at a mean minimum dose of 0.3 mg/kg/d of prednisone equivalent for at least 72 hours within a 30-day period before the onset of bacteremia. The source of bacteremia was clarified according to the Centers for Disease Control (CDC) definitions for nosocomial infections (1988). A catheter-associated bacteremia was defined according to the United States Centers for Disease Control and Prevention guidelines. The Pitt bacteremia score was used to assess the severity of acute illness. An appropriate antimicrobial therapy was defined as the administration of at least q antimicrobial agent for at least 72 hours, to which a pathogen was sensitive according to susceptibility tests, within 72 hours of onset of bacteremia, with an approved route and dosage appropriate for end-organ function. Cefoperazone-Sulbactam therapy was defined as intravenous Cefoperazone-Sulbactam (1:1) treatment for at least 72 hours, within 72 hours of onset of bacteremia, with a dosage of at least 2g every 8 hours. Pneumonia was defined with a confirmatory chest radiograph indicating a new infiltrate, and severe pneumonia was diagnosed according to previous definition: all cases of ventilator-associated pneumonia, requirement for ICU admission, need for vasopressor support, and need for ventilatory support (either invasive or noninvasive). Operations for treating infection include drainage of infection sites, removal or replacement of catheters, and surgical debridement.

Clinical cure and microbiological eradication were measured at 7 days and 14 days after breakthrough *A baumannii* bacteremia. The evaluation of clinical response was made on the basis of resolution of clinical signs and symptoms, including fever, leukocytosis, C-reactive protein level, and improvement of radiological imagine. Clinical cure was defined as the resolution of presenting symptoms and signs of infection. Clinical improvement was defined as partial improvement of presenting symptoms and signs of infection. Clinical failure was defined as persistence or worsening of presenting symptoms and/or signs of infection. Microbiological eradication was defined as a negative culture for *A baumannii* in the specimen culture obtained at follow-up; persistence of the pathogen was defined as persistent growth of *A baumannii* regardless of the clinical outcome of the infection.

*Acinetobacter baumannii* bacteremia-related death was considered if ≥1 of the following criteria were present: blood cultures were positive for *A baumannii* bacteremia at the time of death; death occurred before resolution of signs and symptoms of *A baumannii* bacteremia; and death occurred within 14 days after breakthrough *A baumannii* bacteremia, without another explanation.

2.3. Bacterial isolates and identification

The isolates from blood were identified by the Vitek GNI-card (bioMérieux, Marcy-l’Étoile, France) as *Acinetobacter calcoaceticus-A baumannii* complex. Susceptibility testing of the *A baumannii* isolates was performed using the agar dilution method as defined by the Clinical Laboratory Standards Institute. The susceptibility results were interpreted in accordance with the Clinical and Laboratory Standards Institution. MDRAB is defined as nonsusceptibility to at least 1 agent in 3 or more antimicrobial categories. These *A baumannii* isolates were further defined as MDRAB or non-MDRAB according to the international expert proposal for interim standard definition for *Acinetobacter* spp.

2.4. Statistical analysis

The mean and standard deviation were calculated for continuous variables with a normal distribution, and median and inter-quartile range (IQR) was calculated for those with a non-normal distribution. Student test and the Mann-Whitney test were used to compare continuous variables, and the chi-square test or Fisher exact test was used for independent binomial variables according to the number of observations. A P value of <.05 was considered as statistically significant. All variables with P < .05 in the univariate analysis were included in the logistic regression for multivariate analysis. Statistics were performed with the Statistical Package for Social Science (IBM SPSS (V.19), Chicago, IL).

3. Results

During the 60-month study period, 338 patients were diagnosed with *A baumannii* bacteremia and were included in our study. Of all the enrolled patients, 235 (69.5%) were males, and the mean age was 62.1 years old (ranging from 22 to 98 years). The median hospital stay until isolation of *A baumannii* was 13 days, and the
The median total hospital day was 27.5 days. The 7-day mortality, 14-day mortality, and 28-day mortality rates were 32.8%, 44.1%, and 50.0%, respectively. A baumannii bacteremia-related mortality was 46.4%. The A baumannii isolates included 274 (81.1%) MDRAB and 64 (18.9%) non-MDRAB isolates. The MDRAB was most isolated in January and December, whereas non-MDRAB was isolated in August and September (Fig. 1). Antibiotic susceptibility rate: Gentamycin 36.3%, Tobramycin 41.3%, Amikacin 64.7%, Imipenem 22.7%, Ciprofloxacin 23.7%, Levofloxacin 26.8%, Piperacillin-tazobactam 19.3%, cefoperazone-sulbactam 21.7%, Ampicillin-sulbactam 21.7%, Ceftriaxone 3.4%, Ceftazidime 20.1%, Cefepime 22.7%, Trimethoprim-sulphamethoxazole 37.4%, Tigecycline 79.2%.

3.1. Severity and outcomes of MDRAB and non-MDRAB bacteremia

Variables related to the clinical presentation of A baumannii bacteremia were analyzed and are listed in Table 1. Compared with non-MDRAB bacteremia, MDRAB bacteremia patients had a serious condition at the time of onset of bacteremia, a longer hospital stay, and poor outcomes. In particular, the attributed mortality in MDRAB bacteremia was significantly higher than in non-MDRAB bacteremia (56.2% vs 4.7%).

3.2. Risk factors for development of A baumannii bacteremia

Demographic and clinical characteristic data of patients with MDRAB and non-MDRAB bacteremia are shown in Table 1. Cases of MDRAB bacteremia resulting from catheter-related and respiratory infection were significantly more prevalent than those of non-MDRAB bacteremia, whereas primary bacteremia was more common in cases of non-MDRAB bacteremia. Using univariate analysis, factors associated with MDRAB bacteremia included ICU stay, a longer hospital stay before isolation of A baumannii, emergency surgery, mechanical ventilation, tracheal intubation, central vein catheterization, urinary catheter, continuous renal replacement therapy (CRRT) and other recent invasive procedures, prior use of corticosteroid, carbapenem, penicillins+β-lactamase inhibitors, glycopeptide, quinolones, tigecycline, linezolid and antifungal drugs, and catheter-related infection, respiratory infection and primary bacteremia as source of bacteremia. Patients with MDRAB bacteremia were similar to patients with non-MDRAB bacteremia with respect to age, sex, underlying diseases, elective surgery, and other infection as sources of bacteremia (including surgical wound infection, intra-abdominal infection, central nervous system, skin and soft tissue infection, P > .05, data not shown). Multivariate analysis showed that the risk factors for developing MDRAB bacteremia were previous exposure to carbapenems (odds ratio [OR] 5.78, P = .005) and penicillins +β-lactamase inhibitors (OR 4.29, P = .009). Primary bacteremia tended to develop non-MDR bacteremia (OR 0.10, P = .002).

3.3. Risk factors for MDRAB bacteremia-related mortality

Due to the significant bacteremia-related mortality rates between patients with MDRAB or non-MDRAB bacteremia, analysis was conducted separately.

As shown in Table 2, in patients with MDRAB bacteremia, using univariate analysis, factors independently associated with bacteremia-related outcomes included old age, catheter-related infection, respiratory infection, higher Pitt bacteremia score, bacteremia occurring after severe pneumonia, adequate dosage of cefoperazone-sulbactam therapy, and operations for treatment of infections.
Multivariate analysis showed that old age (OR 1.02, \(P = .366\)), a high Pitt bacteremia score (OR 1.32, \(P < .001\)), bacteremia occurring after severe pneumonia (OR 8.66, \(P < .001\)) were the risk factors for MDRAB bacteremia-related mortality, whereas catheter-related infection (OR 0.47, \(P = .049\)) and operations for treatment of infection (OR 0.51, \(P = .043\)) may have a better outcome.

4. Discussion

Bloodstream infection caused by MDRAB has become a major concern in the clinic. In this study, we sought to conclude the clinical features and outcomes of MDRAB and non-MDRAB bacteremia, identify the risk factors for developing MDRAB bacteremia, and MDRAB bacteremia-related mortality.

Gram-negative bacteria, including \(A\) \(baumanni\), are increasingly recognized as exhibiting seasonal trends in bloodstream infection incidence; that is, significantly higher rates of \(A\) \(baumanni\) bacteremia were observed during the summer months.[25–29] However, in our study, the \(A\) \(baumanni\) strains were mostly isolated in winter months (January and December), whereas non-MDRAB strains were isolated in late summer (August and September). These results can influence clinical diagnosis and empiric antibiotic treatment.

In contrast to non-MDRAB bacteremia, MDRAB bacteremia had a notably higher attributed mortality.[2,30,31] Our results also

### Table 1

Severity and outcomes of MDRAB and non-MDRAB, and risk factors for development of MDRAB bacteremia.

| Risk factors | MDRAB (n = 274) | Non-MDRAB (n = 64) | Univariate \(P\) | Multivariate analysis |
|--------------|----------------|-------------------|----------------|----------------------|
|               | Mean (SD)      | Mean (SD)         |                | OR (95% CI)         | \(P\)              |
| Mean age (y)  | 62.0 (12.5)    | 62.5 (12.5)       | .804           |                     |                   |
| No. of bacteremia-related mortality | 56.2% | 58.8% | \(<.001^{*}\) | 5.20 (1.09, 24.91) | <.001^{*} |
| No. of severe pneumonia before onset of bacteremia (%) | 77 (28.8) | 14 (21.9) | \(<.001^{*}\) | 5.10 (1.34, 19.48) | <.001^{*} |
| No. of ICU stay (%) | 184 (67.2) | 12 (18.8) | \(<.001^{*}\) | 4.50 (1.74, 11.96) | <.001^{*} |
| Mean hospital stay until isolation (d) | 14.0 | 9.5 | \(<.001^{*}\) | 1.00 (0.97, 1.03) | <.001^{*} |
| No. of underlying diseases (%) | 219 (79.9) | 53 (82.8) | \(<.001^{*}\) | 0.60 (0.40, 1.88) | <.001^{*} |
| No. of renal failure (%) | 166 (60.6) | 25 (39.1) | \(<.001^{*}\) | 0.22 (0.09, 0.49) | <.001^{*} |
| No. of corticosteroid use (%) | 106 (38.7) | 3 (4.7) | \(<.001^{*}\) | 0.20 (0.08, 0.48) | <.001^{*} |
| No. of male (%) | 190 (69.3) | 45 (70.3) | .879 (0.527, 1.731) | 1.00 (0.80, 1.25) | .123 |
| No. of ICU stay (%) | 184 (67.2) | 12 (18.8) | \(<.001^{*}\) | 4.50 (1.74, 11.96) | <.001^{*} |
| Median hospital stay until isolation (d) | 14.0 | 9.5 | \(<.001^{*}\) | 1.00 (0.97, 1.03) | <.001^{*} |
| No. of underlying diseases (%) | 219 (79.9) | 53 (82.8) | \(<.001^{*}\) | 0.60 (0.40, 1.88) | <.001^{*} |
| No. of recent invasive procedures (%) | Emergency surgery | 77 (28.1) | 4 (6.3) | \(<.001^{*}\) | 2.00 (1.06, 3.84) | <.001^{*} |
| Elective surgery | 44 (16.1) | 4 (6.2) | .893 (0.527, 1.521) | 1.00 (0.80, 1.25) | .576 |
| Mechanical ventilation | 215 (78.8) | 12 (18.8) | \(<.001^{*}\) | 7.95 (3.15, 20.53) | <.001^{*} |
| Tracheal intubation | 219 (79.9) | 14 (21.9) | \(<.001^{*}\) | 7.33 (2.77, 20.57) | <.001^{*} |
| Central ven catheterization | 205 (74.8) | 40 (62.5) | \(<.001^{*}\) | 1.00 (0.90, 1.11) | <.001^{*} |
| Urinary catheter | 250 (91.2) | 21 (32.8) | \(<.001^{*}\) | 2.42 (1.20, 4.85) | <.001^{*} |
| Percutaneous drainage | 141 (51.5) | 27 (42.2) | .182 (0.397, 1.193) | 1.00 (0.80, 1.25) | .576 |
| CRRT | 92 (33.6) | 3 (4.7) | \(<.001^{*}\) | 0.20 (0.08, 0.48) | <.001^{*} |
| Other invasive procedure | 166 (60.6) | 25 (39.1) | \(<.001^{*}\) | 0.22 (0.09, 0.49) | <.001^{*} |
| No. of immunosuppressant use (%) | 60 (21.9) | 11 (17.2) | .405 (0.66, 2.747) | 1.00 (0.80, 1.25) | .576 |

\(\text{CI} = \text{confidence interval, CRRT = continuous renal replacement therapy, ICU = intensive care unit, IQR = interquartile range, MDRAB = multidrug-resistant Acinetobacter baumannii, OR = odds ratio.}\)

\(\text{\(* = P < .05.\)}\)
demonstrated that MDRAB bacteremia had poor outcomes including a serious condition at the time of onset of bacteremia, a longer hospital stay, a lower clinical cure rate, a lower microbiological eradication rate, and higher mortalities. The total attributed mortality rate of *A baumannii* bacteremia and MDRAB was 46.4% and 56.2%, respectively, which was similar to previously reported rates of 44.8% and 59.4% in a hospital in northern China.

Given the notably high mortality of MDRAB bacteremia, we reviewed the risk factors for developing MDRAB bacteremia. Antibiotic exposure is 1 of the most frequently reported risk factors for MDRAB colonization or infection,[10,11,32,33] and the use of carbapenems, third-generation cephalosporins, and β-lactams has been reported. Antibiotic therapy facilitates the emergence of new resistant mutants or the proliferation of antibiotic-resistant *A baumannii* by exerting selective pressure.[14] Compatible with these reports, we revealed that previous exposure to carbapenems and penicillins+β-lactamase inhibitors were independent risk factors for developing MDRAB bacteremia. As our results showed, recent invasive procedures related to a higher incidence of MDRAB acquisition.[11,13] Invasive procedures may promote the cross-transmission and invasiveness of pathogens; moreover, invasive procedures partly reflect the severity of the illness.

Our results are consistent with previous studies showing that respiratory infections and intravascular catheters were the most frequent sources of nosocomial *A baumannii* bloodstream infections.[22,25] A matched case-control study found no significant difference in the portals of entry of bacteremia between MDRAB and non-MDRAB bacteremia.[11] However, our study revealed that MDRAB bacteremia mostly resulted from catheter-related and respiratory infections, whereas most non-MDRAB bacteremia were primary bacteremia. Our unmatched design may have an effect on these univariate analysis results.

A number of diverse factors have been investigated as potential risk factors for attributable mortality in MDRAB bacteremia patients.[16–10,12,13] As expected, old age and a high Pitt bacteremia score were independent risk factors for mortality, whereas catheter-related infection and operations for treatment of infection were protective factors. Removing the tube can remove the cause of catheter-related infection directly, so patients had a better prognosis when catheter-related infection was the source of bacteremia. Moreover, we found that bacteremia occurred after severe pneumonia was another risk factor; this can be explained that MDRAB bacteremia complicated with severe pneumonia demonstrated a poor condition of patients.

The importance of timely and appropriate antimicrobial therapy for MDRAB bacteremia is well known.[36–39] However, similar to some studies,[12,40,41] our results revealed that the use of appropriate antimicrobial therapy was not found to be associated with the mortality of MDRAB bacteremia. Cefoperazone-Sulbactam can overcome β-lactamase-mediated resistance and restore the activity of the co-formulated β-lactams and possesses intrinsic activity against *Acinetobacter* species.[142] Tigecycline has become a promising option for the treatment of MDRAB infections.[143] Tigecycline/sulbactam combination has synergy and partial synergy activity to *A baumannii* isolates.[144,45] Nevertheless, our results showed that therapy regimes containing tigecycline or Cefoperazone-Sulbactam, even a combination of both, had no significant effect on the mortality of MDRAB bacteremia. The ineffective antimicrobial treatment partially causes high mortality in our study.

### 5. Conclusions

In conclusion, patients with MDRAB had a higher mortality rate, patients with previous carbapenems and penicillins+β-lactamase inhibitor exposure, and patients who received other recent...
invasive procedures are at an increased risk of MDRAB bacteremia. The risk factors for MDRAB bacteremia-related mortality were old age, a high Pitt bacteremia score, and bacteremia occurring after severe pneumonia, whereas catheter-related infection and operations for the treatment of infection may have a better outcome. Further research should determine the effective antimicrobial treatment of MDRAB bacteremia.

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