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ORIGINAL ARTICLE

Comparison of pneumonia- and non-pneumonia-related *Acinetobacter baumannii* bacteremia: Impact on empiric therapy and antibiotic resistance

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Objective: *Acinetobacter baumannii* (AB) bacteremia has increasingly emerged as a nosocomial pathogen in healthcare settings, associated with high patient morbidity and mortality. The objective of this study was to compare clinical features, risk factors, treatment outcome, and antibiotic resistance in patients with pneumonia- and non–pneumonia-related AB bacteremia.
Methods: We conducted a retrospective study in a tertiary teaching hospital in northern Taiwan. The medical records of the 141 episodes of hospital-acquired AB bacteremia between July 1, 2006 and June 30, 2012 were reviewed, and sorted into groups of AB bacteremia with ($n = 59$) and without pneumonia ($n = 82$).
Results: The hospital-acquired pneumonia-related AB bacteremia group were found to be significantly more frequently treated in intensive care units (49.2%, $p < 0.001$), but the AB bacteremia without pneumonia group were significantly more frequently treated on general wards (85.4%, $p < 0.001$). Patients with pneumonia tended to be older than the nonpneumonia group (72.8 years vs. 65.2 years in mean age, $p < 0.01$), and more likely to use mechanical ventilators (62.7% vs. 15.9 %, $p < 0.001$). Pneumonia patients were found to receive broad-spectrum antibiotics significantly earlier than nonpneumonia patients ($p < 0.001$). Compared to those without pneumonia, the patients with pneumonia had significantly higher incidence of

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antibiotic-resistance ($p < 0.05$), longer hospital stay ($p < 0.01$), and higher mortality rate ($p < 0.001$). The incidence of multidrug-resistant AB was significantly higher in patients with pneumonia ($p < 0.05$), and only colistin ($p < 0.01$) and tigecycline ($p < 0.01$) were significantly active against multidrug-resistant AB isolates.
Conclusion: Pneumonia-related AB bacteremia has a worse outcome, more antibiotic resistance, and more comorbidity than the nonpneumonia group.

Introduction

Acinetobacter species, Gram-negative coccobacilli that inhabit water and soil,[1] have emerged from being organisms with questionable pathogenicity to significant pathogens during the late 1970s.[2] It is now recognized as a ubiquitous pathogen responsible for both community- and healthcare-associated infections.[3–5] *Acinetobacter baumannii* (AB), *Acinetobacter* genomic species 3, and *Acinetobacter* genomic species 13TU are the three most clinically relevant species, and AB has emerged as the most troublesome pathogen for healthcare institutions globally.[5–8] As these three *Acinetobacter* species are closely related and it is difficult to distinguish among them in phenotypic properties, some authors have proposed to refer to the species as the AB—*Acinetobacter calcoaceticus* complex.[5,6]

Acinetobacter species with intrinsic resistance to antibiotics are found in nature.[1] Because of its propensity to accumulate diverse mechanisms of antibiotic resistance, multidrug-resistant AB (MDRAB) has become prevalent in many hospitals and healthcare facilities.[4,7–11] Carbapenem-resistant AB- or MDRAB-related infections have been linked to increased mortality, length of hospital stay, and clinical costs.[6] The clinical manifestations of AB bacteremia range from transient bacteremia to fatal infection.[9,12–15] In this study, we compared pneumonia- and non—pneumonia-related AB bacteremia, in terms of clinical features, risk factors, treatment outcome, and antibiotic resistance.

Materials and methods

Study design

We conducted a retrospective study in a teaching hospital in northern Taiwan, which consists of 730-beds with a 50-bed intensive care unit (ICU). After reviewing medical records of the adult patients with AB bacteremia between July 1, 2006 and June 30, 2012, we identified a total of 141 episodes of hospital-acquired AB bacteremia, and sorted them into two groups for comparison, with 59 episodes of pneumonia- and 82 episodes of non—pneumonia-related bacteremic groups respectively.

We included only hospitalized patients of being admitted $>$ 48 hours in this study. Exclusion criteria were: patients $<$ 18 years; patients with AB only isolated from a tip culture of the central catheter line without a peripheral positive blood culture, and with no fever or systemic inflammatory response syndrome; and patients with separated AB bacteremia episodes within 10 days. There was no duplicate case in our study.

Definitions

Pneumonia-related bacteremia was defined as positive blood and sputum culture with clinical diagnosis of pneumonia. The diagnosis of pneumonia required a new or increased infiltration on chest radiography with two or more of the following findings: purulent respiratory tract secretions (having $>$ 25 neutrophils per high-power field); positive sputum culture from a quantitative bacterial culture; and no pulmonary edema or other pulmonary infiltrative diseases.

The definition of MDRAB in this study is modified from the interim standard definitions for multidrug-resistant organism, which was created by international experts from the European Centre for Disease Prevention and Control and the Centers for Disease Control and Prevention.[13] MDRAB was defined as intermediate or complete resistance to at least one agent in three or more of the following nine antimicrobial categories: sulbactam plus β-lactams (either ampicillin or cefoperazone); piperacillin plus tazobactam; aminoglycoside; carbapenem; quinolone; colistin (polymyxin E); tigecycline (glycylcycline); co-trimoxazole; and third- and fourth-generation cephalosporins.[13] Appropriate empirical antimicrobial therapy was defined as: if the initial antibiotics that were administered within 48 hours after the acquisition of a blood culture sample included at least one antibiotic that was active *in vitro* and administration of antibiotics was in accordance with medical guidelines.[16]

The susceptibility of AB isolates to antimicrobial agents was determined using the Phoenix machine automatically (BD Company, Nogales, AZ, USA) or disk-diffusion test as recommended by the Clinical and Laboratory Standards Institutes. In this study, the susceptibility of tigecycline was interpreted by disk-diffusion test (if inhibition zone $\geq$ 19 mm: susceptible, 15—18 mm: intermediate, and $\leq$ 14 mm: resistance).

Data collection

The demographic characteristic data in medical records included age, sex, underlying diseases, invasive medical procedures, and use of steroid and antibiotics in the previous 1 month. We also evaluated the locations of where

the bacteremia occurred, the relation to healthcare infection, and the susceptibility to antimicrobial agents. The Charlson comorbidity index was calculated to reflect the severity of the disease. The outcomes of interest were the cause of death, 30-day survival rate, and the length of hospital stay.

Statistical analysis

Continuous variables were presented as mean ± standard deviation. We compared clinical presentations and outcomes categorically with the Student *t* test for continuous variables, and with Fisher's exact test for discrete variables. We computed all analyses with the SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA). Differences between groups were considered significant if $p < 0.05$.

Results

Tables 1 and 2 list demographic and clinical characteristic data of 141 patients with AB bacteremia with and without pneumonia. All these 141 AB strains were isolated during

Table 1 Demographic and clinical characteristics of 141 patients with *Acinetobacter baumannii* bacteremia with and without pneumonia

Patient characteristics	Pneumonia-related bacteremia ($n = 59$)	Non-pneumonia-related bacteremia ($n = 82$)	*p*
Age (y)	72.8 ± 16.7	65.2 ± 15.5	0.006
Male sex	39 (66.1)	49 (59.8)	0.443
Underlying diseases			
Diabetes mellitus	22 (37.3)	33 (40.2)	0.723
Liver cirrhosis	9 (15.3)	9 (11.0)	0.453
Chronic lung disease	22 (37.3)	10 (12.2)	< 0.001
Malignancy	18 (30.5)	48 (58.5)	0.001
Cerebrovascular disease	25 (42.4)	21 (25.6)	0.036
Hypertension	34 (57.6)	46 (56.1)	0.856
Heart failure	13 (22.0)	12 (14.6)	0.256
Coronary artery disease	13 (22.0)	13 (15.9)	0.351
Renal failure (creatinine > 2.0 mg/dL)	21 (35.6)	21 (25.6)	0.201
Peripheral artery disease	4 (6.8)	10 (12.2)	0.289
Pressure sore	13 (22.0)	1 (1.2)	< 0.001
Charlson Comorbidity index	7.8 ± 3.4	5.9 ± 2.9	< 0.001
Use of steroids	13 (22.0)	9 (11.0)	0.074
Invasive devices and procedures			
Recent major surgery (within 1 mo)	15 (25.4)	21(25.6)	0.980
Mechanical ventilation	37 (62.7)	13 (15.9)	< 0.001
Endotracheal tube	24 (40.7)	9 (11.0)	< 0.001
Tracheostomy	9 (15.3)	4 (3.7)	0.015
Central venous catheterization	44 (74.6)	50 (61.0)	0.091
For CVC access and CVP monitoring	40 (67.8)	34 (41.5)	0.002
Double lumen for hemodialysis	7 (11.9)	3 (3.7)	0.061
Implanted portacath	3 (5.1)	18 (22.0)	0.006
Foley catheterization	44 (74.6)	31 (37.8)	< 0.001
Nasogastric tube	46 (78.0)	23 (28.0)	< 0.001
Previous antibiotic used (within 1 mo)	54 (91.5)	52 (63.4)	< 0.001
Carbapenem	27 (45.8)	9 (11.0)	< 0.001
Sulbactam + β-lactams	12(20.3)	3 (3.7)	0.002
Other β-lactams	40 (67.8)	48 (58.5)	0.263
Quinolone	16 (27.1)	10 (12.2)	0.024
Healthcare-associated infections	55 (93.2)	76 (92.7)	0.902
Bacteremia after hospitalization (> 72 h)	31 (52.5)	37 (45.1)	0.384
Residents from healthcare facilities	8 (13.6)	4 (4.9)	0.068
Recent hospitalization (within 3 mo)	16 (27.1)	29 (35.4)	0.300
Locations of positive blood culture			
Intensive care unit	29 (49.2)	12 (14.6)	< 0.001
General ward	30 (50.8)	70 (85.4)	< 0.001

Data are presented as *n* (%) or mean ± SD.
CVC = central venous catheter; CVP = central venous pressure; SD = standard deviation.

Table 2 Outcomes of *Acinetobacter baumannii* bacteremic patients with and without pneumonia

	Pneumonia-related bacteremia ($n = 59$)	Non-pneumonia-related bacteremia ($n = 82$)	p
Length of hospital stay (d)			
Total hospital stay	50.6 ± 46.4	35.6 ± 27.8	0.018
After onset of bacteremia	23.7 ± 26.9	20.0 ± 21.7	0.503
Outcome			
Survival ≥ 30 d	33 (55.9)	66 (80.5)	0.002
AB-related cause of death	21 (35.6)	6 (7.3)	< 0.001

Data are presented as *n* (%) or mean ± SD.

hospitalization (admission > 48 hours), and had no duplicate case. Nearly half of bacteremic patients with pneumonia (29 of 59, 49.2%) were in ICU, and most of the bacteremic patients without pneumonia (70 of 82, 85.4%) resided in general wards. The survival rates of the pneumonic group and the nonpneumonic group were 55.9% and 80.5%, respectively ($p < 0.005$). Appropriate empirical therapy was administered to 46.2% of patients within 48 hours.

Pneumonia was the most common source (59 cases, 41.8%) of 141 cases of AB bacteremia in our study, followed by central venous catheter-related bacteremia (34 cases, 24.2%), skin and soft tissue infections (20 cases, 14.2%), implanted portacath (18 cases, 12.8%), and urinary tract infections (10 cases, 7%). There were 82 nonpneumonic AB bacteremia cases, and all were nosocomial infections. The patients with pneumonia were older than the non-pneumonia groups (72.8 ± 16.7 years vs. 65.2 ± 15.5 years, respectively), and had higher rates of chronic lung disease and cerebrovascular disease. The higher incidence of pressure sores observed in patients with pneumonia may suggest that there were more nonambulatory patients in the pneumonia group. The nonpneumonia patients tended to have the underlying disease of malignancy, especially solid tumor. The Charlson comorbidity index of the pneumonia group was higher than the nonpneumonia group.

Tables 3 and 4 describe antimicrobial susceptibility to AB determined automatically by Phoenix machine and disk-diffusion methods. Most of the patients with AB bacteremia had received broad-spectrum antibiotics within the past 1 month, especially the patients with pneumonia (54 of 59, 91.5%). In total, 30 MDRAB strains were isolated in these 141 cases of bacteremia. The bacteremic patients with pneumonia had greater risk of MDRAB infection (39%) than patients without pneumonia (8.5%), and most of the MDRAB were isolated from the pneumonia group.

Throughout the 141 cases of AB bacteremia, there was less resistance to colistin than other antibiotics. Cefoperazone plus sulbactam, antipseudomonal carbapenem, tigecycline, and ampicillin plus sulbactam had a relatively low resistance rate (> 80% susceptibility) in AB bacteremia patients without pneumonia, but none of them had > 80% of susceptibility in the pneumonia group. Most of the commercial antibiotics had an increased resistance rate for AB in the recent 5 years, except colistin. Because of the higher rate of MDRAB in the pneumonia group, the clinicians prescribed relatively more colistin and tigecycline as definitive therapy regimen.

Table 3 Antimicrobial susceptibility to *Acinetobacter baumannii* determined by Phoenix machine automatically and disc diffusion methods

Antimicrobial agent	Pneumonia-related bacteremia ($n = 59$) Susceptible (%)	Non-pneumonia-related bacteremia ($n = 82$) Susceptible (%)	p
Colistin	59 (100)	77 (93.9)	0.053
Tigecycline**	34 (57.6)	67 (81.7)	0.002
Cefoperazone + sulbactam***	33 (55.9)	91 (91.5)	< 0.001
Ampicillin + sulbactam***	26 (44.1)	69 (84.1)	< 0.001
Aminoglycoside	29 (49.2)	55 (67.1)	0.032
Carbapenem***	29 (49.2)	72 (87.8)	< 0.001
Piperacillin + tazobactam***	23 (39.0)	57 (69.5)	< 0.001
Quinolone***	23 (39.0)	62 (75.6)	< 0.001
Co-trimoxazole***	20 (33.9)	57 (69.5)	< 0.001
Ceftazidime or cefepime	6 (10.2)	17 (20.7)	0.094
Multidrug-resistant *Acinetobacter baumannii* (drug susceptibility < 3 classes)*	23 (39.0)	7 (8.5)	< 0.001

*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

Table 4 Choice of definitive therapeutic antibiotic for *Acinetobacter baumannii* bacteremia in patients with and without pneumonia

Antimicrobial agent	Pneumonia-related bacteremia ($n = 59$), *n* (%)	Non-pneumonia-related bacteremia ($n = 82$), *n* (%)	*p*
Sulbactam + β-lactams	24 (40.7)	40 (48.8)	0.340
Carbapenem	18 (30.5)	17 (20.7)	0.185
Colistin	11 (18.6)	3 (3.7)	0.003
Tigecycline	10 (16.9)	2 (2.4)	0.002
Quinolone	9 (15.3)	17 (20.7)	0.408
Other β-lactams	8 (13.6)	9 (11.0)	0.642
Aminoglycoside	3 (5.1)	4 (4.9)	0.956

Discussion

AB is ubiquitous in the environment, and the cases number of AB related sepsis has been on the rise in the hospital.[14–16] Identification of risk factors for acquiring infections of *Acinetobacter* species is important. The clinical manifestations of AB infections include pneumonia, urinary tract infection, intra-abdominal infection, bacteremia, and catheter-related infection. Bacteremia is an independent risk factor for unfavorable outcome in intubated patients complicated with nosocomial pneumonia,[17] but only few published papers have focused on comparing pneumonia and non-pneumonia groups in patients with AB bacteremia. As shown in Table 1, we found that the pneumonia group had significantly more comorbidity, such as in Charlson comorbid index ($p < 0.001$), chronic lung disease ($p < 0.001$), pressure sore ($p < 0.001$), and cerebrovascular disease ($p < 0.05$). Contrariwise, bacteremic patients without pneumonia had a more significant likelihood to have malignancy ($p < 0.001$) and implantation of portacath ($p < 0.001$).

The increased longevity in the aging population with chronic diseases and more opportunities to undergo invasive procedures, especially the patients with pneumonia in ICU are more susceptible to AB infection.[4,8,9,13] In our study, the age of patients with pneumonia were found to be more significantly older than the nonpneumonia groups (mean: 72.8 ± 16.7 years vs. 65.2 ± 15.5 years, respectively, $p < 0.01$). In our hospital, AB infection was found to be the third most common healthcare-associated nosocomial pathogens in 2011–2012, and it has become the most common etiology of bloodstream infections.

As expected, intubation with mechanical ventilation increases the risk of hospital-acquired pneumonia. As shown in Table 1, pneumonic patients with AB bacteremia and concurrent with respiratory failure on mechanical ventilation account for 62.7% (37/59) of the pneumonic group, indicating that they were significantly more than the non-pneumonic group (their counterparts) ($p < 0.01$). In our hospital, AB is one of the leading causes of ventilator-associated pneumonia, and MDRAB impacts the choice of antibiotic therapy. Of these 141 in-hospital AB bacteremic isolates, nearly half of bacteremic patients with pneumonia (Table 1) were in the ICU (49.2%), and most of the patients (85.4%) without pneumonia were on general wards. These findings show that AB bacteremic patients with pneumonia were more likely ($p < 0.001$) to be in ICU than in general wards; the findings were the same as found by Brahmi et al.[15]

The frequent use of broad-spectrum antibiotics may contribute to isolating more antimicrobial resistant AB.[16,18,19] Most of the patients with pneumonia with AB bacteremia in our study (Table 1) had received significantly more broad spectrum antibiotics ($p < 0.001$) within the past 1 month (54 of 59, 91.5%) than those without pneumonia (52 of 82, 63.4%).

In the present study, AB bacteremic patients were found to have increased total hospital stay, but there was not a significantly different length of hospital stay after the onset of AB bacteremia between the pneumonia and non-pneumonia groups. The overall 30-day mortality rate in our study was found to be significantly higher in patients with pneumonia than in those without pneumonia group ($p < 0.01$). In Tables 1 and 3, patients with nonpneumonic AB bacteremia had better outcome and their isolates were less resistant to antibiotics. Central venous catheter-related AB bacteremia comprised 34 cases (24.2%), it should be a significant part of them. Among the AB bacteremic patients, the pneumonia group had a significantly greater risk ($p < 0.001$) of MDRAB infection than those non-pneumonia group. The present study revealed that 30 (47.5%) AB isolates were MDRAB, which suggests that the trend of resistant rates has increased when compared with the studies of Hsueh et al[20] in Taiwan and Erbay et al[16] 5 years ago.

Early initiation of effective antibiotic to treat the serious bacterial infections is a strong predictor of improvement of mortality.[17–19,21] Over 25% of reduction in mortality rate is associated with early initiation of adequate empirical antimicrobial therapy for AB bacteremia [15–19]. An effective empirical use of antibiotics should exhibit > 80% of *in vitro* susceptibility.[16] In the bacteremic patients without pneumonia (Table 3), colistin, ampicillin plus sulbactam, cefoperazone plus sulbactam, antipseudomonal carbapenem, and tigecycline had > 80% susceptibility *in vitro* and were suitable for empirical therapy. However, only colistin was reliable in the bacteremic patients with pneumonia. Our study result shows that the AB in bacteremic patients with pneumonia (100%) and without pneumonia (93.9%), had high susceptibility to colistin (Table 3). Traditionally, carbapenems are the most reliable antibiotic against AB infections, but carbapenem was found to have significantly decreased susceptibility from 87.8% in the nonpneumonic group to 49.2% in the pneumonia group (Table 3), making a tremendous impact on the appropriate antibiotic therapy of AB bacteremia in hospital-acquired pneumonic patients.

The prevalence of carbapenem-resistant AB has been increasing in hospital settings in recent years, especially

among critically ill patients.[16,19–22] In this study, we found significantly more frequent use of colistin ($p < 0.01$) and tigecycline ($p < 0.01$) in patients with pneumonia over those without pneumonia, and the inappropriate empirical antimicrobial therapy was 53.8%, higher than in the study of Lee et al,[19] which found that a total of 130 AB bacteremia had 94 (72.3%) individuals acquired MDRAB, and 51 (39.2%) patients received inappropriate empirical antimicrobial therapy. Lee et al[19] also found that empirical combination regimens directed against AB (i.e., a carbapenem plus sulbactam) were less likely to be inappropriate than monotherapy, and had a lower mortality rate. But, the optimal approach for empirical antibiotic therapy for MDRAB remains controversial,[19–21] especially the monotherapy or combination therapy of colistin and tigecycline. Further study of clinical utility of colistin and tigecycline is need in the future.

Limitations of the study

Readers should be cautioned against over-interpreting the results because this study has four major limitations: (1) this is a retrospective study, and there are many biases influencing the outcome of the patients; (2) the study was conducted only at a single medical center and the antibiotic resistance and risk factors may be different in other hospitals; (3) the pneumonia group had significantly more comorbid underlying diseases in this study; and (4) although the susceptibility of AB to colistin and tigecycline are generally in accordance with the criteria against *Enterobacteriaceae* spp., the minimal inhibition concentration should be tested by E-test or broth microdilution test. We used only univariate analysis for our study, we may have missed factors that may impact the mortality rate of both groups.

AB is one of the leading causes of hospital-acquired and ventilator-associated pneumonia. Pneumonia-related AB bacteremia has a worse prognosis, more comorbidity, and is associated with higher antibiotic resistance than non-pneumonic patients.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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