Journal of Microbiology, Immunology and Infection (2012) 45, 356–362

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ORIGINAL ARTICLE

Risk factors and clinical outcomes of patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia

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Received 30 April 2011; received in revised form 1 August 2011; accepted 29 August 2011

KEYWORDS
Acinetobacter baumannii;
Antibiotic resistance;
Carbapenem;
Outcome;
Risk factor

Background: It is still controversial whether carbapenem-resistant *Acinetobacter baumannii* (CRAB) is an independent risk factor for mortality. This study aimed to determine the risk factors and outcomes of patients with CRAB bacteremia, compared to those with carbapenem-susceptible *A. baumannii* (CSAB) bacteremia.
Methods: This retrospective cohort study was conducted in Taipei Veterans General Hospital, Taiwan. Patients with bacteremia due to *A. baumannii* during June 2002 and December 2007 were included.
Results: A total of 62 patients with CRAB and 164 with CSAB bacteremia were included. Among these patients, the independent risk factors for acquiring CRAB bacteremia were hematological malignancy [odds ratio (OR): 4.04; 95% confidence interval (CI): 1.29–12.70; $p = 0.017$], previous use of cefepime (OR: 2.60; 95% CI 1.11–6.08; $p = 0.028$) and use of total parenteral nutrition (OR: 3.06; 95% CI 1.12–8.39; $p = 0.029$). The patients with CRAB bacteremia had higher mortality rate than those with CSAB bacteremia. However, multivariate analysis showed that among patients with *A. baumannii* bacteremia, acquisition of CRAB by itself was not an independent risk factor for 14-day mortality. Instead, the independent factors

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doi:10.1016/j.jmii.2011.12.009

predicting14-day mortality were Acute Physiology and Chronic Health Evaluation (APACHE) score > 20 (OR: 6.33; 95% CI: 2.32−17.26; $p < 0.001$), shock (OR: 2.68; 95% CI: 1.11−6.23; $p = 0.025$) and inappropriate antimicrobial therapy (OR: 2.14; 95% CI: 1.01−4.53; $p = 0.046$). *Conclusion:* Risk factors for CRAB bacteremia were hematological malignancies, previous use of cefepime and use of total parenteral nutrition. Acquisition of CRAB itself is not a poor prognostic factor for the patients with *A. baumannii* bacteremia.

Introduction

Acinetobacter baumannii, the common nosocomial pathogen of ventilator-associated pneumonia and bloodstream infection, is characterized by rapid development of resistance to multiple classes of antimicrobials, including carbapenems.[1,2] Carbapenems are usually the antimicrobial agents of choice for the treatment of serious infections caused by multidrug resistant *A. baumannii*.[3,4] However, carbapenem-resistant *A. baumannii* (CRAB) isolates have been increasingly reported worldwide in recent years[1,3,5,6] and are of great importance because there are limited treatment options for the infected patients, which may be associated with increased mortality.[7] However, it is still controversial whether CRAB itself confers a higher mortality,[8,9] or the higher mortality in patients with CRAB infection is attributed to the inappropriate therapy or other host factors, such as underlying diseases or disease severity.

In this study, we aimed to determine the risk factors and outcome of patients with CRAB bacteremia, compared to those with carbapenem susceptible *A. baumannii* (CSAB) bacteremia.

Materials and methods

Study design and population

This retrospective cohort study was conducted in Taipei Veterans General Hospital, Taiwan. Patients with monomicrobial growth of *A. baumannii* in blood cultures between June 2002 and December 2007 were included.

Data collection and definition

Clinical data or laboratory parameters were collected by a standard form, in which definitions had been predefined. The collected data included demographic characteristics, underlying conditions, use of invasive procedures, laboratory results, antimicrobial therapy and clinical outcome.

A. baumannii bacteremia was diagnosed if an isolate of *A. baumannii* from one or more blood cultures was accompanied by two or more of the following conditions: (1) fever (temperature > 38°C) or hypothermia (temperature < 36°C); (2) tachypnea (respiratory rate > 24 breaths/min); (3) tachycardia (pulse rate > 90 beats/min); (4) leukocytosis (white cell count > 12,000 cells/mm^3); or (5) leukopenia (white cell count < 4000 cells/mm^3).[8] When a patient had more than one bacteremic episode, only the first episode was included. The date of the first positive blood culture was considered the date of onset of bacteremia. The sources of bacteremia were defined as previously described by Chiang et al.[10] The severity of illness was assessed by using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score.[11]

Comorbidity was divided into several categories as follows: autoimmune diseases including rheumatoid arthritis, systemic lupus erythematous and seronegative spondyloarthropathy; and hematological malignancies including leukemia, lymphoma and multiple myeloma. Mechanical ventilation was defined as receiving ventilator within 30 days before onset of bacteremia. Use of steroids or previous antimicrobial agents was defined as those administered within 30 days before bacteremia onset. Neutropenia was defined as an absolute neutrophil count <500 cells/mm^3. Septic shock was defined as sepsis associated with evidence of organ hypoperfusion, and either a systolic blood pressure of <90 or >30 mmHg less than baseline values, or a requirement for the use of vasopressor to maintain blood pressure.[12]

Invasive procedures included central venous catheterization, catheter use for hemodialysis, Foley catheterization, total parenteral nutrition, and mechanical ventilation.

To analyze the impact of antimicrobial resistance on clinical outcome, the appropriateness of antimicrobial therapy was assessed. Appropriate antimicrobial therapy was defined if a patient received at least one antimicrobial agent (including ampicillin/sulbactam) to which *A. baumannii* was susceptible within 72 hours of blood culture collection; otherwise, the antimicrobial therapy was considered inappropriate. An exception was that monotherapy with aminoglycoside was considered as inappropriate. The 14-day mortality rate was used in the outcome analysis, which was defined as death within 2 weeks after the onset of bacteremia.

Phenotypic and genotypic identification of Acinetobacter isolates

Isolates recovered from blood culture were phenotypically identified by using the API ID 32GN system (bioMerieux, Marcy l'Etoile, France). Those identified as *Acinetobacter calcoaceticus−A. baumannii* complex were further analyzed to genomic species level. Genomic species of *A. baumannii* were identified by a multiplex polymerase chain reaction method,[13] and all the *A. baumannii* isolates were detected for the presence of the intrinsic $bla_{OxA\text{-}51}$-like gene by using a previously described PCR detection method.[14]

Antimicrobial susceptibility test

Antimicrobial susceptibility tests were performed by disk diffusion test. Minimum inhibitory concentration of carbapenems (imipenem and meropenem) for *A. baumannii* isolates were determined by using agar dilution test. All the tests were performed and the results were interpreted in accordance with the Clinical and Laboratory Standards Institute guidelines.[15] Interpretation breakpoints for imipenem or meropenem of $\leq$ 4 mg/L were considered as susceptible, 8 mg/L as intermediate resistant, and $\geq$ 16 mg/L as resistant.[15] Intermediate resistance was regarded as resistance in our study.

Statistical analysis

Categorical variables were compared using the χ^2 test with Yates correction or Fisher's exact test. Continuous variables were analyzed using the two-sample *t* test. A *p* value < 0.05 was considered statistically significant. Significant variables in the univariate analysis were further analyzed by multivariate analysis. To assess the independent risk factors of the patients associated with the development of CRAB bacteremia and 14-day mortality of *A. baumannii* bacteremia, multivariate logistic regression analyses with Cox proportional hazard model were performed to control the effects of confounding factors. A survival curve was illustrated with the Kaplan–Meier method. To compare the univariate survival distribution among CRAB and CSAB, a log-rank test was used. All statistical analyses were performed using SPSS for Windows version 18 (SPSS Inc. Chicago, IL, USA).

Results

Patient characteristics

A total of 226 patients with *A. baumannii* bacteremia were included in this study. Among these patients, 62 cases were caused by CRAB and 164 by CSAB. The characteristics of the patients with CRAB and CSAB are listed in Table 1. The sex distribution was similar between both groups of patients ($p = 0.86$). There was also no significant difference in mean age among patients with CRAB or CSAB (69.6 $\pm$ 15.8 vs. 68.5 $\pm$ 17.6 years, $p = 0.662$). One hundred and forty-five patients stayed in the intensive care unit (ICU), including 49 (33.8%) with CRAB and 96 (66.2%) with CSAB.

Risks for acquisition of CRAB bacteremia

Compared to patients with CSAB bacteremia, results of the univariate analysis (Table 1) showed that a greater proportion of patients with CRAB bacteremia stayed in the ICU (79% vs. 58.5%, $p = 0.007$), but the duration of ICU stay before bacteremia onset was similar in both groups (22.92 $\pm$ 22.58 vs. 20.78 $\pm$ 36.59 days, $p = 0.71$). The length from admission to bacteremia was also similar (35.87 $\pm$ 33.58 vs. 28.24 $\pm$ 43.97 days, $p = 0.217$). CRAB bacteremia more likely originated from pneumonia (59.7% vs. 35.4%, $p = 0.002$) and less from urinary tract infection (0% vs. 9.1%%, $p = 0.013$). More patients with CRAB bacteremia had autoimmune diseases (11.3% vs. 1.2%, $p = 0.002$), hematological malignancies (19.4% vs. 6.1%, $p = 0.006$) and received total parenteral nutrition (TPN) (19.4% vs. 7.9%, $p = 0.028$). Patients with CRAB bacteremia were likely to have more severe illness as indicated by higher APACHE score (27.90 $\pm$ 8.56 vs. 23.52 $\pm$ 9.89, $p = 0.002$) at bacteremia onset. More patients with CRAB bacteremia presented with shock (22.6% vs. 9.1%, $p = 0.013$). Patients with CRAB bacteremia were more likely to have received cefepime (33.9% vs. 13.4%, $p = 0.01$) or piperacillin/tazobactam (32.3% vs. 17.7%, $p = 0.028$) therapy before bacteremia onset. Difference of exposure to carbapenems in both group was not statistically significant (54.8% vs. 42.7%, $p = 0.137$). Patients with CRAB bacteremia were also more likely to have received mechanical ventilation (83.9% vs. 60.4%, $p = 0.001$), insertion of central venous catheter (74.2% vs. 55.5%, $p = 0.016$), femoral venous catheter for hemodialysis (16.1% vs. 3.7%, $p = 0.002$) and Foley catheter (83.9% vs. 65.2%, $p = 0.01$).

Compared to patients with CSRB bacteremia, multivariate analysis showed that independent risk factors associated with CRAB bacteremia were hematological malignancy [odds ratio (OR): 4.04; 95% confidence interval (CI): 1.29–12.70; $p = 0.017$], previous use of cefepime (OR: 2.60; 95% CI: 1.11–6.08; $p = 0.028$) and use of TPN (OR: 3.06; 95% CI: 1.12–8.39; $p = 0.029$).

Antimicrobial susceptibility of isolates and patients' outcome

All except four of the isolates were resistant concomitantly to imipenem and meropenem. Two of these isolates were susceptible to imipenem but resistant to meropenem, and two other isolates were susceptible to meropenem but resistant to imipenem. The susceptibility pattern of other antibiotics for CRAB and CSAB are illustrated in Table 2. The resistance rates of amikacin, ceftazidime, ciprofloxacin, cefepime and piperacillin/tazobactem were significantly higher in the CRAB than CSAB group. Therapy with inappropriate antimicrobial agents was more often observed in patients with CRAB bacteremia (80.6% vs. 51.2%, $p < 0.001$). Carbapenem was empirically used in 34 (54.84%) and 70 (42.68%) patients with CRAB and CSAB bacteremia, respectively. The patients with CRAB bacteremia had a higher mortality rate than those with CSAB bacteremia, by survival analysis (Fig. 1, log-rank test, $p = 0.015$).

Prognostic factors of 14-day mortality in patients with *A. baumannii* bacteremia

In the univariate analysis (Table 3), the factors associated with 14-day mortality were acquisition of CRAB (35.5% vs. 20.7%, $p = 0.034$), APACHE score > 20 (35.2% vs. 6.2%, $p < 0.001$), shock (55.2% vs. 20.3%, $p < 0.001$), hematological malignancy (45.5% vs. 22.54%, $p = 0.035$), and inappropriate antimicrobial therapy (30.6% vs. 16.3%, $p = 0.022$). Multivariate analysis revealed that the independent factors associated with 14-day mortality were: APACHE >20 (OR: 6.33; 95% CI: 2.32–17.26; $p < 0.001$),

Table 1 Risk factors for acquisition of carbapenem resistant *Acinetobacter baumannii* bacteremia

	CRAB ($n = 62$)	CSAB ($n = 164$)	Univariate analysis	Multivariate analysis	
			p	Odds ratio (95% CI)	*p*
Characteristics					
Age (years)	69.63 ± 15.83	68.51 ± 17.61	0.662		
Male/female	47/15	127/37	0.86		
ICU stay	49 (79)	96 (58.5)	0.007*	0.98 (0.39-2.42)	0.954
Duration in ICU prior to bacteremia (days)	22.92 ± 22.58	20.78 ± 36.587	0.71		
Length of hospital stay before bacteremia (days)	35.87 ± 33.58	28.24 ± 43.97	0.217		
APACHE II score > 20	50 (80.4)	95 (57.9)	0.003*	1.70 (0.70-4.12)	0.24
Source of bacteremia					
Pneumonia	37 (59.7)	58 (35.4)	0.002*	1.70 (0.81-3.58)	0.16
Urinary tract infection	0 (0)	16 (9.1)	0.013*	0	0.998
Wound infection	2 (3.2)	4 (2.4)	0.667		
Intra-abdominal infection	2 (3.2)	4 (2.4)	0.667		
Catheter related infection	8 (12.9)	14 (8.5)	0.461		
Co-morbidities					
Steroid use	27 (43.5)	59 (36)	0.372		
Hypertension	21 (33.9)	53 (32.3)	0.95		
Chronic kidney disease	16 (25.8)	28 (17.1)	0.197		
Diabetes mellitus	15 (24.2)	40 (24.4)	1		
Coronary artery disease	14 (22.6)	31 (18.9)	0.666		
COPD	14 (22.6)	26 (15.9)	0.324		
Shock	14 (22.6)	15 (9.1)	0.013*	1.60 (0.61-4.21)	0.338
Hematological malignancies	12 (19.4)	10 (6.1)	0.006*	4.04 (1.29-12.69)	0.017*
Solid tumor	11 (17.7)	43 (26.2)	0.247		
Cerebral vascular accident	11 (17.7)	33 (20.1)	0.83		
Autoimmune diseases	7 (11.3)	2 (1.2)	0.002*	4.27 (0.55-32.97)	0.164
Liver cirrhosis	1 (1.6)	10 (6.1)	0.297		
Neutropenia	1 (1.6)	1 (0.6)	0.474		
Previous antimicrobial use					
Aztreonam	1 (1.6)	5 (3)	1		
Ceftriaxone	1 (1.6)	4 (2.4)	1		
Ceftazidime	14 (22.6)	30 (18.3)	0.59		
Ciprofloxacin	18 (29)	38 (23.2)	0.461		
Amikacin	8 (12.9)	29 (17.7)	0.506		
Piperacillin/tazobactam	20 (32.3)	29 (17.7)	0.028*	1.29 (0.55-2.89)	0.588
Cefepime	21 (33.9)	22 (13.4)	0.01*	2.60 (1.11-6.08)	0.028*
Ampicillin/sulbactam	23 (37.1)	42 (25.6)	0.124		
Carbapenem	34 (54.8)	70 (42.7)	0.137		
Invasive procedures uses					
Foley catheter	52 (83.9)	107 (65.2)	0.01*	1.85 (0.69-4.99)	0.225
Mechanical ventilation	52 (83.9)	90 (60.4)	0.001*	1.53 (0.58-4.05)	0.387
CVC	46 (74.2)	91 (55.5)	0.016*	0.97 (0.41-2.33)	0.951
TPN	12 (19.4)	13 (7.9)	0.028*	3.06 (1.12-8.39)	0.029*
FVC for hemodialysis	10 (16.1)	6 (3.7)	0.002*	3.72 (0.99-13.96)	0.052
JVC for hemodialysis	2 (3.2)	2 (1.2)	0.303		
Permanent hemodialysis catheter	1 (1.6)	1 (0.6)	0.474		

* Statistically significant, $p < 0.05$.
Data are presented as mean ± standard deviation or *n* (%).
CRAB = carbapenem resistant *A. baumannii*; CSAB = carbapenem susceptible *A. baumannii*; CI = confidence interval; ICU = intensive care unit; APACHE = acute physiology and chronic health evaluation; COPD = chronic obstructive pulmonary disease; CVC = central venous catheter; TPN = total parenteral nutrition; FVC = femoral venous catheter; JVC = Jugular venous catheter.

Table 2 Antimicrobial susceptibilities of 266 *Acinetobacter baumannii* isolates

	No. of isolates (resistant rate, %)		*p*
	CRAB ($n = 62$)	CSAB ($n = 164$)	
Aztreonam	61 (98.4)	158 (96.3)	0.677
Ceftriaxone	61 (98.4)	152 (92.7)	0.12
Ceftazidime	60 (96.8)	117 (71.3)	<0.001*
Ciprofloxacin	59 (95.2)	119 (72.6)	<0.001*
Amikacin	58 (93.5)	105 (64)	<0.001*
Piperacillin/tazobactam	50 (80.6)	93 (56.7)	0.001*
Cefepime	41 (66.1)	80 (48.8)	0.029*
Ampicillin/sulbactam	30 (48.4)	80 (48.8)	1

* Statistically significant, $p < 0.05$.
Data are presented as *n* (%).
CRAB = carbapenem resistant *A. baumannii*; CSAB = carbapenem susceptible *A. baumannii*.

shock (OR: 2.68; 95% CI: 1.11—6.23; $p = 0.025$), and inappropriate antimicrobial therapy (OR: 2.14; 95% CI: 1.01—4.53; $p = 0.046$). Acquisition of CRAB by itself was not an independent risk factor for 14-day mortality (OR: 1.03; 95% CI: 0.48—2.2; $p = 0.939$).

Discussion

Some studies have compared the risk factors and outcomes of patients with CRAB and CSAB bacteremia.[8,12,16—18] However, some of these[8,12,17,18] have not identified the causative *Acinetobacter* isolates to the genomic species level, therefore, they might have included patients infected with *A. baumannii*, *Acinetobacter* genomic species 3 or *Acinetobacter* genomic species 13TU, which are undifferentiated by phenotypic identification methods.[19,20] Among these three *Acinetobacter* genomic species, *A. baumannii* is more frequently multidrug resistant,[14] and may possess higher pathogenicity.[21] Therefore, the carbapenem resistant and susceptible isolates could actually have belonged to different *Acinetobacter* species, which would severely complicate the comparison and compromise the conclusions. To the best of our knowledge, the present study is the largest to focus on patients with only *A. baumannii* bacteremia.

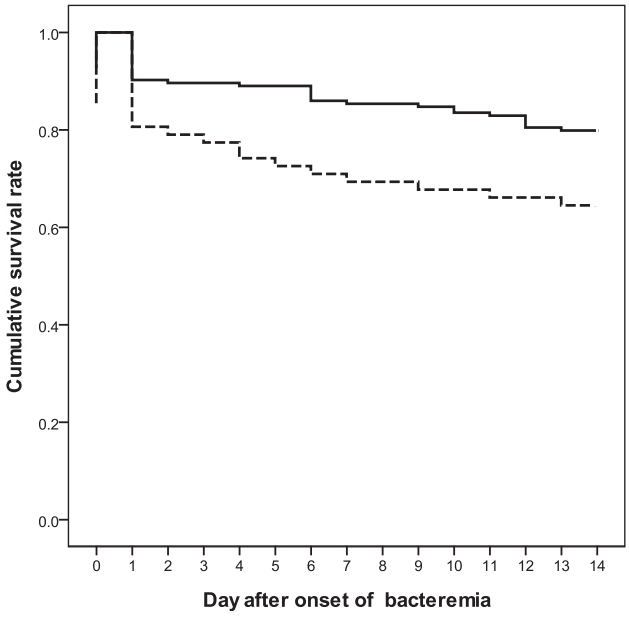

Figure 1. Cumulative survival rate after episode of CRAB and CSAB bacteremia. The curve was illustrated with the Kaplan—Meier method. The patients with CRAB bacteremia had higher mortality rate than those with CSAB bacteremia (log-rank test, $p = 0.015$). CRAB = carbapenem-resistant *Acinetobacter baumannii*; CSAB = carbapenem-susceptible *Acinetobacter baumannii*.

In our study with a large case number, confounding factors associated with patients' outcome could be adjusted. Although the patients with CRAB bacteremia had a higher 14-day mortality rate than those with CSAB bacteremia, we showed that patients with CRAB and CSAB bacteremia had many different characteristics. Compared to patients with CSAB bacteremia, those with CRAB bacteremia had higher prevalence of immunocompromised diseases and worse clinical condition before bacteremia, such as autoimmune diseases, hematological malignancies and shock episodes. They also had greater severity of illness at bacteremia onset, as indicated by higher APACHE II score and requirement for ICU care, and more frequently required the support of invasive procedures, such as TPN, mechanical ventilation, and use of central venous and femoral venous catheters for hemodialysis and Foley catheters. They had more often received broad-spectrum antimicrobial therapy, such as cefepime and piperacillin/tazobactam before bacteremia onset. CRAB bacteremia more often originated from pneumonia and less from urinary tract infection. Furthermore, as the CRAB isolates were more often resistant to multiple classes of antimicrobial agents, the patients with CRAB bacteremia were more likely to receive inappropriate therapy. All the above characteristics found in patients with CRAB bacteremia were likely to affect the patients' outcome. Indeed, the multivariate analysis showed that CRAB by itself was not an independent factor of 14-day mortality in patients with *A. baumannii* bacteremia, but the disease severity and inappropriate therapy were.

As a result, the identification of patients at risk of acquisition of CRAB followed by prompt initiation of appropriate therapy is important for those with *A. baumannii* bacteremia. In our study, the multivariate analysis showed that patients who had hematological malignancies were more likely to acquire CRAB than CSAB. It has been suggested that acquisition of resistance might lead to a compromise in virulence and fitness of bacteria.[22] Therefore, CRAB was likely to be pathogenic in those patients who were more immunocompromised. Previous use of cefepime was also a risk factor for acquiring CRAB. It has been suggested that CRAB occurrence may be facilitated by the selection pressure of previous antimicrobial use.[23] The use of TPN was also a risk factor for CRAB bacteremia in our study. However, the role of TPN in the acquisition of CRAB was not clear. It remains to be investigated whether rich nutrients or the route by which TPN was given played a more important role in the infection.

Table 3 Risk factors of 14-days mortality in patients with *Acinetobacter baumannii* bacteremia

	Mortality ($n = 56$)	Survive ($n = 170$)	Univariate analysis	Multivariate analysis	
			p	Odds ratio (95% CI)	p
Co-morbidities					
Mechanical ventilation	40 (71.4)	111 (65.3)	0.495		
Steroid use	23 (41.1)	63 (37.1)	0.706		
Hypertension	18 (32.1)	56 (32.9)	1		
ICU stay	17 (30.4)	106 (62.4)	0.409		
Shock	16 (28.6)	13 (7.6)	< 0.001*	2.63 (1.11-6.23)	0.025*
Coronary artery disease	14 (25)	31 (18.2)	0.365		
Chronic kidney disease	14 (25)	30 (17.6)	0.312		
Solid tumor	13 (23.2)	41 (24.1)	1		
Diabetes mellitus	12 (21.4)	43 (25.3)	0.685		
Hematological malignancies	10 (17.9)	12 (7.1)	0.035*	1.75 (0.64-4.79)	0.276
Cerebral vascular accident	9 (16.1)	35 (20.6)	0.585		
COPD	8 (14.3)	32 (18.8)	0.569		
Liver cirrhosis	4 (7.1)	7 (4.1)	0.472		
Autoimmune diseases	4 (7.1)	5 (2.9)	0.23		
Neutropenia	0 (0)	2 (1.2)	1		
APACHE II score >20	51 (91.1)	94 (55.3)	< 0.001*	6.33 (2.32-17.26)	<0.001*
Inappropriate therapy	41 (73.2)	93 (54.7)	0.022*	2.15 (1.01-4.53)	0.046*
Carbapenem resistance	22 (39.3)	40 (23.5)	0.034*	1.03 (0.48-2.20)	0.939

* Statistically significant, $p < 0.05$.
Data are presented as n (%).
CI = confidence interval; ICU = intensive care unit; APACHE = acute physiology and chronic health evaluation; COPD = chronic obstructive pulmonary disease.

Nevertheless, the results indicated that an early shift of TPN to alimentary feeding is important in the prevention of acquisition of CRAB.

As expected, disease severity such as high APCHE II score and shock status were independently associated with poor prognosis in patients with *A. baumannii* bacteremia.[5,12] Besides, inappropriate therapy was also independently associated with poor prognosis, despite *A. baumannii* being regarded as a low-pathogenicity pathogen.[8,16] Previously, some studies have suggested that carbapenem resistance is itself associated with poor prognosis.[17] However, the appropriateness of the therapy is not considered in the analysis, which might be the real factor that contributes to the poor patients' outcome.

Although this study included a large number of patients with *A. baumannii* bacteremia, it had the inherent limitations of a retrospective study, including inconsistency of patient care, noncomparability of the patients' background, and variation in treatment, which might have confounded the analysis. To ensure consistency in data collection, a standard form was set up for the process. In addition, multivariate analysis was performed to identify independent factors of interest.

In conclusion, we showed that, among patients with *A. baumannii* bacteremia, the independent risk factors for CRAB bacteremia were underlying diseases with hematological malignancies, previous use of cefepime, and receiving TPN. The APACHE score > 20, shock and inappropriate antimicrobial therapy were independent risk factors for 14-day mortality among these patients. Carbapenem resistance itself was not a risk factor of *A. baumannii* mortality. Early identification of CRAB followed by prompt appropriate antimicrobial therapy, such as colistin or tigecycline, may improve patient outcome.

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