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ORIGINAL ARTICLE

Risk factors of mortality in patients with carbapenem-resistant *Acinetobacter baumannii* bacteremia

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Background/Purpose: Identification of risks of mortality for carbapenem-resistant *Acinetobacter baumannii* (CRAB), with early implementation of an appropriate therapy, is crucial for the patients' outcome. The aim of this study was to survey mortality risk factors in 182 patients with CRAB bacteremia in a medical center in Taiwan.
Methods: A total of 182 isolates of CRAB bacteremia were collected from 2009 to 2012 in Mackay Memorial Hospital, Taipei, Taiwan These isolates were identified by using the genotypic method. Risk of attributable mortality analysis was carried out with a Cox proportional hazards model.
Results: The 182 CRAB isolates belonged to 38 different pulsotypes. The attributable mortality rate of the 182 patients was 58.24%. The risk factors for attributable mortality included intensive care unit stay [hazard ratio (HR): 2.27; $p = 0.011$], an Acute Physiology and Chronic Health Evaluation II score of >20 (HR: 2.19; $p < 0.001$), respiratory tract as the origin of bacteremia

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(HR: 3.40; $p < 0.001$), and previous use of ceftriaxone (HR: 2.51; $p = 0.011$). The appropriateness of antimicrobial therapy was 18.87% (20/106) in the mortality group versus 88.16% (67/76) in the survivor group ($p < 0.001$). The sensitivity of CRAB to colistin was 100% and to tigecycline was 40.11%.

Conclusion: The risk factors for mortality for CRAB included intensive care unit stay, a high Acute Physiology and Chronic Health Evaluation II score, respiratory tract as the origin of bacteremia, and previous use of ceftriaxone. Early implementation of an antimicrobial agent that had the highest *in vitro* activity against CRAB in patients at risk of CRAB bacteremia and high mortality may improve their outcome.

Introduction

Acinetobacter species belong to a group of Gram-negative coccobacilli commonly found both in the environment (such as in water, food, and soil) and in the humans (such as in skin, wounds, and respiratory and gastrointestinal tracts).[1] The *Acinetobacter calcoaceticus—Acinetobacter baumannii* complex (AB complex) consists of four genotypically distinct, but phenotypically very similar, bacterial species: *A. calcoaceticus* (an environmental species), *A. baumannii*, *Acinetobacter pittii*, and *Acinetobacter nosocomialis*.[2–6]

In the past decade, AB complex comprising *A. baumannii*, *A. pittii*, and *A. nosocomialis* has become a common pathogenic cause of health care-associated infections. Associated infections include pneumonia, urinary tract infections, bacteremia, soft tissue infections, meningitis, and empyema.[2] Carbapenem-resistant strains of AB complex have been reported worldwide. These antibiotic resistant strains accounted for 14.1% and 39.4% of all health care-associated infections in Europe and Latin America, respectively, with a worldwide prevalence of 30%.[7,8] From 2000 to 2005, the prevalence of imipenem-resistant AB complex in Taiwan increased from 22% to 25%.[9] Data from the Taiwan Surveillance of Antimicrobial Resistance show that the prevalence of multidrug- and carbapenem-resistant *A. baumannii* (CRAB) complex infections has reached 60—66.8% in recent years.[10] The high incidence rate of CRAB complex infections, especially CRAB, in Taiwan is a threat to numerous patients in the health care system and presents a difficult challenge for hospital infection control. Given limited drug choices and a high infection mortality rate, treatment of CRAB is difficult.[4] Patients with CRAB infections have a higher mortality rate than those infected with AB strains susceptible to carbapenem.[11–14]

The risk factors of mortality of CRAB complex bacteremia have been reported in different parts of the world in recent years.[15–20] However, *A. baumannii* cannot be differentiated from AB complex using phenotypic methods.[21,22] Currently, only a few articles have reported the information concerning the comorbidities associated with mortality risk factors in CRAB bacteremia.[23–25] The aim of this study was to survey mortality risk factors associated with CRAB bacteremia.

Methods

Bacterial isolates, identification, and clonality determination

From January 2009 to December 2012, blood isolates of CRAB complex resistant to imipenem [minimal inhibitory concentration (MIC) $\geq$ 16 mg/L], according to Clinical and Laboratory Standards Institute guidelines,[26] were collected in Mackay Memorial Hospital, a 2200-bed, tertiary teaching hospital in Taiwan. For patients with $\geq$ 2 positive blood cultures, only the first isolate was included. They were phenotypically identified as AB complex by the Vitek 2 system (bioMérieux Vitek Systems Inc., Hazelwood, MO, USA) in a microbiology laboratory. Susceptibility tests were also performed using the Vitek 2 system. Isolates were kept frozen at −70°C in trypticase soy broth (BD, Sparks, MD, USA) containing 20% glycerol (v/v) until further testing. Genotypic identification of *A. baumannii* was performed by identifying the presence of the $bla_{\text{OXA-51-like}}$ carbapenemase gene that is specific to the *A. baumannii* species.[27] Identification of other species in AB complex was performed by sequence analysis of *rpo*B and flanking spaces, according to the protocol by La Scola et al.[28]

Finally, isolates were digested with *Apa*I (New England Biolabs, Beverly, MA, USA) and evaluated with pulsed-field gel electrophoresis to determine clonality.[29]

Study population and data collection

We retrospectively reviewed medical charts of patients infected with CRAB complex and having symptoms and signs of infection. Patients aged > 1 year were included if they had bacteremia due to CRAB complex, regardless of primary infection sites. Patients with CRAB bacteremia were selected for further clinical analysis after genotypic identification from CRAB complex. This retrospective study was approved by the Mackay Memorial Institutional Review Board (protocol numbers 13MMHIS122 and 13MMHIS291).

Medical records were reviewed and the data on the following parameters were collected: patient characteristics, source of bacteremia, comorbidities, previous antimicrobial use, invasive procedure use (Table 1), whether or not the patient was in the intensive care unit (ICU) at the time of

Table 1 Risk factors for attributable mortality in 182 patients with CRAB bacteremia

			Univariate analysis		Multivariate analysis	
	Mortality (n = 106)	Survival (n = 76)	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Characteristics						
Age	69.08	69.20	0.99 (0.98–1.01)	0.373		
Sex	63	53	0.97 (0.66–1.43)	0.876		
ICU stay	93	46	2.89 (1.61–5.17)	<0.001	2.37 (1.26–4.48)	0.008
APACHE II > 20	58	17	2.22 (1.51–3.27)	<0.001	2.08 (1.35–3.21)	0.001
Source						
Respiratory tract	22	7	2.16 (1.34–3.47)	0.002	3.40 (2.04–5.67)	<0.001
Urinary tract	5	10	0.99 (0.40–2.45)	0.990		
Skin/soft tissue	4	1	1.83 (0.67–4.98)	0.238		
Abdominal route	2	1	1.41 (0.35–5.73)	0.633		
Central line	22	19	0.77 (0.48–1.23)	0.275		
Primary	51	38	0.80 (0.54–1.17)	0.244		
Comorbidities						
Hypertension	13	6	1.05 (0.59–1.87)	0.877		
CKD	10	6	1.03 (0.54–1.98)	0.928		
DM	10	3	1.02 (0.53–1.99)	0.945		
CAD	1	2	0.78 (0.11–5.64)	0.809		
COPD	4	3	1.22 (0.45–3.33)	0.694		
Shock	7	6	1.10 (0.51–2.38)	0.805		
Malignancies	15	12	0.82 (0.47–1.41)	0.467		
Autoimmune	0	1	—	—		
Liver cirrhosis	8	3	2.26 (1.09–4.69)	0.028	2.01 (0.96–4.21)	0.064
Neutropenia	0	2	0.05 (0.00–25.08)	0.341		
Previous antibiotics						
Ceftriaxone	9	2	2.17 (1.08–4.34)	0.029	2.35 (1.16–4.75)	0.017
Ceftazidime	7	9	0.54 (0.25–1.17)	0.119		
Ciprofloxacin	8	4	0.74 (0.36–1.54)	0.422		
Amikacin	4	3	0.84 (0.31–2.30)	0.740		
Piperacillin/tazobactam	26	13	1.13 (0.73–1.77)	0.582		
Cefepime	13	2	1.80 (1.00–3.23)	0.051		
Colistin	43	32	0.84 (0.57–1.25)	0.399		
Tigecycline	14	6	1.27 (0.72–2.24)	0.404		
Invasive procedures						
Foley catheter	97	63	1.65 (0.83–3.27)	0.153		
MV	95	67	0.79 (0.42–1.48)	0.467		
CVC	75	48	1.22 (0.80–1.86)	0.354		
TPN	11	4	1.03 (0.55–1.92)	0.938		
FVC for H/D	45	22	1.20 (0.81–1.76)	0.362		
JVC for H/D	8	2	1.32 (0.64–2.71)	0.457		
Permanent H/D	31	22	0.89 (0.58–1.35)	0.579		

APACHE II = Acute Physiology and Chronic Health Evaluation II; CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRAB = carbapenem-resistant *A. baumannii*; CVC = central venous catheter; DM = diabetes mellitus; FVC = femoral venous catheter; H/D = hemodialysis; ICU = intensive care unit; JVC = jugular venous catheter; MV = mechanical ventilation; TPN = total parenteral nutrition; — = not available.

onset of bacteremia, and the patient's Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Documentation of previous antibiotic use included antibiotics that were given to the patient in the14-day period prior to the onset of bacteremia. Central line-associated infection was defined according to the United States Centers for Disease Control and Prevention guidelines.[30] Liver cirrhosis was diagnosed by gastroenterologists based on laboratory and radiological evidence. Chronic kidney disease was defined as an estimated glomerular filtration rate of $<$ 60 mL/minute/1.73 m^2. An appropriate antimicrobial therapy was defined as the administration of at least one antimicrobial agent, to which a pathogen was sensitive *in vitro*, within 48 hours of bacteremia, with an approved route and dosage appropriate for end organ function. Otherwise, a therapy that did not meet these criteria was considered inappropriate. A therapy was considered inappropriate if only an aminoglycoside was used.[31] Attributable mortality indicated that a patient died during the admission period of the CRAB bacteremia episode.

Statistical analysis

The hazard ratios (HRs) of uni- and multivariate analyses were performed using a Cox proportional hazards ratio model (Cox PH regression). For all analyses, a two-tailed $p < 0.05$ was considered significant. All biological variables with $p < 0.05$ in the univariate analysis were included in the Cox PH regression for multivariate analysis. SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) was used for performing the statistical analysis.

Results

A total of 195 AB complex blood isolates were collected during the study period. There were 182 CRAB, 11 carbapenem-resistant *A. nosocomialis*, and two carbapenem-resistant *A. pittii* isolates. The pulsed-field gel electrophoresis patterns of 182 CRAB isolates were identified as belonging to 38 different pulsotypes, as presented in Fig. 1. The attributable mortality rate of the 182 patients with CRAB bacteremia was 58.24% (106/182). The risk factors for CRAB mortality are shown in Table 1. The mean age of 182 patients (± standard deviation) was 69.13 ± 16.31 years. The mean age (± standard deviation) of 106 patients in the mortality group was 69.08 ± 16.86 years, and that of 76 patients in the survivor group was 69.20 ± 15.73 years. Male patients accounted for 63.74% of the total 182 patients, 59.43% of the mortality group, and 69.74% of the survival group. Of total 182 patients, 139 (76.37%) stayed in ICU during bacteremia, 93 (87.74%) of whom were in the mortality group and 46 (60.53%) in the survival group. Of these 182 patients, 75 [41.21%; 58 (54.72%) in the mortality group and 17 (22.37%) in the survival group] had APACHE II scores of > 20. Liver cirrhosis was a univariate risk factor for attributable mortality among CRAB bacteremia patients. High mortality (72.73%, 8/11) was found in patients with liver cirrhosis. Female patients were predominant among the 11 liver cirrhosis patients (6/11, 55.55%). The mean age was 65.45 ± 14.34 years. Most of the patients stayed in ICU (10/11, 90.91%) and had a mean APACHE II score of 24.18 ± 5.79. Two of the three surviving liver cirrhosis patients received adequate antibiotics (colistin) within 24 hours after blood culture, while one of the three surviving patients did not receive adequate antibiotics (colistin) until 48—72 hours after positive blood culture.

In multivariate analysis, the independent risk factors for mortality included stay in ICU [HR: 2.27; 95% confidence interval (CI): 1.21—4.26; $p = 0.011$), APACHE II scores of >20 (HR: 2.19; CI: 1.42—3.36; $p < 0.001$), respiratory tract as the origin of bacteremia (HR: 3.40; CI: 2.04—5.67; $p < 0.001$), and use of ceftriaxone prior to the onset of CRAB bacteremia (HR: 2.51; CI: 1.23—5.09; $p = 0.011$).

The sensitivity of CRAB to meropenem was 0% (0/182), to colistin was 100% (Fig. 2), and to tigecycline was 40.11%. The MICs of colistin and tigecycline for CRAB are listed in Fig. 3. Of the isolates, 3.85% and 7.14% had tigecycline MIC < 0.5 mg/L and MIC < 1.0 mg/L, respectively, while 61.54% and 76.92% had colistin MIC < 0.5 mg/L and MIC < 1.0 mg/L, respectively. The percentage of appropriate antimicrobial therapy among the182 CRAB bacteremia patients was 18.87% (20/106) in the mortality group versus 88.16% (67/76) among survivors ($p < 0.001$). The appropriate therapy included a colistin-based therapy (85 patients; 20 in the mortality group and 65 in the survival group), either a monotherapy or a combination therapy. Of the patients,

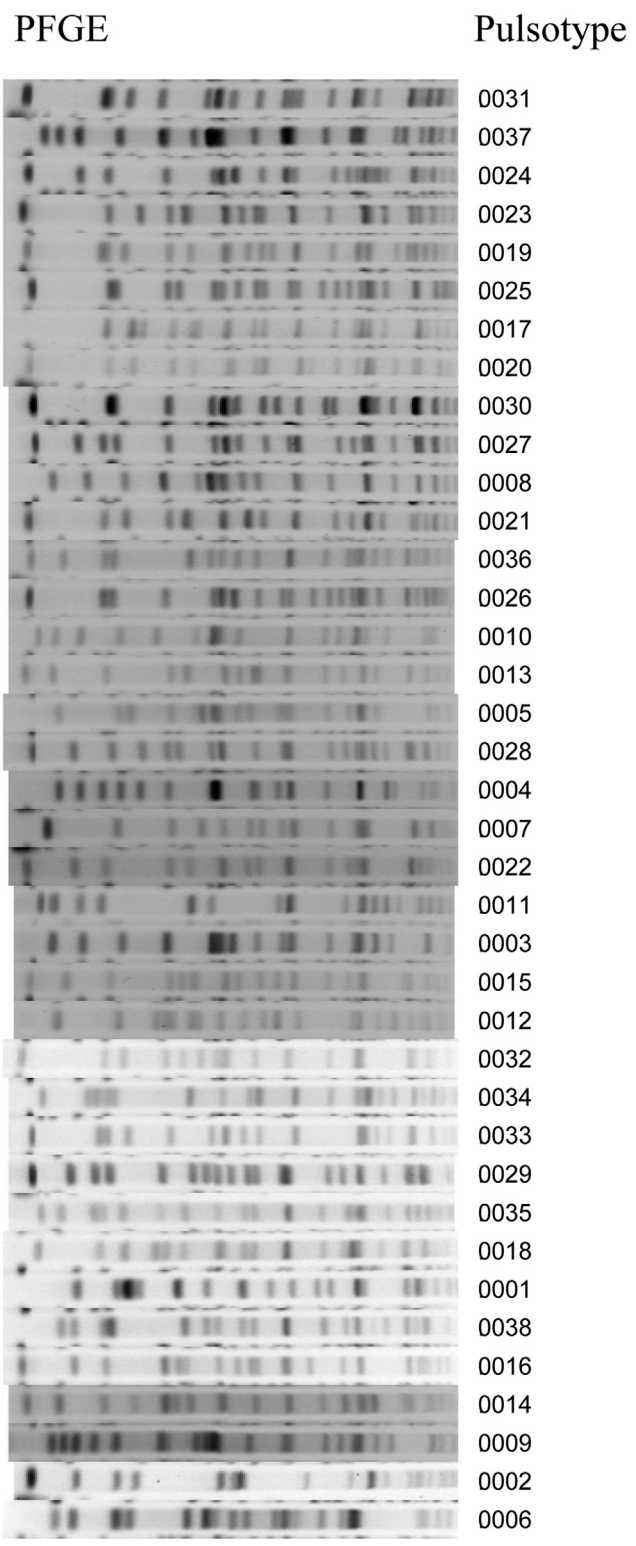

Figure 1. Demonstration of 38 pulsotypes from 182 *Acinetobacter baumannii blood isolates*. PFGE = pulsed-field gel electrophoresis.

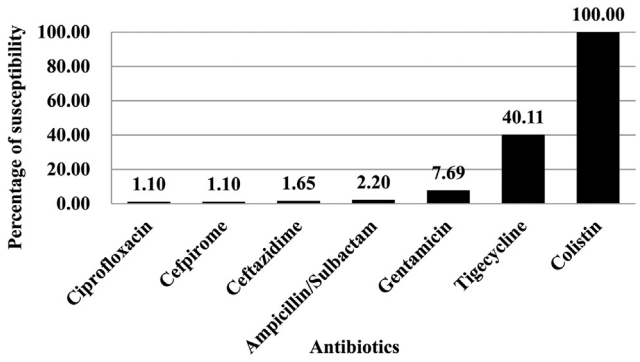

Figure 2. Percentage of susceptibility to antibiotics of 182 CRAB isolates. CRAB = carbapenem-resistant *Acinetobacter baumannii*.

76.47% (65/85) under an appropriate antimicrobial therapy (colistin-based therapy) survived. Two patients received an appropriate therapy with tigecycline and both of them survived after management.

Discussion

A. baumannii is distinct from *A. nosocomialis* and *A. pittii* in that it possesses greater antimicrobial resistance and results in more severe patient outcomes. However, in routine clinical practice, all these bacteria present similar phenotypic reactions, cannot be readily identified, and are instead reported as AB complex.[3–6] This generalization becomes a challenge in research on infections, since the AB complex infection is caused by a mixture of different *Acinetobacter* species. Therefore, it is reasonable to separate *A. baumannii* from AB complex in research studies, and investigate its distinct risk factors and survival analysis.

With its intrinsic resistance to many antibiotics and rapid acquirement of resistance mechanisms, *A. baumannii* adapts to the hospital environment quickly and can cause

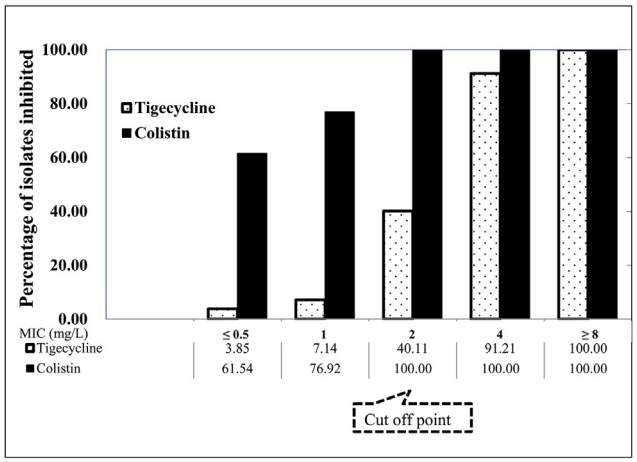

Figure 3. MIC values of tigecycline and colistin for 182 carbapenem-resistant *Acinetobacter baumannii* isolates. MIC = minimal inhibitory concentration.

outbreaks that are difficult to control.[31] CRAB infections are independently associated with increased hospital mortality, as well as prolonged ICU and hospital stays.[12,13] In an investigation of risk factors for the isolation of multidrug-resistant *A. baumannii*, Falagas et al[32] suggested that a separate outbreak investigation should be performed in each hospital setting, and innovative control strategies should be developed to limit the spread of pathogens. Since a central line-associated source (41/182, 22.53%) was related to CRAB bacteremia, we suggest that a care bundle intervention be utilized to reduce central line-associated bacteremia in high-risk units. The central line bundle would include the several key components according to the United States Centers for Disease Control and Prevention guidelines.[30] It is hoped that with the implementation of a central line bundle in our institution, we can decrease incidences of central line-associated bacteremia through infection control measures. Cleaning of the environment is also needed for decreasing the incidence of CRAB overgrowth.

Given that ceftriaxone is ineffective against CRAB, its previous use was found to be associated with increased mortality in CRAB bacteremia in this clinical analysis. Our CRAB isolates from blood showed 100% sensitivity to colistin and 40.11% sensitivity to tigecycline. In general, colistin is the preferred drug of choice for treatment of CRAB, except in the case of severe renal insufficiency. Lee et al[33] found that an appropriate antimicrobial therapy can significantly reduce the 14-day mortality of patients with *A. baumannii* bacteremia. In this study, the rate of appropriate antimicrobial therapies for CRAB in the mortality group and survivors were 18.87% and 88.16% ($p < 0.001$), respectively. These results clearly indicate that an appropriate antimicrobial therapy can influence the survival rate in bacteremia caused by CRAB infections.

The attributable mortality rate of the 182 patients with CRAB bacteremia was 58.24% (106/182). Liver cirrhosis was a risk factor for attributable mortality among CRAB bacteremia patients under univariate analysis. High mortality (72.73%, 8/11) within 14 days after onset of bacteremia was found in 11 liver cirrhosis patients with CRAB bacteremia. There are very few previous large-series studies regarding *A. baumannii* infections associated with liver cirrhosis.[34] Four of the 11 liver cirrhosis patients died within 24 hours after blood cultures were obtained. Two of the three surviving liver cirrhosis patients received colistin within 24 hours, while one of the three patients received colistin within 48—72 hours after blood culture. Controversy surrounds the benefits of combination treatment or monotherapy against multidrug-resistant *A. baumannii* infections in clinical practice. According to a systematic review of the literature, combination treatment may be preferred for severely ill patients.[35] Combination treatment with colistin is preferred in severely ill patients, for example, ICU patients with CRAB bacteremia.

The limitation of this study is that this study was conducted in a single medical center, and the results may not be applied to other hospital. We use attributable mortality as the endpoint of our study, which is a relatively subjective endpoint. However, there is also an inherent bias for using overall mortality in the study of *A. baumannii* infection, because the hosts are frequently

immunocompromised and had multiple underlying diseases, which may contribute to the mortality.

In conclusion, the independent risk factors for mortality in patients with CRAB bacteremia included stay in ICU, APACHE II scores of $>$ 20, respiratory tract as the origin of bacteremia, and use of ceftriaxone prior to the onset of CRAB bacteremia. Rapid identification of patients at risk of mortality and early implementation of an appropriate antimicrobial therapy are crucial for patients with CRAB bacteremia, especially those with liver cirrhosis.

Conflicts of interest

The authors declare that they have no conflicting interests.

Acknowledgments

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