RISK FACTORS AND CLINICAL OUTCOMES OF MULTIDRUG-RESISTANT *ACINETOBACTER BAUMANNII* BACTEREMIA AT A UNIVERSITY HOSPITAL IN THAILAND

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Abstract. Multidrug-resistant (MDR) *Acinetobacter baumannii* has become a major cause of hospital-acquired infection worldwide. There are few papers regarding this particular subject. Our aim was to assess the incidence of bacteremia due to MDR *Acinetobacter baumannii*, factors associated with the infection, and clinical outcomes. We studied 49 cases of *A. baumannii* bacteremia in adult patients admitted to a university hospital in Northeast Thailand between 2005 and 2007. The incidence of MDR *A. baumannii* bacteremia was 3.6 episodes per 10,000 hospital admissions. Significantly independent factors associated with MDR *A. baumannii* bacteremia were previous: 1) ICU admission [odds ratio (OR) 10.01; 95% confidence interval (CI) 1.39-72.20]; 2) use of beta-lactam/beta-lactamase inhibitor antibiotics (OR 8.06; 95%CI 1.39-46.64); and 3) use of a carbapenem antibiotics (OR 11.40; 95%CI 1.44-89.98). The overall mortality rate was significantly higher in the MDR group than in the susceptible group (91.7% *vs* 48%, respectively) (p=0.001). The significantly independent factors related to mortality were: 1) APACHE II score (OR 1.25; 95%CI 1.03-1.52) and 2) secondary bacteremia (OR 14.86; 95%CI 1.37-161.90). This study revealed the significantly independent factors associated with MDR *A. baumannii* bacteremia were prior ICU admission and prior use of broad spectrum antibiotics. This infection has a high mortality rate. Emphasis needs to be on prevention, strict application of infection control and appropriate use of antibiotics.

Keywords: *Acinetobacter*, bacteremia, multidrug-resistant, Thailand

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INTRODUCTION

Acinetobacter baumannii has emerged as a major cause of healthcare-associated infections worldwide and has recently been associated with hospital outbreaks (Villegas and Hartstein, 2003; Pimentel *et al*, 2005; Enoch *et al*, 2008; Peleg *et al*, 2008). The alarming features of the organism are its development of resistance to all commercially available antibiotics and

its becoming a leading cause of death, especially among critically ill patients (Dijkshoorn *et al*, 2007; Perez *et al*, 2007; Gootz and Marra, 2008; Peleg *et al*, 2008). Control of this organism is difficult because of its ability to survive for prolonged periods in the environment. *A. baumannii* can cause a wide range of nosocomial infections, among which the most frequent presentations are ventilator-associated pneumonia and bacteremia. The clinical manifestations of bacteremia range from transient bacteremia to fulminant septicemia, with a high crude mortality rate particularly associated with multidrug-resistant (MDR) strains.

Risk factors for infection with MDR-*Acinetobacter* include prolonged hospitalization, admission to an intensive care unit (ICU), mechanical ventilation, colonization, exposure to broad spectrum antimicrobial agents, recent surgery, invasive procedures, and underlying severity of illness (Fournier and Richet, 2006; Playford *et al*, 2007). Different sites of infection and geographic distribution may result in a difference in risk factors and outcomes; however, there have been few studies evaluating risk factors for MDR-*Acinetobacter* bacteremia and its outcomes.

The purpose of the present study was to evaluate the incidence of MDR *A. baumannii* bacteremia and identify the risk factors for contracting this infection. The clinical outcomes and factors related to mortality among the patients were evaluated.

MATERIALS AND METHODS

A retrospective study was conducted among adult patients (over 15 years old), admitted between 2005 and 2007 at Srinagarind Hospital, a 1,000-bed, tertiary care, university hospital located in Northeast Thailand. Study patients were identified through the records of the clinical microbiological laboratory and data retrieved from their medical records. Patients were included if there was evidence of sepsis with at least one positive blood culture containing *A. baumannii*. For patients with more than one episode of *A. baumannii* bacteremia, only the first episode was considered. Patients with a positive blood culture containing multiple organisms including *A. baumannii* were excluded.

Information retrieved from medical records included: demographics, potential risk factors for developing MDR *A. baumannii* bacteremia, the clinical management, and the potential risk factors for death among the patients contracting *A. baumannii* bacteremia. The following data were recorded: age, sex, type of infection (community-acquired *vs* nosocomial infection following the definitions of the Centers for Diseases Control), admission ward at onset of *A. baumannii* bacteremia, co-morbid diseases/conditions, previous antibiotic therapy (receipt of a systemic antimicrobial agent for at least 24 hours during the three months preceding bacteremia), site of infection, drug susceptibility pattern, prescribed antimicrobial agents, clinical response to therapy, clinical outcome, and duration of hospitalization.

The severity of illness was estimated using the APACHE II score on the day of the positive blood culture (or within 24 hours). Also recorded were: 1) recent ICU stay, 2) prior surgery, 3) prior *A. baumannii* colonization, 4) prior bacteremia from other organisms, 5) treatment with cytotoxic drugs or corticosteroids (≥20 mg/day for >5 days) which occurred within 30 days of the onset of bacteremia, and 6) invasive procedures performed at least 48 hours to one week prior to the onset of bacteremia.

Definitions

MDR *A. baumannii* was defined as resistance to at least two β-lactam antimicrobials (including ceftazidime, cefotaxime, cefepime, cefpirome, ampicillin-sulbactam, piperacillin-tazobactam, cefoperazone-sulbactam), gentamicin or amikacin, ciprofloxacin or ofloxacin, and trimethoprim-sulfamethoxazole. Pan-drug-resistant (PDR) *A. baumannii* was defined as: "resistance to all currently available antimicrobials except colistin or tigecycline by routine disk-diffusion method" (Falagas *et al*, 2006a).

Empirical antimicrobial therapy was considered appropriate if the organism was susceptible *in vitro* to at least 1 of the drugs administered within 72 hours after the onset of bacteremia. Clinical outcomes were assessed 72 hours after the onset of bacteremia and defined as: 1) a complete response (*ie*, resolution of clinical sepsis); 2) a partial response (*ie*, improvement of clinical sepsis without complete resolution); and 3) failure (*ie*, absence of resolution, worsening of sepsis).

Blood cultures were processed using the BacT/Alert automated culture system (Organon Teknika, Durnham, NC) following the manufacturer's instructions. *A. baumannii* isolates were identified by standard microbiological techniques and antimicrobial susceptibility testing was determined by the disk diffusion technique, in accordance with Clinical and Laboratory Standards Institute criteria (NCCLS, 2000). Intermediate susceptibility to antibiotics was considered as having resistance.

Ethical approval

The study protocol was approved by the Institutional Review Board of Khon Kaen University.

Statistical analysis

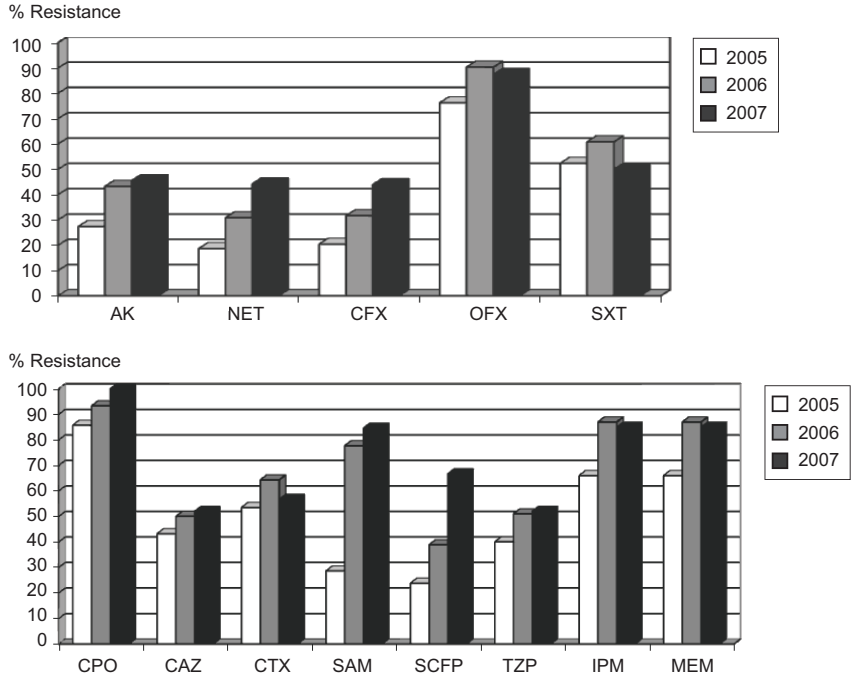
Data analysis was performed using SPSS (SPSS, Chicago, IL), version 11.5. The Fisher's exact or Pearson's chi-square tests were used to compare categorical variables, where appropriate. The Student's *t*-test or Wilcoxon and Kruskal-Wallis tests were used to test for statistical significance of continuous variables, where appropriate. Univariate analysis was used to identify significant factors; the results being presented as an odds ratio (OR) with a 95% confidence interval (95%CI). Multiple logistic regression analysis, using the backward likelihood ratio selection method, was used to assess independent factors related to contracting MDR *A. baumannii* bacteremia and those related to mortality. A *p*-value ≤0.05 was considered statistically significant.

RESULTS

During the 3-year period of the study, there were 84 episodes in 79 patients with positive blood cultures for *A. baumannii*, indicating an incidence of 7.8 cases per 10,000 hospital admissions. Among these, the incidences of MDR- and PDR- *A. baumannii* bacteremia were 3.6 and 1.8 cases per 10,000 hospital admissions, respectively. There was an increasing trend in antimicrobial resistance to several drugs during the 3-year study (Fig 1).

Medical records were available for 65 cases (82.3%). Of these, 16 cases were excluded from the study due to contamination (6 cases), mixed infection (9 cases) and transfer to another hospital (1 case). Among the remaining 49 cases, 25 (51%) and 24 cases (49%), respectively, had non-MDR and MDR *A. baumannii* bacteremia and 15 of the 24 MDR *A. baumannii* cases (62.5%) had PDR *A. baumannii* infection.

The demographic data are presented in Table 1. The mean age of the two patient groups (*ie*, non-MDR and MDR



AK, amikacin; NET, netilmicin; CFX, ciprofloxacin; OFX, ofloxacin; SXT, trimethoprim/sulfamethoxazole; CPO, cetriaxone; CAZ, ceftazidime; CTX, cefotaxime; SAM, ampicillin-sulbactam; SCFP, cefoperazone/sulbactam; TZP, piperacillin-tazobactam; IPM, imipenem; MEM, meropenem

Fig 1–Antimicrobial susceptibility patterns of *A. baumannii* isolated from patients with *A. baumannii* bacteremia during 2005-2007 at Srinakarin Hospital.

A. baumannii bacteremia) were comparable [56.9 (SD, 17.5) *vs* 59.4 (SD, 16.8) years]. There were no differences in sex distribution or admission wards. All patients with MDR *A. baumannii* bacteremia, compared to two-thirds of those with non-MDR *A. baumannii* infection, had hospital-acquired infections (p=0.02). The majority of patients in the two groups had similar underlying diseases except for those with chronic kidney disease, for which the proportion of disease was significantly higher in patients with MDR *A. baumannii* bacteremia than those with non-MDR *A. baumannii* bacteremia (8 cases; 33.3% *vs* 2 cases; 8%, p=0.04). About two-thirds of the patients in each group had secondary bacteremia, of which pneumonia (20 cases; 40.8%) was the most common source of bacteremia, followed by intra-abdominal infection (9 cases; 18.4%). There was no significant difference in the proportion of pneumonia between the two groups [7/25 (28%) in non-MDR group *vs* 13/24 (54.2%) in MDR group, p=0.08]. Intra-abdominal infections, as a source of bacteremia, were found in 6 and 3 cases with non-MDR and MDR, respectively. The remaining sources of bacteremia were urinary tract, sinus, and skin/soft tissue infections, which were found in one case each in the non-MDR group.

Table 1
Demographic data and risk factors for MDR *A. baumannii* bacteremia.

Variable	No. (%) of cases		*p*-value	OR (95%CI)
	Non-MDR *A. baumannii* (*n*=25)	MDR *A. baumannii* (*n*=24)		
Mean age; year (±SD)	56.9 (17.5)	59.4 (16.8)	0.62	NS
Male	12 (48)	16 (66.7)	0.25	NS
Type of infection			0.02	-
Hospital-acquired	19 (76)	24 (100)		
Community-acquired	6 (24)	0		
Admission ward			0.11	NS
Medicine	11 (44)	16 (66.7)		
Non-medicine	14 (56)	8 (33.3)		
Underlying diseases	25 (100)	23 (95.8)	0.49	NS
Malignancy	15 (60)	8 (33.3)	0.06	NS
Received prednisolone or immunosuppressive drugs	4 (16)	8 (33.3)	0.16	NS
Chronic kidney disease	2 (8)	8 (33.3)	0.04	5.75 (1.08-30.72)
Diabetes mellitus	4 (16)	4 (16.7)	1.00	NS
Heart disease	4 (16)	3 (12.5)	1.00	NS
Autoimmune disease	2 (8)	4 (16.7)	0.42	NS
Neutropenia	1 (4)	3 (12.5)	0.35	NS
Chronic obstructive lung disease	1 (4)	3 (12.5)	0.35	NS
Chronic liver disease	2 (8)	1 (4.2)	1.00	NS
Prior ICU stay	3 (12)	9 (37.5)	0.04	4.40 (1.02-18.99)
Median (range) duration of prior ICU stay; days (*n*=12)	4 (2-6)	6 (1-21)	0.4	NS
Prior *A.baumannii* colonization	4 (16)	11 (45.8)	0.02	4.42 (1.17-16.92)
History of prior bacteremia	1 (4)	8 (33.3)	0.01	12 (1.37-105.41)
History of prior antibiotic use	14 (56)	24 (100)	<0.001	-
3rd generation cephalosporin	9 (36)	17 (70.8)	0.02	4.32 (1.30-14.34)
Beta-lactam/Beta-lactamase inhibitor	4 (16)	16 (66.7)	<0.001	10.5 (2.68-41.12)
Metronidazole	5 (20)	11 (45.8)	0.05	NS
Carbapenem	2 (8)	13 (54.2)	<0.001	13.59 (2.60-70.98)
Aminoglycoside	2 (8)	10 (41.7)	0.006	8.21 (1.57-43.08)
Fluoroquinolone	5 (20)	4 (16.7)	1.00	NS
Penicillin group	3 (12)	6 (25)	0.29	NS
Cotrimoxazole	1 (4)	5 (20.8)	0.098	NS
1st or 2nd generation cephalosporin	2 (8)	3 (12.5)	0.67	NS
Vancomycin	0	4 (16.7)	0.05	NS
Macrolides	1 (4)	1 (4.2)	1.00	NS
Clindamycin	1 (4)	1 (4.2)	1.00	NS
Median (range) no. of prior antibiotics (*n*=38)	2 (1-6)	4.5 (2-9)	0.003	1.89 (1.16-3.07)[a]
No. of antibiotics used prior to bacteremia (*n*=38)			0.04	
1-3	10 (71.4)	9 (37.5)		1
≥4	4 (28.6)	15 (62.5)		4.17 (1.003-17.31)

Table 1 (Continued).

Variable	No. (%) of cases		*p*-value	OR (95%CI)
	Non-MDR *A. baumannii* (*n*=25)	MDR *A. baumannii* (*n*=24)		
Median (range) duration of prior antibiotics used; days (*n*=38)	14 (1-25)	19 (8-76)	0.06	NS
Median (range) duration of hospitalization prior to having bacteremia; days	3 (0-50)	15.5 (0-94)	0.008	1.04 (1.002-1.08)[a]
Intervention				
Nasogastric tube	6 (24)	16 (66.7)	0.003	6.33 (1.81-22.11)
Central venous catheter	3 (12)	17 (70.8)	<0.001	17.81 (4.00-79.28)
Foley catheter	7 (28)	12 (50)	0.11	NS
On ventilator	4 (16)	14 (58.3)	0.002	7.35 (1.92-28.14)
Parenteral nutrition	5 (20)	9 (37.5)	0.18	NS
Recent surgery	5 (20)	8 (33.3)	0.29	NS
Type of bacteremia			0.85	NS
Primary	9 (36)	8 (33.3)		
Secondary	16 (64)	16 (66.7)		
Median (range) of APACHE II score (*n*=48)[b]	17 (4-35)	24 (14-45)	0.005	1.11 (1.02-1.21)[a]

[a]Per 1-point increment; [b]1 missing data in susceptible group

On univariate analysis, the factors significantly associated with developing MDR *A. baumannii* bacteremia included: 1) hospital-acquired infection, 2) chronic kidney disease, 3) recent ICU stay, 4) prior *A. baumannii* colonization, 5) prior bacteremia from other organisms, 6) prior antibiotic therapy, 7) prolonged duration of hospitalization prior to contracting bacteremia, 8) received interventions, including nosogastric intubation, central venous catheterization, and mechanical ventilator, and (9) a higher APACHE II score (Table 1).

Prior receipt of any of the following four antimicrobial classes was significantly associated with MDR *A. baumannii* bacteremia: 3rd generation cephalosporins (OR 4.32; 95%CI 1.30-14.34), beta-lactam/beta-lactamase inhibitor (OR 10.5; 95%CI 2.68-41.12), carbapenem (OR 13.59; 95%CI 2.60-70.98), and aminoglycoside (OR 8.21; 95%CI 1.57-43.08). The median (range) number of prior antibiotics used was significantly higher among those with MDR *A. baumannii* bacteremia [4.5 (2-9) *vs* 2 (1-6), *p*=0.003]. Patients with MDR *A. baumannii* bacteremia had a significantly higher median (range) APACHE II score than those with non-MDR *A. baumannii* infection [24 (14-45) *vs* 17 (4-35), *p*=0.005].

On multivariate analysis, three factors were independently related to contracting MDR *A. baumannii* bacteremia: recent ICU stay (OR 10.01; 95%CI 1.39-72.20) and prior receipt of a carbapenem antimicrobial (OR 11.40; 95%CI 1.44-89.98) or beta-lactam/beta-lactamase inhibitor antimicrobial (OR 8.06; 95%CI 1.39-46.64).

Table 2
Treatment and clinical outcomes in patients with non-MDR and MDR *A. baumannii* bacteremia.

Factors	No. (%) of cases		*p*-value
	Non-MDR *A. baumannii* (*n*=25)	MDR *A. baumannii* (*n*=24)	
No. of patients receiving appropriate empirical antibiotic within 72 hours of bacteremia (*n*=46)[a]	21/22 (95.5)	6/24 (25)	<0.001
No. of patients receiving appropriate antibiotic during the course of bacteremia (*n*=48)[a]	23/24 (95.8)	10/24 (41.7)	<0.001
Median (range) duration from bacteremia to receiving appropriate antibiotic; days (*n*=33)	0 (0-9)	2.5 (0-5)	0.006
No. of patients alive at 72 hours of empirical treatment	19 (76)	10 (41.7)	0.02
Median (range) duration of hospitalization since bacteremia; days (*n*=29)	14 (2-86)	21.5 (4-161)	0.18
Clinical outcomes at 72 hours of bacteremia (*n*=29)			0.02
Complete response	12/19 (63.2)	1/10 (10)	
Partial response	2/19 (10.5)	1/10 (10)	
Failure	5/19 (26.3)	8/10 (80)	
Overall in-hospital mortality	12 (48)	22 (91.7)	0.001

[a]Missing data = patients received an antibiotic for which the susceptibility pattern was not known.

The proportions of patients who received appropriate empirical antimicrobial therapy and appropriate antimicrobial therapy during the course of bacteremia were significantly lower in patients with MDR *A. baumannii* bacteremia (25% *vs* 95.5%, $p<0.001$; 41.7% *vs* 95.8%, $p<0.001$; respectively) (Table 2). The median (range) duration from the onset of bacteremia to receipt of appropriate antimicrobial therapy was significantly longer in patients with MDR *A. baumannii* bacteremia [2.5 (0-5) *vs* 0 (0-9) days, $p=0.006$]. Seventy-two hours after the onset of bacteremia, there was a significantly lower proportion of patients who survived with MDR *A. baumannii* bacteremia (41.7% *vs* 76%, $p=0.02$). Of the 29 patients surviving at 72 hours; there was a significantly greater proportion with worse outcomes among patients with MDR *A. baumannii* bacteremia ($p=0.02$). The overall mortality rate was significantly higher in patients with MDR *A. baumannii* bacteremia (22 cases; 91.7% *vs* 12 cases; 48%, $p=0.001$).

On univariate analysis, the factors significantly related to mortality in patients with *A. baumannii* bacteremia were: 1) higher APACHE II score, 2) older age, 3) secondary bacteremia, 4) having pneumonia, and 5) MDR *A. baumannii* infection (Table 3). On multivariate analysis, two factors were related to mortality: a higher APACHE II score (OR 1.25; 95%CI 1.03-1.52) and secondary bacteremia (OR 14.86; 95%CI 1.37-161.90).

DISCUSSION

MDR *A. baumannii* has become a serious

Table 3
Factors associated with mortality in patients with MDR *A. baumannii* bacteremia.

Variables	OR (95%CI)
Not receiving appropriate empirical antibiotic within 72 hours of bacteremia	3.14 (0.73-13.51)
Not receiving appropriate antibiotic during the course of bacteremia	3.71 (0.71-19.32)
APACHE II score	1.36 (1.12-1.66)
Medical patients	2.42 (0.70-8.40)
Drug-resistant *A. baumannii*	11.92 (2.30-61.83)
Secondary bacteremia	7.71 (1.98-29.99)
Pneumonia	17.73 (2.09-150.53)
Delayed time to receipt of appropriate antibiotic (days)	0.91 (0.67-1.25)
Age	1.05 (1.004-1.09)

nosocomial pathogen causing a variety of clinical manifestations. Nosocomial septicemia is one of the most important problems facing modern medicine. Patients with MDR *A. baumannii* bacteremia have higher mortality and medical costs than non-MDR *A. baumannii* bacteremia patients. These bacteria must be identified quickly in order to adjust empirical treatment (Lee *et al*, 2007; Sunenshine *et al*, 2007). In a case-control study, Shih *et al* (2008) found four independent risk factors associated with multidrug resistance in *A. baumannii* septicemia: previous colonization with *A. baumannii*, antecedent antimicrobial therapy, the number of prescribed antibiotics, and a recent invasive procedure. In contrast to the present study, they did not identify the effect of different classes of antibiotics on the development of MDR-*A. baumannii* septicemia. The present study showed exposure to broad spectrum antibiotics, such as carbapenem or beta-lactam/beta-lactamase inhibitor antimicrobials was independently related to MDR-*A. baumannii* bacteremia.

Our findings are similar to a meta-analysis done on the association between exposure to broad spectrum antibiotics and the development of MDR-*A. baumannii* infection (Falagas and Kopterides, 2006b). Exposure to these antibiotics results in the emergence of resistance due to selective pressure and interruption of the colonization resistance mechanism. Previous colonization with *A. baumannii* was not an independent risk factor in the present study but prior ICU stay was. Using passively collected culture data may underestimate the significance of colonization in our study. Conditions in the ICU provide an environment conducive to the development and maintenance of MDR-*A. baumannii*. Most patients admitted to the ICU are severely ill, need interventions and frequently receive antibiotics, all of which promote multidrug resistant colonization and subsequent infection in susceptible patients. The present study may have underestimated the significance of bacterial colonization because of limited surveillance culture data.

Therapeutic options are limited for MDR-*A. baumannii* infection, especially if the isolates are resistant to carbapenem class antibiotics, of which polymyxin or tigecycline may be the only ones available for treatment (Maragakis and Perl, 2008).

Compared to previous studies (Kuo *et al*, 2007; Lee *et al*, 2007), the overall mortality rate for *A. baumannii* bacteremia at our hospital was high: 48% in non-MDR *A. baumannii* infection and > 90% in MDR-*A. baumannii*. During the study period, polymyxin and tigecycline were not available at our hospital, which led to a high proportion of patients with MDR-*A. baumannii* bacteremia not receiving appropriate antimicrobial therapy resulting in a significantly higher mortality rate than expected. Previous studies have found the administration of ineffective antimicrobial therapy for carbapenem-resistant *A. baumannii* bacteremia is a predictor of mortality (Kwon *et al*, 2007; Jamulitrat *et al*, 2009). The present study supports the association between inappropriate antimicrobial treatment and increasing mortality among patients. Awareness by the physician of risk factors for MDR- *A. baumannii* infection, available effective antimicrobial agents, and intensive care support may improve clinical outcomes among these patients.

Although MDR-*A. baumannii* bacteremia is associated with mortality in the present study as demonstrated on univariate analysis; it was not a major determinant of mortality. The present study showed the independent factors related to death among patients with *A. baumannii* bacteremia were severity of illness and secondary bacteremia. On multivariate analysis assessing the risk factors for mortality showed increasing trend in mortality in patients contracting MDR- *A. baumannii* bacteremia, albeit not statistically significant (OR 10.243; 95% CI 0.792-132.513) possibly due to small sample size.

The higher mortality rate in patients with MDR- *A. baumannii* bacteremia may not be directly attributable to drug resistance but may be confounded by the effects of underlying disease severity, inappropriate antibiotic treatment and primary source of infection (Jamulitrat *et al*, 2009). Approximately 40% of patients in the present study had pneumonia as a primary source of *A. baumannii* bacteremia, which is nearly 2 times more common in MDR than in the non-MDR group. Our results support the findings of Agbaht *et al* (2007) that the bacteremic ventilator-associated pneumonia is more often caused by multidrug-resistant organisms with a higher risk of death.

The present study had limitations. Based on the retrospective study design, some missing data could have resulted in selection bias. Moreover, the small sample size may have affected the power of the study to detect differences. The study design, which used cases with non-MDR-*A. baumannii* bacteremia as the comparable group, may have overestimated the significance of antibiotics as a risk factor for contracting MDR-*A. baumannii* bacteremia (Harris *et al*, 2002).

In conclusion, this study revealed the significant independent factors associated with MDR *A. baumannii* bacteremia were previous ICU admission and prior use of broad spectrum antibiotics. This infection is associated with a high mortality rate, especially in patients not receiving appropriate treatment. Emphasis needs to be placed on prevention, strict application of infection control, and appropriate use of antibiotics, all of which might reduce the risk and improve the control of this infection.

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