

Clinical Outcomes and Risk Factors Affecting 30-day Mortality and Treatment Failure of Patients Infected with Carbapenem-Resistant *Acinetobacter baumannii* in a General Hospital

Wichai Santimaleeworagun^{1*}, Wandee Sumret², Kanokwan Limsubjaroen¹, Nattaporn Ruangnara¹, Parada Sujariththam¹, Ploypailin Mulmek¹, and Weerayuth Saelim¹

¹*Department of Pharmacy, Silpakorn University, Nakhon Pathom, Thailand*

²*Pharmacy Department, Hua Hin Hospital, Prachuap Khiri Khan, Thailand*

**Corresponding author. Email address: swichai1234@gmail.com*

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Abstract

This study aimed to determine 30-day mortality and treatment failure rates in patients infected with carbapenem-resistant *Acinetobacter baumannii* (CRAB) and to evaluate predictive factors associated with 30-day mortality and treatment failure. This retrospective study collected data from medical records of patients admitted to Hua Hin Hospital from January to December, 2012. Seventy-three patients with CRAB infections met the eligible criteria, while 57.5 and 61.6 % were death and treatment failure rate, respectively. Risk factors associated with 30-day mortality were appropriate antimicrobial therapy (OR 0.22; 95% CI 0.08-0.62) and shock (OR 5.80; 95% CI 1.19-28.20). In addition, the appropriate antimicrobial therapy (OR 0.11; 95% CI 0.03-0.37) and shock (OR 10.97; 95% CI 1.35-89.34) were also predictors for treatment failure. In multivariate analysis, a factor associated with 30-day mortality and treatment failure remained the appropriate antimicrobial therapy. In conclusion, the appropriate antimicrobial treatment was a strategy associated with better treatment outcomes in patients with CRAB infections.

Key Words: *Acinetobacter baumannii*; Carbapenem-resistant; Clinical outcomes; Risk factors

Introduction

Acinetobacter baumannii, an aerobic Gram-negative bacilli, is a major cause of nosocomial infections, especially in the respiratory tract, urinary system, bloodstream and central nervous system (Bergogne-Berezin and Towner, 1996). With such infections, *A. baumannii* is a major public health problem in various parts of the world, including Thailand. Wisplinghoff et al. (2004) performed the nationwide surveillance study (SCOPE study) to

examine the causative pathogens in nosocomial bloodstream infection among 24,179 cases during March, 1995 to September, 2002. This study showed that *A. baumannii* was the second cause of death in patients admitted to intensive care unit. According to Alvarez-Lerma et al. (2007) study, which reported the national rates of acquired invasive device-related infections in the ICU during 2003-2005, *A. baumannii* was the third predominant etiology of pneumonia related with mechanical ventilation in

Spain. Similar to the other countries, in Thailand, *A. baumannii* was identified in the sputum during year 2004 and 2006 at a rate of 14 and 17% of pathogenic organisms, respectively. In addition, this organism was ranked the fourth of isolated clinical pathogens in Thailand (National Antimicrobial Resistance Surveillance Thailand Center, 2010).

Besides the increasing rate of *A. baumannii* infections, the multi-mechanisms of antimicrobial resistance might also enhance problematic treatment such as producing enzymes (especially carbapenemases) destroying drugs, reducing amount of the drug into the cells (porin loss), driving drug out of the cell (efflux pump), or changing the target site of antimicrobial action (Bergogne-Berezin et al., 1996; Bonomo and Szabo, 2006). Thus, *A. baumannii* infections were hardly treated by effective medications. From the National Antimicrobial Resistance Surveillance Thailand Centre (NARST), Dejsirilert et al. (2009) reported the 6 years period of antimicrobial resistance surveillance (in 2000-2005). The result showed the increasing rate of infections, by carbapenem-resistant *A. baumannii* (CRAB), from 2.1 to 46.7% in 2000 and 2005, respectively.

Due to the increasing rates of both infection and the spreading of resistant pathogen, the therapeutic choices for *A. baumannii* eradication were scant. Cefoperazone/sulbactam, colistin and tigecycline remain the last three options in the resistant era. However, mortality rate and treatment failure have been reported in some previous studies, which lots of unfavorable factors revealed the treatment outcomes (Deris et al., 2009; Erbay et al., 2009; Livermore et al., 2010; Sheng et al., 2010; Santimaleeworagun et al., 2011a).

Currently, the risk factors associated with clinical outcomes includes age, shock, renal dysfunction, ICU stay, immunocompromised host, bloodstream infection, mechanical ventilation use,

and the appropriate antimicrobial therapy (Deris et al., 2009; Erbay et al., 2009; Livermore et al., 2010; Sheng et al., 2010; Santimaleeworagun et al., 2011a). However, such reports were often done in medical schools or large-sized hospitals. Thus, severity of problems in the general hospital might be different.

Problem of antimicrobial resistance in Hua Hin Hospital, a general hospital located in Prachuap Khiri Khan Province, Thailand, is increasing. One percent of MDR-AB (defined as resistance to ceftazidime, ciprofloxacin and aminoglycoside) was only sensitive to imipenem in year 2010. This phenomenon could be considered as an urgent problem. Therefore, the objective of this present study was to retrospectively collect data of patients infected with CRAB, to determine risk factors associated with 30-day mortality and treatment failure. Our results might be useful to plan the patient care for reducing the unexpected outcomes in patient with CRAB infections.

Materials and Methods

This was a retrospective cohort study that gathered the data of patients infected with CRAB during January to December, 2012 from electronic medical records database. The protocol was approved by the institutional review board of Faculty of Pharmacy, Silpakorn University and Hua Hin Hospital with a waiver for informed consent.

Participants

This study was to identify risk factors associated with clinical outcomes of patients infected with CRAB. The inclusion criteria for CRAB infections consisted of 1) *A. baumannii* was resistant to carbapenems; 2) Patients had clinical signs of infection, such as systemic inflammatory syndrome (SIRS) at least 2 out of 4 items (body temperature > 38 or < 36 °C, respiratory rate > 20 breaths/min, heart rate > 90 beats/min, leukocytosis

> 12,000 cells/mL or < 4,000 cells/mL) with suspected source of infections (Levy et al., 2003; Calandra and Cohen, 2005); 3) Sepsis occurred 48 hours or more after admission. Patients had CRAB grew up in specimen without any signs and symptoms (also called *A. baumannii* colonization), patients died before the susceptibility test results came out, patients transferred between hospital, treatment was not be able to followed-up, or patients with incomplete medical records were excluded.

Definitions

Carbapenem-resistant Acinetobacter baumannii (CRAB) was referred to *A. baumannii* which resists to all carbapenems (imipenem and meropenem) based on disk diffusion method. *Combination antimicrobial therapy* were treatment with more than 2 agents which have scientific evidence to enhance the effect of the treatment. *Appropriate antimicrobial therapy* meant treatment with at least one active antimicrobial agent within 24 hours after reporting the CRAB susceptibility. Septic shock was diagnosed by a physician, but not includes the other shocks (hypovolemic shock, cardiogenic shock, and obstructive shock). *Impaired renal function* defined as serum creatinine greater than 100% of the baseline level. *Impaired liver function* were 5-times increase of ALT from the upper normal limit or 3-time increase of ALT concomitant with clinical symptoms of hepatitis. *Immunocompromised host* included systemic lupus erythematosus, human immunodeficiency virus (HIV) infection, cancer, patients with an absolute neutrophil count $< 0.5 \times 10^9$ cells/L, patients with organ transplantation or immunosuppressive agents use (steroids at a dosage greater than 10 mg of prednisolone daily for more than 2 weeks or chemotherapy)

According to clinical outcome definitions; *presumptive success* was a cure or clinical improvement. Cure was classified as clinical improvement and microbiological success (culture negative after treatment). Clinical improvement

defined as having normal body temperature, normal level WBC, and stable vital signs. Treatment failure included failure and death. Failure patients were ones with clinical symptoms got worse or antimicrobial therapy had to be changed or added to be against CRAB. Death defined as decease within 30 days of CRAB infection.

Data Collection

Patient data were reviewed, via database and medical records from medical record unit, for clinical information, including age, sex, underlying diseases, admitted ward, mechanical ventilator use, shock, hepatic function, renal function, immunocompromized status, antimicrobial regimens (date of start, dosage, administration and duration), antimicrobial susceptibility, length of hospital stay, source of infections, vital signs and clinical outcomes. The primary outcome measurements were all-cause 30-day mortality and risk factors related to failure and mortality.

Statistical Analysis

Descriptive statistics were used for 30-day mortality and treatment failure rates of CRAB infections. Chi-square or Fisher's exact test statistics was analyzed the relationship between the discrete factors and clinical outcomes. Kolmogorov - smirnov Z test or Student t-test were used to compare the median or mean, respectively, between continuous data and clinical outcomes. All significant variables in the univariate analysis were considered for the multivariate analysis by logistic regression analysis. Analysis and data interpretation were processed via SPSS 17.0 for windows data analysis at $\alpha = 0.05$ for statistical significance.

Results

During the study period, 131 patients were included. Only 73 cases were eligible according to inclusion criteria (47 cases with *A. baumannii* colonization, 7 patients died before the susceptibility

test results came out and 3 of them were transferred out). Among 73 patients with CRAB infections, 35 patients (47.95%) were male, mean age was 64.7 years (SD \pm 16.5), mean duration of hospitalization was 44.5 days (SD \pm 23.79) and 32 patients (43.84%) admitted at ICU. Pneumonia was the most common site of infection (84.9%) (Table 1).

Clinical Outcomes

Of the clinical outcomes among ones infected with CRAB, 30-day mortality and treatment failure rates were 57.5 and 61.6 %, respectively. The percentage of appropriate antimicrobial use was only 57.5%.

Predictive Factors of Clinical Outcomes

Univariate analysis found that significant risk factors associated with treatment failure and 30-day mortality were the appropriate antimicrobial therapy and shock. Whereas age \leq 65 years, gender, the antimicrobial combination, more than one types of bacterial infection, duration of hospitalization, admitted at the ICU, renal function impairment, impaired liver function, diabetes, mechanical ventilation use, and immunocompromised factors were not found to be predictive factors of treatment failure or death (Table 2 and 3). For multivariate analysis, the factors found to reduce the rate of

Table 1 Characteristics of patients with carbapenem-resistant *Acinetobacter baumannii* infections (CRAB) (n=73)

Characteristics	Number (%)
Sex ; male	35 (47.95)
Age (years; Mean \pm SD)	64.66 \pm 16.53
Duration of hospitalization (days; Mean \pm SD)	44.52 \pm 23.79
Intensive care unit stay	32 (43.84)
Combination antimicrobial therapy	25 (34.25)
Appropriate antimicrobial use	42 (57.53)
Shock	16 (21.92)
Renal dysfunction	27 (36.99)
Hepatic dysfunction	3 (4.11)
Diabetes mellitus	25 (34.25)
Mechanical ventilator use	54 (73.97)
Immunocompromized status	5 (6.85)
Site of infections	
- Pneumonia	62 (84.9)
- Skin and Soft tissue	6 (8.2)
- Bloodstream	3 (4.1)
- Urinary tract	1 (1.4)
- Central nervous system	1 (1.4)

Table 2 Univariate and multivariate analysis to identify risk factors influencing treatment failure (failure or death) among patients with carbapenem-resistant *Acinetobacter baumannii* infections (N=73)

Variable	Presumptive success (n=28)	Treatment failures (n=45)	Crude odd ratio (95%CI)	Adjusted odd ratio (95%CI)
Age ≤ 65 years	13 (17.8)	19 (26.0)	0.843 (0.33-2.18)	
Sex ; Male	12 (16.4)	23 (31.5)	0.72 (0.28-1.85)	
Intensive care unit stay	9 (12.3)	23 (31.5)	2.21 (0.82-5.91)	
The combination antimicrobial therapy	14 (25.0)	11 (19.6)	0.65 (0.22-1.87)	
The appropriate antimicrobial therapy	24 (32.9)	18 (24.7)	0.11 (0.03-0.37)	
Shock	1 (1.4)	13 (17.8)	10.97(1.35-89.34)	
Renal dysfunction	10 (13.7)	17 (23.5)	1.09 (0.41-2.91)	
Hepatic dysfunction	0 (0)	3 (4.1)	1.07 (0.99-1.16)	0.14 (0.04-0.47)
Diabetes mellitus	9 (12.3)	16 (21.9)	1.17 (0.43-3.17)	
Mechanical ventilator	19 (26.0)	35 (47.9)	1.66 (0.58-4.78)	
Immunocompromized status	1 (1.4)	4 (5.5)	2.63 (0.28-24.86)	

Table 3 Univariate and multivariate analysis to identify risk factors influencing 30-day mortality among patients with carbapenem-resistant *Acinetobacter baumannii* infections (N=73)

Variable	Survivor (n=31)	30-day mortality (n=42)	Crude odd ratio (95%CI)	Adjusted odd ratio (95%CI)
Age ≤ 65 years	14 (19.2)	18 (24.7)	0.91 (0.36-2.32)	
Sex ; Male	14 (19.2)	21 (28.8)	1.21 (0.48-3.08)	
Intensive care unit stay	10 (13.7)	22 (30.1)	2.31 (0.88-6.07)	
The combined antimicrobialtherapy	14 (25.0)	11 (19.6)	0.74 (0.26-2.12)	
The appropriate antimicrobial use	24 (32.9)	18 (24.7)	0.22 (0.08-0.62)	0.27 (0.09-0.79)
Shock	2 (2.7)	12 (16.4)	5.80(1.19-28.20)	
Renal dysfunction	11 (15.1)	16 (21.9)	1.12 (0.43-2.93)	
Hepatic dysfunction	0 (0)	3 (4.1)	1.08 (0.99-1.17)	
Diabetes mellitus	10 (13.7)	15 (20.5)	1.17 (0.44-3.12)	
Mechanical ventilator use	21 (28.8)	33 (45.2)	1.75 (0.61-5.01)	
Immunocompromized status	2 (2.7)	3 (4.1)	1.12 (0.18-7.11)	

treatment failure and 30-day mortality were the appropriate antibiotics therapy (adjusted OR 0.14; 95% CI 0.04-0.47 and adjusted OR 0.27; 95% CI 0.09-0.79, respectively).

Discussion

CRAB-causing nosocomial infections are becoming a major problem worldwide (Hsueh et al., 2005; Marshall et al., 2007). Therefore, this important issue is challenging for medical treatment. The main reason making CRAB treatment complicated is the pathogen carrying multi-mechanisms of resistance. As in previous studies, the resistant mechanism in *A. baumannii*, were identified as producing enzymes destroying antimicrobial agents (OXA, metallo- β -lactamase, Amp-C, aminoglycoside-modifying enzyme), loss of porins, efflux pumps or changing antibiotic target (penicillin-binding proteins), ribosomal RNA, or DNA gyrase) (Bergogne-Berezin et al., 1996; Bonomo et al., 2006). For β -lactam antibiotics, the highly efficient enzyme is carbapenemases which inactive carbapenems, cephalosporins and penicillins. OXA-23, is the most common type of carbapenemase found in Thailand, (Niumsup et al., 2009; Thapa et al., 2010; Santimaleeworagun et al., 2011b)

Owing to lack of carbapenem activity against *A. baumannii*, sulbactam, colistin and tigecycline are still the active antimicrobials. Using available agents for CRAB infection, treatment outcomes have been unsuccessful with high mortality rate. Hello *et al.* showed that the cases infected with CRAB had significantly higher 30-day mortality rate than ones of patients infected with other MDR bacteria (Hello et al., 2010). This present study indicated that overall mortality rate for CRAB infections was 57.5% in the general hospital. This findings was similar with results from a study of Lee et al (2013)., which revealed that the mortality rate

in CRAB infection was 45 % but our result seems to have higher mortality rate than the previous two studies performed in Thailand, even as the university medical schools (33.8 and 30%, respectively) (Jamulitrat et al., 2007; Santimaleeworagun et al., 2011a). However, the results from different studies might vary in the mortality rate depending patient status, age, underlying diseases, source of infection, and appropriate antimicrobial agents (Apisarnthanarak and Mundy, 2009; Deris et al., 2009; Erbay et al., 2009; Livermore et al., 2010; Sheng et al., 2010). Santimaleeworagun et al. (2011a) reported the overall mortality rate as 30% among cases with a higher percentage of appropriate antimicrobial use (82.7%)) than in the present study (57.5%). Thus, this study revealed that the treatment outcome might be the higher mortality rate if the patients had more unfavorable factors, regardless types of hospital level.

According to predictive factors for treatment failure and mortality, the appropriate antimicrobial use remained only favorable factor in multivariate analysis. This result was accorded with that from the study by Deris et al. (2009). Falagas et al. (2006) and Santimaleeworagun et al. (2011a) indicated that appropriate antimicrobial agents for the treatment of *Acinetobacter* infections could significantly reduce the mortality.

The present study did not find the differences between patients given single and combination antimicrobial therapy. Even, presumptive or survivor groups were more likely to have higher percentage of combination regimen, but the authors could not detect the statistical difference. The explanation for insignificant analysis might result from a small sample size.

Another limitation of this study was the authors could not calculate APACHE that are the severity of illness scoring because of its retrospective study pattern and lack of Glasgow coma score.

Obviously, APACHE II scores was proved to be associated with mortality in CRAB infections (Prates et al., 2010). However, the characteristic data (including; age, immunocompromized status, renal or liver function, mechanical ventilator use or shock) were important parameters in APACHE II scores, had been herein analyzed.

Conclusion

The appropriate antimicrobial treatment was associated with better treatment outcomes in patients with CRAB infections. Thus, this is a strategy to improve outcomes of CRAB treatment. A larger study could identify the risk factors for clinical outcomes based on severity of disease and the benefit of combination therapy.

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