Clinical Outcomes of Patients Infected with Carbapenem-Resistant *Acinetobacter Baumannii* Treated with Single or Combination Antibiotic Therapy

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Objective: *To evaluate treatment outcomes in patients with carbapenem-resistant Acinetobacter baumannii (CRAB) nosocomial infections treated with antimicrobial agent either alone or in combination.*
Material and Method: *Clinical data were retrospectively evaluated in patients with CRAB nosocomial infections admitted to Songklanagarind Hospital, Songkhla, Thailand from January-December 2008.*
Results: *One hundred ten patients with CRAB nosocomial infections were identified. Most patients (57.3%) had site of infection in the lower respiratory tract and the majority of them (61.8%) received a single antimicrobial agent. Crude mortality was 30%. The presumptive success rate was 60.3% (41/68) for patients given monotherapy and 81.0% (34/42) for patients given combination therapy (p = 0.024). Patients given combination therapy were more likely to have been given at least one antibiotic to which the organism was susceptible (p = 0.004). In multivariate analysis, renal impairment, bloodstream infection, and inappropriate antimicrobial regimen were independent predictors of treatment failure.*
Conclusion: *The combination therapy regimen yielded more presumptive treatment success by increasing the likelihood of an appropriate antimicrobial therapy. Additionally, inappropriate antimicrobial treatment, renal impairment, and bloodstream infection were associated with poor treatment outcomes in patients with CRAB nosocomial infections.*

Keywords: *Clinical outcomes, Combination therapy, Fosfomycin, Carbapenem-resistant Acinetobacter baumannii*

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Nosocomial infections with *Acinetobacter baumanni* have increased dramatically[1-3]. In the United States, *Acinetobacter* spp. was the tenth most common organism causing nosocomial bacteremia in patients admitted to an intensive care unit and ranked the third as the cause of death among all types of pathogens[4]. In Taiwan, *A. baumannii* infection has increased from 25 to 55 episodes per 10,000 discharged patients between 1999 and 2003[1]. Similar to the other countries, the prevalence of carbapenem resistant *A. baumanii* (CRAB) in Thailand increased from 2.1 in 2000 to 46.7% in 2005[5].

Nosocomial *A. baumannii* infections are associated with severe adverse outcomes. Bacteremia due to multi drug-resistant *A. baumannii* (MDR-*A. baumannii*) resulted in 13.4 days of additional hospital days, US$ 3,758 of additional hospital costs[6] and the 30-day mortality rate of 49%[7].

At Songklanagarind Hospital, the percentage of CRAB strains has increased from 3% in 2001 to 60% in 2007. These strains retained susceptibility to cefoperazone/sulbactam and colistin both of which have susceptibility greater than 90%. These strains were generally susceptible to fosfomycin with the MIC_{50} and MIC_{90} values of 64 and 96 mg/L, respectively[8]. Based on this data, many clinicians at Songklanagarind

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Hospital have used cefoperazone/sulbactam or colistin as monotherapy or in combination with fosfomycin or cefoperazone/sulbactam plus colistin for CRAB nosocomial infections. Combination therapy with fosfomycin for CRAB nosocomial infections has not been previously reported and clinical outcome data of patients treated with cefoperazone/sulbactam and colistin either alone or in combination is limited. The aim of the present study was to evaluate treatment outcomes in patients with CRAB nosocomial infections treated with antimicrobial agent either alone or in combination.

Material and Method

Setting

The present study was a retrospective cohort study of hospitalized patients with CRAB nosocomial infection admitted to Songklanagarind Hospital, an 850-bed university affiliated, hospital located in Songkhla, Thailand between January and December 2008. The present study was approved by the ethics committees of Faculty of Medicine, Prince of Songkla University, and Songklanagarind Hospital.

Participants

Clinical data were obtained from the medical records of inpatients with CRAB nosocomial infections. Patients were eligible for the present study if a CRAB was isolated from the patient while hospitalized more than 48 hours and the patients met the definition of having a systemic inflammatory response syndromes (SIRS) at the time of culture with no other known or suspected source of infection[9]. Briefly, SIRS is considered to be present when patients have more than one of the following clinical findings: body temperature, more than 38°C or less than 36°C; heart rate, more than 90 beats/min; respiratory rate more than 20 breaths/min or a PaCO2 less than 32 mm Hg; and a white blood cell count more than 12,000 cells/L or less than 4,000 cells/L[9]. The authors defined infection by the invasion of CRAB in sterile sites or fluid or any tissues as previously described[10-15]. Patients with insufficient information for assessment of infection or clinical outcomes were excluded from the present study.

Data collection

The medical records of patients were reviewed for demographic and outcome variables including: age, gender, hospital ward, presence of underlying disease, the organ or source of infections, diagnosis of infections, immunocompromised status, duration of hospitalization, using of mechanical ventilator, list of antibiotic usage, doses, administration, and duration, clinical laboratory data and clinical outcome of infections. The authors of the present study were responsible for data collection and interpretation.

Definitions and evaluation of clinical outcomes

CRAB was defined as a strain of *A. baumanii* resistant to imipenem and meropenem according to the disk diffusion method of the Clinical and Laboratory Standards Institute (CLSI)[16]. Patients with CRAB infection were assessed for overall mortality and presumptive treatment success (defined as patients whose nosocomial infection was cured) based on antimicrobial regimen received. Cure was classified as clinical or microbiological cure. Clinical cure was defined as resolution of signs and symptom of infections at the end of antibiotic therapy. Microbiological cure was defined as eradication of *A. baumannii isolates* as noted by the follow-up culture collection. Appropriate antibiotic regimen was defined as the initial anti-microbial regimens that were started within 48 hours after culture sample were obtained and the regimen containing at least one antibiotic that were later proved to be active *in vitro* against isolates of CRAB. Organ dysfunction was assessed including; unstable hemodynamic (SBP less than 90 mm Hg; or less than 2 SD below normal for age), renal impairment (serum creatinine increase more than 0.5 mg/dL from baseline), coagulation abnormalities (INR more than 1.5 or a PTT more than 60 seconds or platelet count less than 100,000 μL^{-1}), or hepatic disorder (plasma total bilirubin more than 2 mg/dL)[17].

Antimicrobial susceptibility testing

A. baumannii were identified at division of Clinical Microbiology, Songklanagarind Hospital, using conventional cultures and biochemical methods. Antimicrobial susceptibility against β-lactam antibiotics (ceftazidime, cefoperazone/sulbactam, piperacillin/tazobactam, imipenem, and meropenem), ciprofloxacin, aminoglycosides (amikacin and gentamicin), trimethoprim/sulfamethoxazole and colistin were evaluated using the disk diffusion method on agar plate according to CLSI protocol[16].

Statistical analysis

Data were summarized as the mean with standard deviation (SD) or median with interquartile range (IQR) based on the characteristics of their

distributions. Overall mortality, presumptive treatment success (clinical and microbiological cure) based on treatment with mono-or combination therapy was assessed using the Chi-square test or Fisher's exact test. In addition, the predictive factors for treatment failure (non-presumptive success) in the patients with CRAB infections were evaluated based on treatment failure (failure, or died) compared with presumptive success. The following factors were assessed: age, gender, hospital ward, infection site, immuno-compromised status, appropriate antibiotic regimen. In univariate analysis, the mean of each group was compared by using the unpaired Student's t test for normally distributed variables and the Mann-Whitney U test for non-normally distributed continuous variables. Chi-square or Fisher's exact test were used for categorical data. A multivariate analysis with logistic regression was performed to evaluate prognostic factors or mortality, including all variables with p-value less than 0.05 in the univariate analysis. A p-value < 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

One hundred ten patients with CRAB infection were identified. The lower respiratory tract was the most common site of infection (57.3%), followed by the blood (19.1%), intraabdominal tissues (8.2%), urine (5.5%), and other sites (9.9%). The mean (± SD) age of patients was 46.1 (± 29.5) years of which 60% were male). The median (IQR) duration of hospitalization was 44 (5-215) days. Demographic and clinical features including gender, site of infection, duration of hospitalization, ICU status, requirement for mechanical ventilation, co-morbid conditions and immunocompromised status did not differ based on treatment given (Table 1).

While all CRAB isolates from 110 patients were resistant to ceftazidime, piperacillin/tazobactam, imipenem, meropenem and ciprofloxacin by disk diffusion method, they were all susceptible to colistin. The percentage of susceptible strains varied for other antimicrobial agents. However, the patterns of antimicrobial resistance were not significantly

Table 1. Demographic data of the patients (n = 110 cases) with carbapenem-resistant *Acinetobacter baumannii* infection in monotherapy and combination therapy

Variables	Monotherapy (n = 68) n (%)	Combination (n = 42) n (%)	p-value
Age (year; mean ± SD)	44.91 ± 30.74	48.02 ± 27.72	0.60
Male	38 (55.9)	28 (66.7)	0.26
Duration of hospitalization (day; median; interquartile range)	43.5 (28.5-70)	46 (26.5-86.5)	0.72
ICU patients	40 (58.8)	26 (61.9)	0.75
Immunocompromized patients	26 (38.2)	13 (30.9)	0.44
Diabetes	5 (7.4)	2 (4.8)	
Cancers	13 (19.1)	8 (19.1)	
Neutropenia	10 (14.7)	4 (9.5)	
HIV/AIDS	2 (2.9)	1 (2.4)	
Mechanical ventilation	53 (77.9)	31 (73.8)	0.62
Shock	31 (45.6)	19 (45.2)	0.97
Coagulopathy	21 (30.9)	9 (21.4)	0.28
Renal impairment	21 (30.9)	8 (19.0)	0.17
Liver impairment	12 (17.6)	7 (16.7)	0.90
Source of infections			
Lower respiratory tracts	39 (57.4)	24 (57.1)	0.98
Bloodstream	13 (19.1)	8 (19.1)	0.99
Urinary tract	4 (5.9)	2 (4.8)	0.99
Skin and soft tissues	5 (7.4)	3 (7.1)	0.99
Intra-abdominal tissues	6 (8.8)	3 (7.1)	0.99
Central nervous system	1 (1.5)	1 (2.4)	0.99
Other sources	0	1 (2.4)	0.38
Outcomes of treatment			
Presumptive success	41 (60.3)	34 (81.0)	0.024

different between isolates from patient who received either monotherapy or combination therapy (Table 2).

Sixty-eight of 110 (61.8%) patients received antimicrobial monotherapy. Of these 68 patients, 52 (76.5%) received cefoperazone/sulbactam, 5 (7.4%) received colistin and 11 (16.1) received other antimicrobial agents. The median (IQR) total daily dose of sulbactam was 3 (2-3) grams. Of the 42 (38.2%) patients treated with combination antibiotics, 19 (45.2%) received cefoperazone/sulbactam plus colistin, 18 (42.9%) patients received fosfomycin in combination with other antibiotics including, cefoperazone/sulbactam plus colistin (10 cases), cefoperazone/sulbactam (5 cases), colistin (1 case), sulfamethoxazole/trimethoprim (1 case) and amikacin (1 case). The mean total daily dose (range) of fosfomycin was 7.79 (1-24) grams with median treatment duration of seven days. Five of 42 patients (11.9%) received other antimicrobial agents.

Clinical outcomes of patients with CRAB infection based on receipt of mono- or combination antibiotic therapy

The overall mortality rate was 30%. Seventy-five of 110 patients (68.2%) were identified as having overall presumptive treatment success, 74 of 110 (67.3%) with clinical cure and 29 of 110 (26.4%) with microbiologic cure. Ninety-one of 110 (82.7%) patients were identified as having received appropriate treatment for CRAB infections. Inappropriate treatment identified in 19 cases included receiving of non-susceptible (n = 16) and sub-therapeutic dose of antibiotics (n = 1) and starting antibiotic later than 48 hours of initial culture time (n = 2). The overall mortality rate was 26 of 68 (38.2%) patients given monotherapy and seven of 42 (16.7%) patients given combination therapy (p = 0.016). Presumptive treatment success was observed in 41 of 68 (60.3%) patients given monotherapy and 34 of 42 (81.0%) patients given combination therapy (p = 0.024). Patients given combination therapy were more likely to have been given at least one antibiotic to which the organism was susceptible (p = 0.004). Clinical cure was 60.3% and 78.6% for patients given mono- vs. combination therapy, respectively (p = 0.047). Microbiologic cure was 14.7% and 45.2% for patients given mono- vs. combination therapy, respectively (p = 0.00).

Presumptive treatment success was 83.5% in patients given appropriate antibiotic and 0% in patients given inappropriate antibiotic (p = 0.00). When excluding patients that received inappropriate antibiotic, presumptive success of treatment was observed in 41 of 51 (80.4%) given monotherapy and 34 of 40 (85%) patients given combination therapy (p = 0.57). The mortality rate did not differ significantly in 9 of 51 patients given monotherapy (17.6%) versus 5 of 40 patients given combination therapy (12.5%; p = 0.49). In patients given antibiotic regimen with or without fosfomycin, the presumptive treatment success was 72.2% (13 of 18 cases) and 84.9% (62 of 73 cases), (p = 0.30) respectively. The overall mortality rate was not different in patient who received antimicrobial regiment with fosfomycin (22.2%) or without fosfomycin (13.7%, p = 0.47).

Table 2. Percentage of susceptibility of carbapenem-resistant *Acinetobacter baumannii* in monotherapy and combination therapy against various antimicrobial agents by disc diffusion method

Antimicrobial agents	Monotherapy (n = 68) n (%)	Combination therapy (n = 42) n (%)	p-value
Amikacin	11 (16.2)	6 (14.3)	0.79
Gentamicin	6 (8.8)	3 (7.1)	0.53
Ciprofloxacin	0 (0)	0 (0)	NA
Ceftazidime	0 (0)	0 (0)	NA
Piperacillin/tazobactam	0 (0)	0 (0)	NA
Imipenem	0 (0)	0 (0)	NA
Meropenem	0 (0)	0 (0)	NA
Trimethoprim/sulfamethoxazole	3 (4.4)	3 (7.1)	0.67
Cefoperazone/sulbactam	49 (72.1)	23 (54.8)	0.06
Colistin	68 (100)	42 (100)	NA

NA = not applicable

Risk factors for treatment failure

In the univariate analysis, admission to an ICU (odd ratio (OR) 3.12, 95% confident interval (CI) 1.26-7.74), bloodstream infection (OR 4.95, 95% CI 1.81-13.50), requirement for mechanical ventilation (OR 7.77, 95% CI 1.72-35.06), shock (OR 2.84, 95% CI 1.24-6.52), coagulopathy, (OR 5.60, 95% CI 2.25-13.75), renal impairment (OR 4.96, 95% CI 2.00-12.27), hepatic impairment (OR 2.93, 95% CI 1.07-8.07), immunocompromised status (OR 2.72, 95% CI 1.18-6.26), use of combination antimicrobial therapy (OR 0.36, 95% CI 0.14-0.89) and use of an appropriate antimicrobial regimen (OR 0.21, 95% CI 0.12-0.37) were significant predictors for treatment failure (Table 3). These variables were included in a multivariate analysis. In the multivariate model, renal impairment (adjusted OR 8.86, 95% CI 1.19-39.54), bloodstream infection (adjusted OR 6.42, 95% CI 1.22-33.76) and use of an appropriate antimicrobial regimen (adjusted OR 0.01, 95% CI 0.00-0.07) remained as predictors of treatment failure.

Discussion

Nosocomial infections with *A. baumannii* particularly CRAB is associated with high mortality rate. Hello et al showed that the cases infected with CRAB had significantly higher mortality rate at 30 day than patients infected with other MDR bacteria[18]. Previous studies on CRAB have shown mortality rate from 32-34%[19,20], which was very similar to the mortality rate observed in the present study (30%).

Appropriate treatment of CRAB infections is important as use of appropriate antimicrobial agents for treatment of *Acinetobacter* bacteremia has been shown to significantly reduce mortality[21,22]. In the present study, the authors investigated patients with CRAB infections displaying signs and symptoms of SIRS treated with single compared to combination antibiotic therapy. Patients given combination therapy were much more likely to have been given an antibiotic to which the organism was susceptible. This is an important finding as the two antibiotics given as monotherapy (colistin and cefoperazone/sulbactam) had susceptibilities greater than 90% according to the most recent antibiogram of the institution. Patients given monotherapy had significantly higher mortality rates compared to patients given combination therapy. These results add important clinical data to the appropriate use of combination antibiotic therapy. Currently, the conclusion of the advantage of combination antimicrobial regimen over monotherapy for treatment of CRAB infection cannot be drawn secondary to the

Table 3. Univariate analysis of clinical characteristics impacted on treatment failure in patients with carbapenem resistant *A. baumannii* infection

Variables	Failures (n = 35) n (%)	Presumptive success (n = 75) n (%)	Crude odd ratio	OR 95% CI
Age < 65	18 (51.4)	53 (70.7)	2.28	0.99-5.21
Male	20 (57.1)	46 (61.3)	1.19	0.53-2.69
ICU patients	27 (77.1)	39 (52.0)	3.12	1.26-7.74
Immunocompromised status	18 (51.4)	21 (28.0)	2.72	1.18-6.26
Mechanical ventilation	33 (94.3)	51 (68.0)	7.77	1.72-35.06
Shock	22 (62.9)	28 (37.3)	2.84	1.24-6.52
Coagulopathy	18 (51.4)	12 (16.0)	5.60	2.25-13.75
Renal impairment	17 (48.6)	12 (16.0)	4.96	2.00-12.27
Liver impairment	10 (28.6)	9 (12.0)	2.93	1.07-8.07
Source of infections				
Lower respiratory tracts	19 (54.3)	44 (58.7)	1.20	0.53-2.68
Bloodstream	13 (37.1)	8 (10.7)	4.95	1.81-13.50
Urinary tract	0	6 (8.0)	-	-
Skin and soft tissues	0	8 (10.7)	-	-
Intra-abdominal tissues	3 (8.6)	6 (8.0)	0.93	0.22-3.95
Central nervous system	0	2 (2.6)	-	-
Others	0	1 (1.3)	-	-
Combination antimicrobial therapy	8 (22.9)	34 (45.3)	0.36	0.14-0.89
Appropiate antimicrobial regimen	16 (45.7)	75 (100)	0.21	0.12-0.37

lack of good designed studies with adequate number of patients[23-25].

The present finding indicated that the combination therapy regimen could reduce the risk of treatment failure by increasing the likelihood of treatment with an appropriate antimicrobial. In a meta-analysis investigating the benefit of combination antibiotic therapy for serious infections, Kumar et al demonstrated that combination therapy could reduce mortality rates in patients with higher odds of mortality (defined as mortality rate of patients given monotherapy greater than 25%)[26]. The present study extends these findings to demonstrate that this improved survival may be due to the higher likelihood of treatment with appropriate antibiotic. Moreover, the patients with renal failure and bacteremia had the risk of poor outcome as previously reported by Katsaragakis et al[27] and Livermore et al[20], respectively.

Fosfomycin is an emerging treatment option for multidrug resistant Gram-negative bacilli and has in vitro activity against *E. coli* and *K. pneumoniae* including ESBL-producers[28]. It is used as an oral regimen for the treatment of acute uncomplicated cystitis but data on treatment of other Gram-negative bacteria is limited[29]. The present findings add important information on the usefulness of combination of active antimicrobial agents that includes fosfomycin against CRAB infections. The beneficial effects observed in the present study will need to be validated in further study. Studies investigating the toxicities of these agents will also be required as use in critically ill patient populations expands. The information required for calculating of APACHE scores was not available. Therefore, the authors studied patients with critical illness displaying signs and symptoms of SIRS. Future studies will require investigations based on underlying differences in critical illness to assess use of these agents based on severity of disease.

In conclusion, inappropriate antimicrobial treatment and renal impairment were associated with poor treatment outcomes in patients with CRAB nosocomial infections. Patients given combination antibiotics were more likely to be given at least one antibiotic to which the organism was susceptible.

Potential conflicts of interest

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ผลลัพธ์ทางคลินิกของการรักษาการติดเชื้อ *Acinetobacter baumannii* ในโรงพยาบาลที่ดื้อต่อยากลุ่มคาร์บาพีเนมด้วยยาต้านจุลชีพเดี่ยวและยาหลายชนิดร่วมกัน

วิชัย สันติมาลีวรกุล, โพยม วงศ์ภูวรักษ์, พรรณทิพย์ ฉายากุล, สุทธิพร ภัทรชยากุล, พิมพ์พิมล ตันสกุล, *Kevin W Garey*

วัตถุประสงค์: *เพื่อศึกษาผลลัพธ์ทางคลินิกของการรักษาผู้ป่วยติดเชื้อ Acinetobacter baumannii ในโรงพยาบาลที่ดื้อต่อยากลุ่มคาร์บาพีเนมด้วยยาเดี่ยว และการใช้ยาร่วมกัน*

วัสดุและวิธีการ: *ประเมินข้อมูลทางคลินิกแบบย้อนหลังในผู้ป่วยติดเชื้อ A. baumannii ที่ดื้อต่อยากลุ่มคาร์บาพีเนมในโรงพยาบาลสงขลานครินทร์ จังหวัดสงขลา ในระหว่างเดือนมกราคม ถึง ธันวาคม พ.ศ. 2551*

ผลการศึกษา: *มีผู้ป่วยติดเชื้อ A. baumannii ที่ดื้อยากลุ่มคาร์บาพีเนมในโรงพยาบาลจำนวน 110 ราย โดยร้อยละ 57.3 เป็นผู้ป่วยที่ติดเชื้อทางเดินหายใจส่วนล่าง ร้อยละ 61.8 ได้รับยาต้านจุลชีพแบบเดี่ยว มีอัตราการตายโดยรวมร้อยละ 30 ผลการรักษาการติดเชื้อแบบประสบผลสำเร็จเกิดขึ้นร้อยละ 60.3 (41/68 ราย) และ 81.0 (34/42 ราย) ในกลุ่มผู้ป่วยที่ได้รับยาต้านจุลชีพแบบเดี่ยว และการใช้ยามากกว่าหนึ่งชนิดร่วมกันตามลำดับ (p = 0.024) กลุ่มผู้ป่วยที่ได้รับยาต้านจุลชีพหลายชนิดร่วมกัน มีร้อยละของการได้รับยาต้านจุลชีพที่เชื้อมีความไวต่อยามากกว่ากลุ่มผู้ป่วยที่ได้รับยาต้านจุลชีพแบบเดี่ยว (p = 0.004) จากการวิเคราะห์การถดถอยเชิงเส้นแบบพหุพบว่าความผิดปกติในการทำงานของไต การติดเชื้อในกระแสเลือด และการได้รับยาต้านจุลชีพไม่เหมาะสมเป็นปัจจัยในการทำนายความล้มเหลวของการรักษา*

สรุป: *การได้รับยาต้านจุลชีพหลายชนิดร่วมกันให้ผลการรักษาการติดเชื้อประสบผลสำเร็จที่ดี โดยเพิ่มเป็นไปได้ในการรับยาต้านจุลชีพที่เหมาะสมนอกจากนี้การได้รับยาต้านจุลชีพไม่เหมาะสมความผิดปกติในการทำงานของไตและการติดเชื้อในกระแสเลือดเป็นปัจจัยที่สัมพันธ์กับความล้มเหลวของการรักษาโรคติดเชื้อ A. baumannii ที่ดื้อยากลุ่มคาร์บาพีเนมในโรงพยาบาล*