

Clinical outcomes of colistin in combination with either 6-g sulbactam or carbapenems for the treatment of extensively drug-resistant *Acinetobacter baumannii* pneumonia with high MIC to sulbactam, a prospective cohort study

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Abstract

Background: Extensively drug-resistant *Acinetobacter baumannii* (XDRAB) is an important cause of nosocomial pneumonia with limited therapeutic options. Colistin based regimen is recommended treatment. Which drugs should be combined with colistin remains uncertain. The aim of this study was to investigate the clinical outcomes of patients with XDRAB pneumonia who were treated with colistin, combined with either 6-g sulbactam or carbapenems, in the setting of high MIC to sulbactam. **Methods:** In this prospective cohort study, hospitalized patients diagnosed with XDRAB pneumonia in Phramongkutkiao Hospital were enrolled. The primary outcome was the 28-day mortality. Secondary outcomes were 7 and 14-day mortality, length of stay, ventilator days and factors associated with mortality. **Results:** From 1 July 2016 to 30 September 2017, 192 patients were included; 92 received colistin plus sulbactam and 90 received colistin plus carbapenems. Most of the patients were male diagnosed with ventilator associated pneumonia in medical intensive care unit. Overall mortality rates at 7, 14, 28 days were 24.2%, 37.4%, 53.3%, respectively. Mortality rates did not differ between sulbactam group and carbapenems groups at 7 days (19.6% vs. 28.9%, p-value 0.424, adjusted HR 1.277; 95% CI = 0.702-2.322), 14 days (34.8% vs. 40%, p = 0.658, adjusted HR 1.109; 95% CI = 0.703-1.749) and 28 days (51.1% vs. 55.6%, p = 0.857, adjusted HR 1.038; 95% CI = 0.690-1.562). Length of stay, ICU days and ventilator days did not differ. Complications of treatment including acute kidney injury were not statistically different. **Conclusions:** In XDRAB pneumonia with high MIC to sulbactam, mortality rates were not statistically significant between colistin plus 6-g sulbactam and colistin plus carbapenems. **Keywords:** XDR A. baumannii pneumonia, mortality rate, colistin based, sulbactam, carbapenems

Background

Infection with extensively drug-resistant *Acinetobacter baumannii* (XDRAB) is a serious emerging disease commonly found in hospitals with an increasing global trend.(1) The overall mortality rate of XDRAB infection was as high as 64%.(2) Pneumonia is among the most common site of infection.(3) The current guidelines for management of XDRAB hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP) recommend treatment with intravenous colistin.(4) However, colistin has poor lung tissue penetration in the animal model.(5) Moreover, synergistic activities between colistin and carbapenems or sulbactam were found in in-vitro studies.(6-9) Therefore, colistin therapy might improve the outcome of XDRAB treatment. Nevertheless, these combinations failed to improve significant mortality outcomes.(10-13) Which drugs should be combined with colistin remains uncertain. The previous study found that factors associated mortality were chronic obstructive pulmonary disease, diabetes(10), higher severity score, old age, and prolonged intensive care unit (ICU) stay before *the* infections.(12)

This study was aimed to investigate the clinical outcomes of patients with XDRAB pneumonia who were treated with colistin, combined with either sulbactam or carbapenems.

Methods

Study design, sites, and participants

This prospective cohort study included consecutive patients with XDRAB pneumonia in Phramongkutkiao Hospital, a 1200-bed tertiary care military hospital in Thailand, from 1 July 2016 to 30 September 2017. After the approval of the protocol by the Institutional Review Board, Royal Thai Army Medical Department (www.irbrta.pmk.ac.th reference number R061h/59), patients aged ≥ 18 years with XDRAB pneumonia, who received definite treatment with colistin, combined with sulbactam or carbapenems (imipenem or meropenem) were enrolled in the study. XDRAB pneumonia was diagnosed when patients with clinical diagnosis of pneumonia had a single pathogen of XDRAB isolated from their sputum culture, which was collected from tracheal suction or mouth on the date of diagnosis. The sputum collected from mouth must have >25 neutrophils and <10 squamous epithelial cells per low power field to be determined as significant. The exclusion criteria included patients who developed a new infection during the treatment, had concurrent diagnosis of another site of infection, had organisms other than XDRAB obtained from blood or sputum culture or received switch regimens between sulbactam and carbapenems.

Eligible patients were categorized in 2 groups as followed; those who received colistin with sulbactam (CL+SB) and those who received colistin with carbapenems (CL+CB). The maximum dosage of 6 g/day of sulbactam was derived from ampicillin/sulbactam and cefoperazone/sulbactam. The maximum dosage of imipenem and meropenem were 2g and 3g/day, respectively. Colistin was used at the maximum dosage of 300 mg/day. These antibiotics were intravenously administered with dosage adjustment according to renal function.

Variables and definitions

The primary outcome was 28-day mortality rate after initiation of antibiotic. The secondary outcomes were 7-day and 14-day mortality rates, length of hospital stay, length of ICU stay and ventilator days. The baseline demographics data included: sex, age, underlying condition, hospital service, ventilator status, antimicrobial treatment (empirical and definite), intubation and susceptibility data of sputum. Additionally, blood culture samples were collected. The clinical outcomes included: duration of admission, duration of ventilator use, length of hospital stay, length of ICU stay, vital signs, APACHEII severity score (14), kidney functions and complete blood counts.

XDRAB was defined as *A. baumannii* with at least 1 drug resistance in 3 or more drug groups including antipseudomonal carbapenems, antipseudomonal fluoroquinolones, and antipseudomonal cephalosporins by using automate broth microdilution test. CLSI recommendations were used for susceptibility interpretation.(15) Pneumonia and definition of HAP and VAP were defined according to CDC definition.(16)

Mortality rates were measured regarding the day when sputum culture was collected (considered as day 1). Ventilator day was defined as duration between the day of intubation (in HAP patients with respiratory failure) or the day when sputum culture was collected (in VAP patients) and the day of extubation or death. Acute kidney injury was defined according to KDIGO 2012 guidelines,(17) and disseminated intravascular coagulation (DIC) was defined if ISTH score ≥ 5 , (18) septic shock was defined when patients received vasopressor.

Statistical analysis

Comparisons between the groups were performed using Pearson's chi-square test, or Fisher's exact test, as appropriate for proportions and with Student's T-test or Mann-Whitney U test, as appropriate for continuous outcomes. Variables with a p-value < 0.2 in univariate analysis were introduced into multivariate analyses, which were performed using Cox regression analyses. All p-values were two-tailed with those less than 0.05 considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, USA).

Results

Characteristics of the study population

A total of 182 patients with XDRAB pneumonia were included (92 received CL+SB, and 90 received CL+CB). The mean age (SD) was 70 (17.6) years, with 115 (63.2%) male patients. Most common comorbidity was hypertension (61.5%). 75.2% of patients received colistin based treatment as empirical therapy, which was defined as appropriate treatment. Baseline characteristics of patients are shown in **Table 1**. There were no statistically significant differences in baseline characteristics between the two groups, except for higher cirrhosis in carbapenems group and higher stroke in sulbactam groups. Complication of acute kidney injury after the treatment was not significantly different.

Treatment outcomes

The overall 28-day mortality rate was 53.3%. There were no statistically significant differences in mortality between the two groups (**Table 2**). The mean survival time was not statistically different between the treatment groups. Trends toward higher length of stay, ICU days, and ventilator days were observed in CL+CB group (**Table 3**). Complication of acute kidney injury after the treatment was not significantly different.

Risk factors associated with mortality

On multivariate analysis, factors associated with 28-day mortality were gout (adjusted HR, 2.71; 95% CI, 1.15-6.38; $p = 0.02$), APACHEII score of more than 20 (adjusted HR, 2.5; 95% CI, 1.54-4.07; $p < 0.001$), and septic shock (adjusted HR, 3.52; 95% CI, 2.06-6; $p < 0.001$) (**Table 4**).

Discussion

In this prospective cohort study, the treatment with CL+SB and CL+CB had the comparable outcome of mortality at 7, 14, and 28 days. This is consistent with those found in the related studies.(10-13) However, trends toward lower morbidities were observed in CL+SB group. From our previous findings,(19) minimum inhibitory concentrations (MIC) of sulbactam against XDRAB in Phramongkutklao Hospital were so high that the dosage of sulbactam up to 9-12 g/day with prolonged infusion might be needed to achieve therapeutic targets. Thus, higher dosage and longer infusion might be needed to show the superiority of sulbactam group.

In this study, the 28-day mortality rate of XDRAB pneumonia was comparable to those found in previous studies, despite the slightly different selection criteria. Nevertheless, the 28-day mortality rate of colistin and sulbactam group (51.1%) was lower than a study which used lower sulbactam at a dosage of 3g/day(10) (70%) and slightly higher than the one which used higher sulbactam at a dosage of 8g/day (50%).(11) Considering 14-day mortality rate of sulbactam group in this study (34.8%), a study of colistin with the same dosage of sulbactam at 6g/day in XDRAB bacteremia, with VAP diagnosed in the majority of patients, the 14-day mortality rate was comparable to this study (31.9%).(12) Surprisingly, a study in VAP patients with 9g/day of sulbactam revealed 14-day mortality at 73%.(13) Whether sulbactam dosage contributes to the outcome need to be further explored.

High APACHEII score and septic shock were also found to still be reliable predictors of mortality. The kidney injury was still a common complication of colistin treatment.

Despite this study is a prospective cohort study with large sample size, it has certain limitations. First, this is not a randomized study. Other factors affecting the decision of antibiotic regimens were not well-controlled. Second, to control factors resulting in cross-over of treatment regimens, those who received both sulbactam and carbapenems were excluded. Therefore, the mortality rate in this study might not reflect the true rate. Third, the study might be underpowered to exclude the clinical meaningful difference between groups.

Conclusions

Patients with pneumonia caused by XDRAB in Phramongkutklao hospital had a higher mortality rate than previous studies but were not statistically significant between 2 regimens. Colistin combination with sulbactam had lower ventilator days in patients with HAP.

Declarations

Ethics approval and consent to participate: approval of the protocol by the Institutional Review Board, Royal Thai Army Medical Department (www.irbrta.pmk.ac.th reference number R061h/59).

Consent for publication: not applicable

Availability of data and material: not applicable

Competing interests: the authors declare that they have no competing interests.

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Authors' contributions: CU led the study, and wrote the first draft of the report. DC designed the study. VV analysed the data. All authors critically reviewed and approved the final version.

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Tables

Table 1. Demographic data

	Colistin/Sulbactam (n = 92)	Colistin/Carbapenems (n = 90)	p-value
Male sex	56 (60.9)	59 (65.6)	0.51
Age (years) (mean ± SD)	72.08 ± 16.46	68.6 ± 18.57	0.18
Underlying disease			
Diabetes	32 (34.8)	23 (25.6)	0.18
Hypertension	63 (68.5)	49 (54.4)	0.05
COPD	8 (8.7)	13 (14.4)	0.23
Gout	4 (4.3)	3 (3.3)	0.72
Cirrhosis	1 (1.1)	7 (7.8)	0.03
Stroke	26 (28.3)	13 (14.4)	0.02
Malignancy	15 (16.3)	24 (26.7)	0.19
CKD stage3-4	16 (17.4)	14 (15.5)	0.75
CKD stage 5 & ESRD	4 (4.3)	6 (6.7)	
Diagnosis			
HAP	25 (27.2)	29 (32.2)	0.46
VAP	67 (72.8)	61 (67.8)	
Empirical antibiotics			
<i>Appropriate antibiotics</i>			
Colistin + sulbactam or carbapenems	66	71	0.26
<i>Inappropriate antibiotics</i>			
Carbapenems	14	14	0.95
Others	12	5	0.08
Time to definite antibiotics (days) (mean ± SD)	3.65 ± 1.26	3.68 ± 1.25	0.94
APACHEII score			
0-9	2 (2.2)	3 (3.3)	0.75
10-19	41 (44.6)	33 (36.7)	
20-29	44 (47.8)	18 (53.3)	
≥30	5 (5.4)	6 (6.7)	
Septic shock	49 (53.3)	58 (64.4)	0.13
DIC	42 (45.7)	48 (53.3)	0.30
Bacteremia	17 (18.5)	10 (11.1)	0.16

Table 2. Mortality rate, according to the treatment

Mortality rate, frequency (Percent)	Colistin/ Sulbactam (n = 92)	Colistin/ Carbapenems (n = 90)	p- value	HR (95% CI)	p- value	Adjusted HR (95% CI)
7 days	18 (19.6)	26 (28.9)	0.23	1.43 (0.79- 2.59)	0.42	1.28 (0.70- 2.32)
14 days	32 (34.8)	36 (40.0)	0.53	1.16 (0.75- 1.81)	0.66	1.11 (0.70- 1.75)
28 days	47 (51.1)	50 (55.6)	0.52	1.14 (0.77- 1.70)	0.86	1.04 (0.69- 1.56)

Table 3. Length of stay, ICU days and ventilator days after treatment with colistin plus sulbactam or colistin plus carbapenems

	Colistin/Sulbactam	Colistin/Carbapenems	p-value
Length of stay, days (mean ± SD)			
Overall admission	58.65 ± 51.28	92.47 ± 73.11	0.06
After the diagnosis	33.5 ± 8.40	34.7 ± 7.70	0.88
ICU days, days (mean ± SD)	31.97 ± 20.51	40.11 ± 42.44	0.35
Ventilator days, days (mean ± SD)			
HAP (from intubation)	12.40 ± 13.44	19.85 ± 14.79	0.30
VAP (from diagnosis)	26.68 ± 22.00	31.54 ± 21.54	0.40
Complication (AKI)	33 (35.9)	32 (35.6)	0.97

Table 4. Univariate and multivariate analyses of risk factors associated with 28 mortality using cox regression model

Variables	Crude Analysis		Adjusted Analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Female sex	1.33 (0.89-2)	0.16		
Age ≥70	1.07 (0.71-1.61)	0.75		
Diabetes	0.89 (0.57-1.38)	0.61		
Hypertension	1.1 (0.73-1.67)	0.65		
Dyslipidemia	1.11 (0.75-1.66)	0.60		
Gout	2.45 (1.07-5.62)	0.03	2.71 (1.15-6.38)	0.02
COPD	0.55 (0.27-1.14)	0.11		
Pulmonary Tb	0.52 (0.21-1.28)	0.16		
CKD stage ≤ 2	reference			
CKD stage 3-4	1.16 (0.68-2)	0.59		
CKD stage 5&ESRD	1.26 (0.58-2.73)	0.56		
Ischemic heart	1.11 (0.58-2.14)	0.75		
Cirrhosis	1.2 (0.49-2.95)	0.70		
Stroke	0.81 (0.48-1.36)	0.42		
Dementia	0.28 (0.09-0.9)	0.03		
Malignancy	1.83 (1.18-2.85)	0.01	1.43 (0.91-2.26)	0.12
Diagnosis				
HAP	reference			
VAP	1.06 (0.69-1.65)	0.78		
APACHEII score ≥ 20	3.01 (1.91-4.76)	< 0.001	2.5 (1.54-4.07)	< 0.001
Definite treatment				
Colistin/Sulbactam	reference		1.04 (0.69-1.56)	0.86
Colistin/Carbapenems	1.14 (0.77-1.7)	0.52		
Septic shock	3.83 (2.36-6.22)	< 0.001	3.52 (2.06-6)	< 0.001
DIC	1.83 (1.21-2.75)	< 0.001	1.29 (0.8-2.09)	0.3
Bacteremia	1.8 (1.1-2.94)	0.02	1.54 (0.91-2.61)	0.11