Research Article

ผลลัพธ์ทางคลินิกของยาปฏิชีวนะแบบแผน cephalosporins, meropenem และ colistin ในการรักษาผู้ป่วยปอดอักเสบที่ติดเชื้อ *A. baumannii* ในโรงพยาบาลระดับทุติยภูมิในประเทศไทย: การศึกษาแบบย้อนหลัง

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บทคัดย่อ

ผลลัพธ์ทางคลินิกของยาปฏิชีวนะแบบแผน cephalosporins, meropenem และ colistin ในการรักษาผู้ป่วยปอดอักเสบที่ติดเชื้อ *A. baumannii* ในโรงพยาบาลระดับทุติยภูมิในประเทศไทย: การศึกษาแบบย้อนหลัง

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เนื่องด้วยผลลัพธ์ทางคลินิกของการรักษาโรคติดเชื้อ *Acinetobacter baumannii* ยังมีความไม่ชัดเจน โดยเฉพาะการติดเชื้อในโรงพยาบาลระดับทุติยภูมิ การศึกษานี้จึงมีวัตถุประสงค์เพื่อศึกษาผลลัพธ์ทางคลินิกและอัตราการเสียชีวิตในผู้ป่วยที่ติดเชื้อดังกล่าวและได้รับการรักษาด้วยยาปฏิชีวนะแบบแผนต่าง ๆ **วิธีดำเนินการวิจัย:** ผู้วิจัยทบทวนเวชระเบียนของผู้ป่วยทั้งหมดในโรงพยาบาลระดับทุติยภูมิสองแห่งที่ได้รับการวินิจฉัยว่าเป็นโรคปอดอักเสบจากการติดเชื้อ *Acinetobacter baumannii* ตั้งแต่วันที่ 1 มกราคม พ.ศ. 2560 ถึงวันที่ 31 สิงหาคม พ.ศ. 2563 ผู้วิจัยบันทึกข้อมูลทั่วไปของผู้ป่วย ยาปฏิชีวนะที่ได้รับ การรักษาหายเมื่อสิ้นสุดการรักษา และการเสียชีวิตของผู้ป่วย ผลลัพธ์จากแบบแผนต่าง ๆ จะถูกวิเคราะห์โดย Kaplan-Meier curve และ log-rank test **ผลการวิจัย:** มีผู้ป่วยจำนวน 43, 35 และ 26 รายที่ได้รับยาปฏิชีวนะกลุ่ม cephalosporins, meropenem และ colistin ตามลำดับ โดยพบว่าลักษณะพื้นฐานของผู้ป่วยก่อนรักษาไม่มีความแตกต่างกันทั้งในด้านเพศ อายุ โรคร่วม และค่าทางห้องปฏิบัติการที่เกี่ยวข้อง ผู้ป่วยส่วนใหญ่ติดเชื้อชนิด carbapenem-resistant และ multidrug-resistant *Acinetobacter baumannii* ผลการศึกษาระบุอัตราการหายจากโรคของผู้ป่วยที่ได้รับยากลุ่ม cephalosporins, meropenem และ colistin ไม่แตกต่างกันอย่างมีนัยสำคัญ (58.14%, 48.57% และ 38.46% ตามลำดับ, p-value 0.279) อัตราการเสียชีวิตของผู้ป่วยที่ได้รับยากลุ่ม cephalosporins, meropenem และ colistin ไม่แตกต่างกันเช่นกัน (34.88%, 51.43% และ 50.00% ตามลำดับ, p-value 0.271) นอกจากนี้ พบผู้ป่วยจำนวน 4 รายที่เกิดภาวะไตวายเฉียบพลันจากการได้รับยา colistin และไม่พบในผู้ป่วยที่ใช้ยาอื่น **สรุปผลการวิจัย:** ผลการศึกษาแสดงให้เห็นว่าผู้ป่วยที่ติดเชื้อ *Acinetobacter baumannii* ในโรงพยาบาลระดับทุติยภูมิและได้รับยาปฏิชีวนะ cephalosporins, meropenem หรือ colistin มีอัตราการหายจากโรคและอัตราการเสียชีวิตไม่แตกต่างกันอย่างมีนัยสำคัญ

คำสำคัญ: secondary hospital; Acinetobacter baumannii; cephalosporin; carbapenem; colistin

Clinical outcomes of cephalosporins, meropenem, and colistin-based regimens in the treatment of pneumonia caused by *A. baumannii* infection in secondary care hospitals in Thailand: A retrospective study

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Abstract

Clinical outcomes of cephalosporins, meropenem, and colistin-based regimens in the treatment of pneumonia caused by *A. baumannii* infection in secondary care hospitals in Thailand: A retrospective study

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As there has been inconsistency in the clinical outcomes of antibiotic treatment for *Acinetobacter baumannii* infection, particularly in secondary care hospitals, this study aimed to investigate the clinical outcomes and mortality rates of patients with such conditions who received different types of antibiotics. **Methods:** All medication charts of patients who were admitted to the settings due to pneumonia, which was caused by *Acinetobacter baumannii* infection, between 1 January 2017 and 31 August 2020 were reviewed. Patient data were collected, including the used antibiotics, clinical cure at the end of the treatment course, and mortality status. Kaplan-Meier curve with log-rank test was used to analyse the results of each antibiotic regimen. **Results:** There were 43, 35, and 26 patients who were recruited to cephalosporins, meropenem, and colistin groups, respectively. Baseline characteristics of the three groups were similar, including gender, age, comorbid diseases, and laboratory values. The majority of them were infected with carbapenem-resistant and multidrug-resistant *Acinetobacter baumannii*. The results indicated that clinical cure rates of cephalosporins, meropenem and colistin treatments were not significantly different (58.14%, 48.57%, and 38.46%, respectively, p-value 0.279). Moreover, the mortality rates of all were not significantly different (34.88%, 51.43%, and 50.00%, respectively, p-value 0.271). Acute kidney injury was observed in four patients using colistin but not other antibiotics. **Conclusion:** This study highlighted a non-significant difference in clinical cure and mortality rates among cephalosporins, meropenem, and colistin in patients infected with *Acinetobacter baumannii* in secondary care hospitals in Thailand.

Keywords: secondary care hospital; Acinetobacter baumannii; cephalosporins; carbapenem; colistin

Introduction

Acinetobacter baumannii is one of the bacteria that raise global concern regarding antimicrobial resistance (WHO, 2021). For instance, high incidence and prevalence of carbapenem-resistant *Acinetobacter baumannii* were reported in Europe, Eastern Mediterranean, and Africa (Ayobami, 2019). In Thailand, the recent report from National Antimicrobial Resistance Surveillance Center Thailand (NARST) indicated a very high prevalence of Acinetobacter species that were resistant to imipenem (70.1%), cefepime (69.1%), piperacillin/tazobactam (67.4%),

ciprofloxacin (66.8%), and ampicillin/sulbactam (66.0%) (NARST, 2020). Furthermore, the prevalence of carbapenem-resistant Acinetobacter species has been increasing from 45% in 2015 to 70% in 2020. This, therefore, emphasised the urgency of antimicrobial resistance control in all countries, including Thailand.

In order to reduce the antimicrobial resistance rate, an appropriate selection of antibiotics is essential. It is widely known that unsuitable consumption of antibiotics, such as selection of too broad-spectrum and too short duration of treatment, was associated with antimicrobial resistance (Cižman and Plankar, 2018). Several studies in Thailand tried to demonstrate the efficacy of different antibiotics used for the treatment of *Acinetobacter baumannii* infection (Sirijatuphat and Thamlikitkul, 2014; Santimaleeworagun *et al*., 2011; Koomanachai *et al*., 2007; Kanankaeng and Sriphong, 2019; Saelao and Utiswannakul, 2008). In case narrow-spectrum antibiotics were clinically effective against such bacteria, the recommendation of not starting treatment with broad-spectrum antibiotics should be made.

Nonetheless, all studies were performed in tertiary and university hospitals in Thailand. Also, almost all of the settings were in Central, Northern, and Northeastern Thailand. In general, tertiary and university hospitals have a high consumption of antibiotics, especially broad-spectrum every day, so it is highly possible to observe various drug-resistant bacteria in such settings. Unlike high-level hospitals, primary and secondary care hospitals have lower daily rates of broad-spectrum antibiotic use, and then there is less chance to develop antimicrobial resistance.

Moreover, different areas of hospitals might have different antimicrobial resistance patterns. The report from NARST indicated that the prevalence of carbapenem-resistant *Acinetobacter baumannii* in the Southern part was remarkably lower than in the other parts of Thailand. (NARST, 2020). Therefore, the purpose of this study was to investigate the clinical outcomes, including clinical response and mortality rate, of different antibiotics, including cephalosporins, meropenem, and colistin, for the treatment of pneumonia infection caused by *Acinetobacter baumannii* infection in secondary care hospitals in Southern Thailand.

Methods

Patient population

This retrospective study was conducted in two secondary care hospitals that locate in different areas in Southern Thailand. Patient medication charts of individuals who were admitted to the settings with *Acinetobacter baumannii* infection between 1 January 2017 and 31 August 2020 were reviewed. The inclusion criteria of this study were patients who were older than 18 years old, were diagnosed with pneumonia, had the presence of *Acinetobacter baumannii* in sputum, and received one of the antibiotics (i.e., cephalosporins, meropenem, and colistin) as a monotherapy. The exclusion criteria were patients who had presented *Acinetobacter baumannii* in specimens other than sputum, had evidence that *Acinetobacter baumannii* was not the leading cause of infection, and had no complete medication charts.

Variables and outcomes

The variables that were collected from patient medication charts included gender, age, diagnosis, comorbid diseases, intensive care unit (ICU) status, septic shock status, mechanical ventilator use, *Acinetobacter baumannii* antimicrobial susceptibility results, antibiotic use, including drug, dose, route, frequency and duration, concurrent medication use, clinical evaluation by physician, chest x-ray, mortality status, and laboratory test results including complete blood count (CBC), blood urea nitrogen (BUN) and serum creatinine (SCr).

This study focused on three independent variables: cephalosporin use, meropenem use, and colistin use. The cephalosporins in this study included ceftriaxone, cefotaxime, ceftazidime, cefepime, and cefoperazone/sulbactam. The antimicrobial susceptibility test for each antibiotic, except colistin, was performed using the disc diffusion method with the minimum inhibitory concentrations (MICs) determined by the Clinical and Laboratory Standards Institute. Susceptibility to colistin was not available due to the incapability of secondary care hospitals to perform broth dilution tests.

The primary outcome of this study was a clinical cure at the end of the treatment of antibiotics. This was assessed by the physician who was responsible for the individual patient based on the patient clinical manifestation, chest x-ray, and laboratory data. Clinical cure was defined as a patient had at least three out of four criteria: (1) no

shortness of breath, (2) body temperature ranged between 36.0-37.5 ^{o}C, (3) WBC count ranged between 4-12 x 10^3 cell/m^3, and (4) no infiltration from chest x-ray. Secondary outcomes were mortality rate and adverse drug reactions.

Statistical analysis

Baseline characteristics of all patients were analysed and described as number, mean, and percentage. The clinical cure rate of each used antibiotic was analysed and reported using the Chi-square test, as well as the mortality rate of each drug. Kaplan-Meier curve with log-rank test was used to analyse the time to result of each antibiotic regimen. Adverse drug reaction was described as number and percentage. Statistical analyses were performed with SPSS version 28, and statistical significance was set as a p-value <0.05 for all analyses.

Ethical approval

The methodology of this study was approved by the Human Research Ethics Committee of Walailak University (HREC WU; registration number WUEC-20-330-01). The patient informed consent requirement was waived due to the HREC WU regulation because it was a retrospective study and did not directly contact any patients. However, patient data confidentiality and compliance were performed according to the Declaration of Helsinki.

Results

Patient characteristics

During 1 January 2017 and 31 August 2020, there were 43, 35, and 26 patients who were treated *Acinetobacter baumannii* infection with cephalosporins, meropenem, and colistin, respectively. For cephalosporins, there were 20, 18, and 5 patients who received ceftriaxone, ceftazidime, and cefoperazone/sulbactam, respectively. Table 1 describes the characteristics of patients collected in this study. The majority of the patients in the three groups were male, with an average age of over 65 years. Percentages of patients with chronic diseases such as hypertension, dyslipidaemia, diabetes mellitus, and chronic kidney disease were similar in all groups, as well as mean Charlson comorbidity index, percentages of patients with shock, ICU status, and mechanical ventilator use. All laboratory results of the three groups were similar. For example, all patients had high white blood cell counts, high ratios of neutrophils, average blood urea nitrogen (BUN), and high serum creatinine (SCr).

Table 1 Baseline characteristics of patients prior to three antibiotic treatments.

Characteristics	Cephalosporins (n = 43)	Meropenem (n = 35)	Colistin (n = 26)
Male (Number [%])	23 (53.49)	21 (60.00)	16 (61.54)
Age (Mean [95%CI])	68.65 (63.67 – 73.63)	67.84 (61.62 – 74.06)	71.76 (65.87 – 77.65)
Comorbidity disease (Number [%])			
Cerebrovascular diseases	7 (16.28)	6 (17.14)	4 (15.38)
Dementia	2 (4.65)	5 (14.28)	2 (7.69)
COPD	9 (20.93)	6 (17.14)	4 (15.38)
Diabetes mellitus	13 (30.23)	10 (28.57)	5 (19.23)
Hypertension	22 (51.16)	17 (48.57)	12 (46.15)
Dyslipidaemia	15 (34.88)	16 (45.71)	7 (26.92)
Chronic kidney disease	5 (11.63)	5 (14.28)	3 (11.54)
Cancer	3 (6.98)	4 (11.43)	3 (11.54)
ICU admission (Number [%])	9 (20.93)	9 (25.71)	6 (23.08)
Septic shock status (Number [%])	7 (16.28)	9 (25.71)	5 (19.23)
Using mechanical ventilator (Number [%])	18 (41.86)	17 (48.57)	13 (50.00)
Charlson comorbidity index (Mean [95%CI])	3.80 (3.28 – 4.32)	3.97 (3.32 – 4.62)	4.16 (3.44 – 4.88)

Table 1 Baseline characteristics of patients prior to three antibiotic treatments. *(Continue)*

Characteristics	Cephalosporins (n = 43)	Meropenem (n = 35)	Colistin (n = 26)
Laboratory results (Mean [95%CI])			
White blood cell (x10^9 cell/L)	11.82 (10.08 – 13.57)	13.37 (10.83 – 15.91)	13.40 (10.92 – 15.87)
Neutrophil (%)	76.88 (72.53 – 81.23)	76.19 (70.27 – 82.10)	76.89 (72.54 – 81.24)
Lymphocyte (%)	9.81 (6.51 – 13.11)	12.50 (8.84 – 16.16)	9.30 (5.93 – 12.67)
BUN (mg/dL)	24.66 (18.07 – 31.26)	23.54 (17.06 – 30.01)	22.33 (14.44 – 30.22)
Serum creatinine (mg/dL)	1.85 (0.51 – 3.20)	1.51 (0.86 – 2.17)	1.10 (0.68 – 1.52)
Type of *Acinetobacter baumannii* (Number [%])			
Cephalosporin resistant	19 (44.19)	18 (51.43)	19 (73.08)
Carbapenem resistant	21 (48.84)	19 (54.29)	20 (76.92)
Multi-drug resistant	21 (48.84)	19 (54.29)	20 (76.92)

Abbreviations: BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

Table 2 Percentages of antimicrobial susceptibility of *Acinetobacter baumannii* cultured from patients' isolates.

Drug	Resistant (%)	Intermediate (%)	Sensitive (%)
Ceftriaxone	58.06	32.26	9.68
Cefotaxime	70.83	20.83	8.33
Ceftazidime	63.64	0.00	36.36
Cefepime	45.45	4.55	50.00
Cefoperazone/Sulbactam	50.00	10.00	40.00
Imipenem	66.67	4.17	29.17
Meropenem	67.92	0.00	32.08

Notes: Colistin susceptibility was not performed in the research setting due to the limitation of broth dilution tests in secondary care hospitals.

Regarding the antimicrobial susceptibility of *Acinetobacter baumannii*, the percentages of resistance of the isolates cultured from all patients are shown in Table 2. More than half of the culture results showed that *Acinetobacter baumannii* were resistant to almost all the antibiotics used in this study, except cefepime which half of the isolates were still sensitive. For cephalosporins, less than 10% of isolates were sensitive to third-generation cephalosporins, including ceftriaxone and cefotaxime, while less than 40% of isolates were sensitive to ceftazidime, the fourth-generation cephalosporins. Likewise, only approximately 30% of isolates were susceptible to carbapenems, including imipenem and meropenem.

Moreover, of all 43 patients who received cephalosporins, 44.19% had the isolates of cephalosporin-resistant *Acinetobacter baumannii*. Similarly, approximately half of the patients (54.29%) who received meropenem had the infection of carbapenem-resistant *Acinetobacter baumannii*. In contrast, approximately 75% of the patients who were treated with colistin had the isolates of both cephalosporin- and carbapenem-resistant *Acinetobacter baumannii*.

Clinical outcomes

The overall clinical cure rate of all patients in this study was 50.00%, divided into 58.14% for cephalosporin treatment, 48.57% for meropenem treatment, and 38.46%

for colistin treatment. There was no significant difference in cure rates between the three regimens (p-value 0.279) (Table 3). Figure 1 provides the cumulative trends of clinical cure among patients using each antibiotic drug. The median clinical cure time of patients treated with cephalosporins was 24 days (95%CI 17.73 – 30.27 days). The median clinical cure time of patients treated with meropenem was 36 days (95%CI 22.99 – 49.00 days). The median clinical cure time of patients treated with colistin was 42 days (95% CI 23.78 – 60.22 days). However, there was no significant difference in median time to clinical cure among those three groups (log-rank p-value 0.050).

Table 3 Clinical cure rates and mortality rates of patients who were treated with cephalosporins, meropenem, and colistin

Antibiotic regimen	Clinical cure		Mortality	
	N (%)	OR (95%CI)	N (%)	OR (95%CI)
Cephalosporins	25 (58.14)	2.22 (0.82 – 6.02)	15 (34.88)	0.54 (0.20 – 1.45)
Meropenem	17 (48.57)	1.50 (0.54 – 4.24)	18 (51.43)	1.06 (0.38 – 2.92)
Colistin	10 (38.46)	Reference	13 (50.00)	Reference
P-value	0.279		0.271	

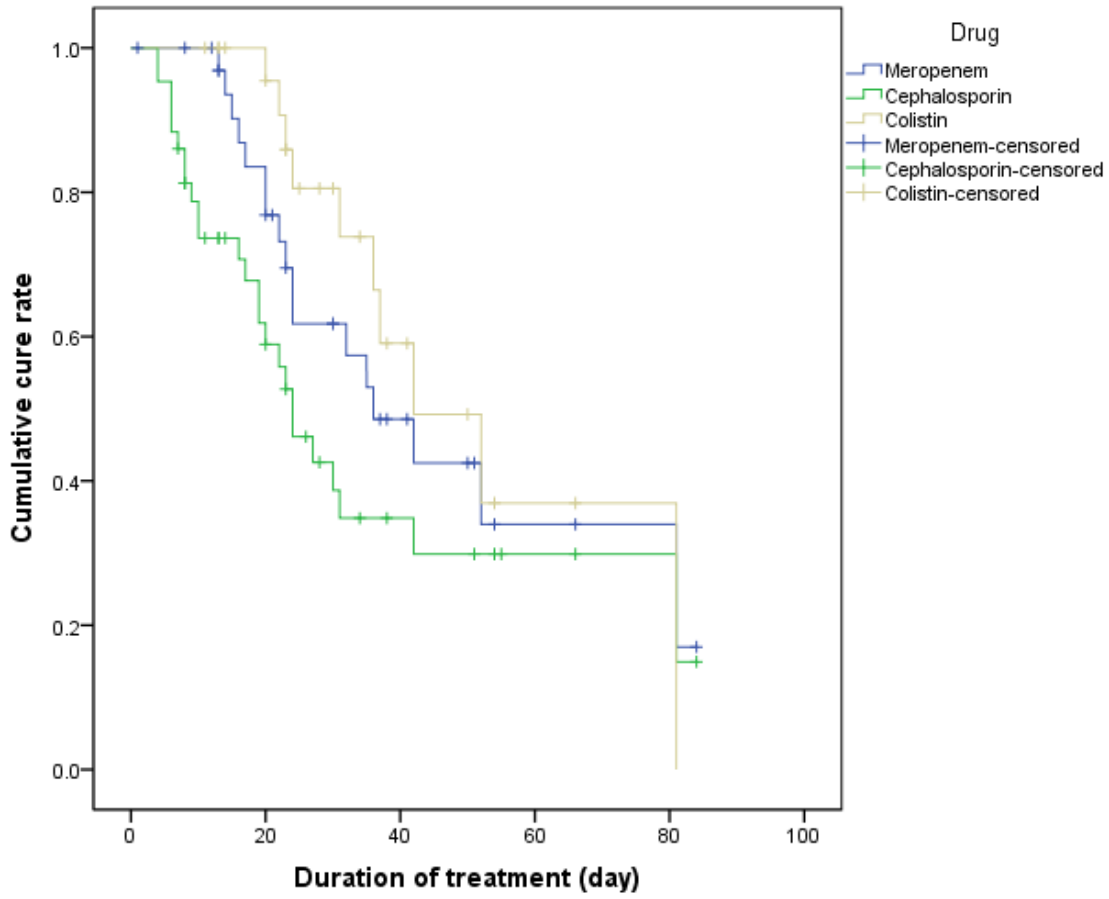

Figure 1 Kaplan-Meier curves of the clinical cure rate of patients receiving each antibiotic regimen, including cephalosporins, meropenem, and colistin.

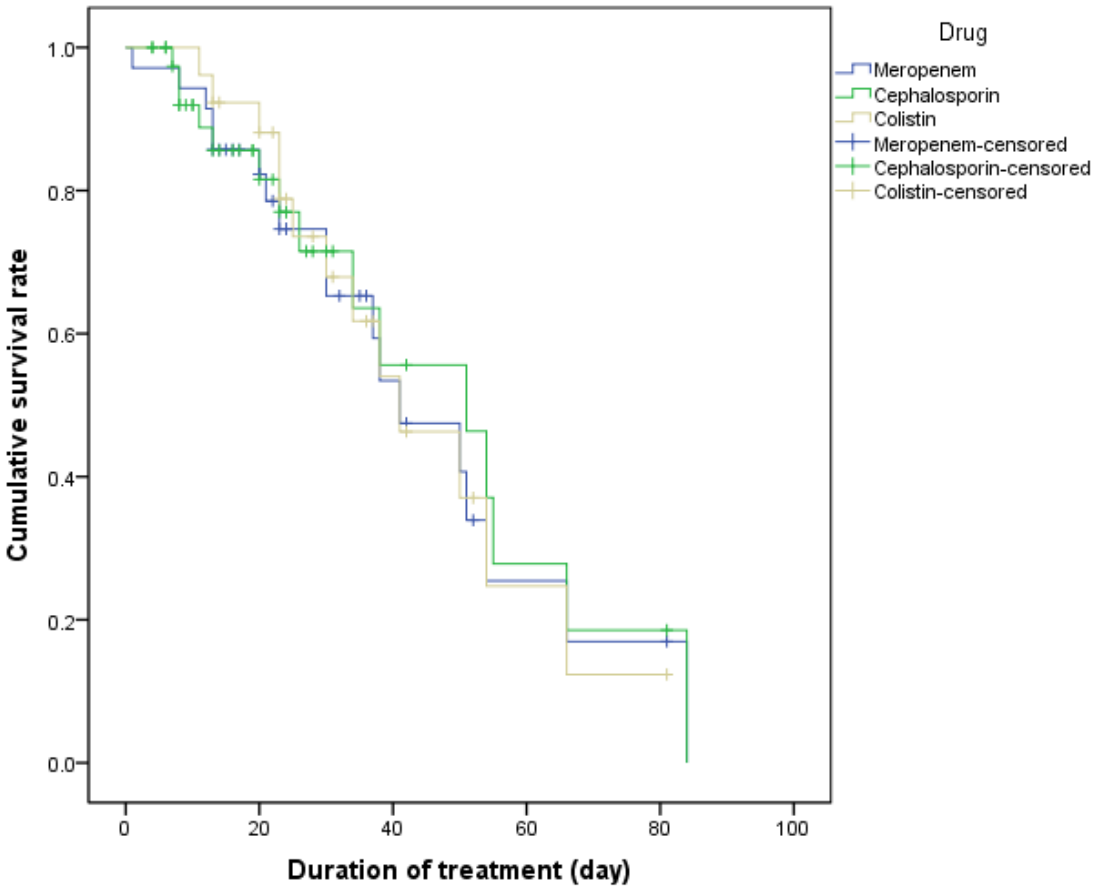

Figure 2 Kaplan-Meier curves of the mortality rate of patients receiving each antibiotic regimen, including cephalosporins, meropenem, and colistin.

Regarding mortality rates of patients, the results indicated no significant difference in mortality rates of patients who were treated with cephalosporins, meropenem, and colistin (34.88%, 51.43%, and 50.00%, respectively, p-value 0.271) (Table 3). The overall mortality rate of this study was 44.23%. Cumulative survival rates of all treatment groups are shown in Figure 2. The median survival times of patients with cephalosporin treatment, meropenem treatment, and colistin treatment were 51 (95%CI 28.67 – 73.33), 41 (95%CI 25.89 – 56.11), and 41 (95%CI 25.06 – 56.94) days, respectively. Statistical analysis showed no difference in patient survival time among all treatments (log-rank p-value 0.961).

The only adverse drug reaction that was observed in this retrospective study was nephrotoxicity. All events were in patients who received colistin. Four patients (15.38% of patients using colistin) had post-treatment serum creatinine more than 2.5 times higher than their baselines, which was defined as acute kidney injury. No other side effect was recorded in all patient medication charts.

Discussion and Conclusion

This study was the continuation of the pilot study conducted by Suphansatit et al. in a secondary care hospital in Thailand (Suphansatit and Uitrakul, 2020). That study showed the favour of using cephalosporin-based regimens in inpatients with *Acinetobacter baumannii* infection. Although it did not provide statistical significance between cephalosporin use and the other two antibiotics, the results supported using cephalosporin antibiotics for the treatment of *Acinetobacter baumannii* infection in secondary care hospitals. This markedly indicated that cephalosporin-based

regimens were not inferior to meropenem- or colistin-based regimens in the outcomes of clinical cure and survival.

Many studies have shown inconsistency in clinical outcomes of antibiotics in the treatment of *Acinetobacter baumannii* infection, even though colistin and carbapenems were used. For instance, a study by Koomanachai *et al*. reported higher mortality rates in patients receiving colistin than non-colistin regimens (46.2% and 80.0%, respectively) (Koomanachai *et al.*, 2007). However, they mentioned that patients with colistin had a higher clinical response than those without colistin (80.8% and 26.7%, respectively). Another study by Kanankaeng et al. indicated no advantage of colistin compared to non-colistin regimens in terms of clinical response and in-hospital mortality (p-value 0.54 and 0.94, respectively) (Kanankaeng and Sriphong, 2019). On the other hand, a study conducted by Saelao et al. reported that the clinical cure rate for cephalosporin use was 36.4%, and carbapenem use was 53.8% (Saelao and Utiswannakul, 2008).

Regarding all the above-mentioned studies, they were conducted in either tertiary or university hospitals, which had massive use of broad-spectrum antibiotics daily. Therefore, there was a high probability of antibiotic resistance circumstances in such studies, which might be different from primary and secondary care hospitals usually located in more rural areas. A study in China reported different susceptibility results in bacteria cultured from different areas in the countries as well as a study in Korea (Tang *et al.*, 2018; Lee *et al.*, 2007). This highlighted the importance that the clinical efficacy of antibiotics used in primary and secondary care hospitals should be further studied in order to provide more information on appropriate antibiotic selection for patients in such hospitals.

To the best of our knowledge, not many clinical studies related to *Acinetobacter baumannii* infection were conducted in primary and secondary care hospitals, especially the studies focusing on the clinical efficacy of antibiotics. Only a study by Sun *et al.* reported the success of treating patients with multidrug-resistant *Acinetobacter baumannii* infection with ampicillin/sulbactam in primary care hospitals (Sun *et al.*, 2018). The main reason for limited research in small settings such as primary and secondary care hospitals might be the limited number of patients and scarce types of antibiotics. However, according to the surveillance study in Thailand, the number of patients infected with *Acinetobacter baumannii*, particularly multidrug-resistant species, has been increasing every year since 2000 (Dejsirilert *et al.*, 2009), and there is a very high possibility that it will spread to the rural community in the near future (Vázquez-López *et al*., 2020).

The results from this study indicated that despite the secondary care hospitals in small towns of Thailand, more than half of *Acinetobacter baumannii* isolates were resistant to most antibiotics, including carbapenems. This specie of bacteria found in the settings could be defined as carbapenem-resistant or multidrug-resistant *Acinetobacter baumannii*. Based on several meta-analyses, this sort of infection needed treatment regimens of colistin or tigecycline with or without sulbactam-based regimens (Kengkla *et al*., 2018; Liu *et al*., 2021; Mei *et al*., 2019). Nevertheless, approximately half of the patients in this study received cephalosporins while they had the infection of cephalosporin-resistant species. Likewise, half of the patients who received meropenem had carbapenem-resistant *Acinetobacter baumannii*. This might result in low cure rates in the patients in both groups, as well as non-significance in cure rates among them. Moreover, approximately three-fourths of the patients who received colistin had the infection of multidrug-resistant *Acinetobacter baumannii*, including carbapenem. Therefore, there was a possibility that the bacteria were resistant to colistin as well, resulting in low cure rates for the patients in this group.

The major limitation of this study was still the small sample size of each treatment, notwithstanding the fact that there were not many patients in total in these secondary care settings. Due to the small numbers of patients who used each cephalosporin drug, this study analysed the results of cephalosporins as a group of drug to increase statistical power of analysis. However, it should be noted that the results of cephalosporins were from only three

medicines, that are ceftriaxone, ceftazidime, and cefoperazone/sulbactam, so the results should not be extrapolated to other cephalosporin drugs. Latter, as this study was conducted retrospectively, it was very difficult to control all confounding factors of all patients. These factors included age, the severity of patients on admission, changing of antibiotics prior to the full course of treatment, and using other concomitant medicines. A drug such as sulbactam might cause better results than other cephalosporins. However, there were only five patients received sulbactam, and only half of the isolates were sensitive to the drug, so it was unlikely that the overall results were affected by sulbactam. Lastly, as a consequence of retrospective analysis, the association between used antibiotics and clinical outcomes could not be robustly concluded. Further studies should focus on prospectively collecting more patients and more areas of hospitals in order to provide more information on the efficacy and increase the generalisability of the results.

In conclusion, clinical cure and mortality rates of patients with *Acinetobacter baumannii* infection, who received different regimens of antibiotics including cephalosporins, meropenem, and colistin in secondary care hospitals in Thailand, were not significantly different. Nephrotoxicity was observed in only patients who used colistin.

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