

A Pilot Study of Antibiotic Regimens for Infections Caused by *Acinetobacter baumannii* in a Secondary Hospital in Thailand

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Purpose: This retrospective pilot study aimed to investigate the antibiotic regimens used to treat *Acinetobacter baumannii* infections at a secondary hospital in southern Thailand. Additionally, the clinical outcomes and mortality of each regimen are described.

Patients and Methods: The medical charts of all patients admitted to Phang-Nga Hospital, Thailand, between 1 January 2019 and 31 May 2020 due to *Acinetobacter baumannii* infection were reviewed. Data were collected on the antibiotics that patients received before and after sensitivity testing, along with the clinical cure, mortality rates, and nephrotoxicity.

Results: Of the 32 inpatients recruited in the study, the most prescribed antibiotic regimen for empirical therapy was beta-lactam/beta-lactamase inhibitor monotherapy (22%), and for definitive therapy was meropenem monotherapy (28%). Combination therapy with two, three, or four antibiotics was prescribed less than 50% of cases for both empirical and definitive therapy. Moreover, the results indicated that patients receiving combination therapy had a lower clinical response and higher mortality than those receiving monotherapy. Furthermore, regimens containing colistin did not provide a higher clinical cure compared to those without colistin.

Conclusion: The results of this pilot study support the use of monotherapy antibiotic regimens, including ceftazidime and meropenem, for the treatment of *Acinetobacter baumannii* infections in secondary hospitals. However, as these results are from a single hospital with limited number of patients, the application of the results should be done carefully. More patient data from other hospitals will be collected in the next phase of this study.

Keywords: *Acinetobacter baumannii*, antibiotic regimen, southern Thailand

Introduction

Acinetobacter baumannii has been one of the most problematic nosocomial drug resistant bacteria over the past two decades worldwide. In 2019, the United States Centers for Disease Control and Prevention (US CDC) reported approximately 8500 cases of carbapenem-resistant *Acinetobacter* in the United States, and over 60% of them tended to be resistant to any extended-spectrum β -lactam antibiotics, including ampicillin/sulbactam.¹ Likewise, the National Antimicrobial Resistance Surveillance Center Thailand (NARST) reported that more than 60% of *Acinetobacter* species in Thailand were resistant to imipenem, ciprofloxacin, cefepime, and piperacillin/tazobactam.² Moreover, patients infected with *Acinetobacter* were found to have a high mortality rate. Several studies indicated that patients with *Acinetobacter* infections had up to a 49–60% 30-day mortality rate.^{3–5}

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However, most studies on multi-drug resistant *Acinetobacter baumannii* were conducted in tertiary or university hospitals in Thailand. These hospitals use many antibiotics every day, thereby having a higher chance of developing antibiotic resistance than secondary hospitals. Regarding the epidemiology of *Acinetobacter* species by NARST, upper southern Thailand had the lowest prevalence of carbapenem-resistant *Acinetobacter baumannii* (CRAB).⁶ Secondary hospitals in upper southern Thailand should therefore have a low incidence of CRAB.

To improve Antibiotic Smart Use in Thailand, the authors were intrigued to investigate the antibiotic regimens used in the treatment of *Acinetobacter baumannii* infections in secondary hospitals in southern Thailand. Phang-Nga Hospital was selected as the first clinical setting in this project. Phang-Nga Hospital is a secondary hospital with 206 beds located in Phang-Nga province, southern Thailand. Although this hospital is in the center of the province because this location is between Phuket and Trang provinces, which have tertiary hospitals, Phang-Nga Hospital does not have many severe patients with infections and has different antibiotic regimens from other tertiary hospitals in Thailand.

This was a pilot study of the main project which aims to compare the antibiotic regimens prescribed in secondary hospitals in Thailand. Phang-Nga Hospital was chosen as the first hospital. The results were compared with previous studies in other tertiary hospitals in Thailand to decide whether the project should continue. This study mainly focusses on the clinical outcomes and mortality rates.

Patients and Methods

This was a retrospective cohort study. All medical charts of individuals diagnosed with an *Acinetobacter baumannii* infection between 1 January 2019 and 31 May 2020 at Phang-Nga Hospital, Phang-Nga province, Thailand, were reviewed. Patients were included in the study if they were older than 18 years, were admitted to Phang-Nga Hospital with an infection caused by *Acinetobacter baumannii* as confirmed by a microbiological culture, and received at least one antibiotic drug during their treatment course. Both hospital- and community-acquired *Acinetobacter baumannii* infections were included. The exclusion criteria were as follows: patients who were infected with other multiple drug resistant gram-negative bacteria, patients who were infected with methicillin-resistant *Staphylococcus aureus*, *Acinetobacter baumannii* found

was not the main cause of infection and patients who did not have complete information in their medical charts.

The parameters collected from the included patients were sex, age, diagnosis, comorbid diseases, history of antibiotic use, intensive care unit (ICU) status, septic shock status, mechanical ventilator use, site of infection, culture specimen, other bacteria found, *Acinetobacter baumannii* antimicrobial susceptibility test results, antibiotic use (including drug, dose, route, frequency, and duration) before and after bacterial cultures, seven-day mortality status, and blood urea nitrogen (BUN) and serum creatinine (SCr) before and after the antibiotic course. In addition, the clinical responses of all patients as determined by a doctor(s) were recorded.

The antimicrobial susceptibility test used in this hospital was the disc diffusion method with the minimum inhibitory concentrations (MICs) determined by the Clinical and Laboratory Standards Institute. The breakpoints for each antimicrobial collected are presented in [Supplementary Table 1](#).

Only a few cases of *Acinetobacter baumannii* infection were expected in this study due to the limited number of patients at this secondary hospital. All patient data were only descriptively analyzed as raw numbers, percentages, mean, and median without statistical analysis because the power was too low to perform statistical tests. However, the results are discussed and compared to other studies in the discussion session. The methodology of this study was submitted and approved by the Human Research Ethics Committee of Walailak University (HREC WU; registration number WUEC-20-330-01). According to the HREC WU regulation, any research which uses routinely collected information, such as medical charts, does not require patient informed consent because some patients may not be able to be contacted. However, patient data confidentiality and compliance were performed according to the Declaration of Helsinki.

Results

Patient Characteristics

From 1 January 2019 to 31 May 2020, there were a total of 32 patients admitted to Phang-Nga Hospital because of *Acinetobacter baumannii* infection. The ratio of male and female patients was 1.13 (Table 1). The average age of patients was 63.6 years. The most common diagnosis was respiratory tract infection (28.1%), with pneumonia accounting for the highest number of cases. The average

Table 1 Characteristics of 32 Patients Admitted to Phang-Nga Hospital During 1 January 2019 and 31 May 2020 Due to *Acinetobacter baumannii* Infection

Variables	Number (%)
Gender	
Male	17 (53.1)
Female	15 (46.9)
Average age (Range) (Year)	63.6 (18–97)
Main diagnosis	
Respiratory tract infection	9 (28.1)
Wound infection	8 (25.0)
Sepsis	4 (12.5)
Stroke	3 (9.4)
Cancer	3 (9.4)
Others	5 (15.6)
Site of infection	
Lung	16 (50.0)
Urinary tract	4 (12.5)
Extremities	3 (9.4)
Unknown	9 (28.1)
Site of <i>Acinetobacter baumannii</i> isolation	
Sputum	16 (50.0)
Blood	7 (21.9)
Pus	8 (25.0)
Urine	1 (3.1)
Charlson Comorbidity Index (Range)	3.67 (1–6)
ICU admission	8 (25.0)
Septic shock incidence	9 (28.1)
Mechanical ventilator use	11 (34.4)

Charlson comorbidity score was 3.67. Eight patients were admitted to the ICU, nine patients had septic shock during admission, and 11 patients needed mechanical ventilators. The bacteria found to be co-infections in patients included *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*. Sites of isolation that were positive for *Acinetobacter baumannii* in this study were the sputum (50%), pus (25%), blood (21.9%), and urine (3.1%). It should be noted that the sites of isolation of nine patients (28.1%) were not associated with their signs and symptoms, so the sites of infection were recorded as unknown.

Antibiotic Regimens

The antibiotic regimens collected in this study were divided into two phases: empirical therapy (before antimicrobial susceptibility testing) and definitive therapy (after

antimicrobial susceptibility testing). For empirical therapy, the antibiotic monotherapy regimen was the most prescribed (17 cases), followed by two, three, and four antibiotic combinations (12, two, and one cases, respectively). Table 2 indicates the number of antibiotic regimens used in this study. The most prescribed monotherapy regimen was beta-lactam/beta-lactamase inhibitors, including ampicillin/sulbactam (1.5–3 g intravenously every 6 h) and piperacillin/tazobactam (2.25–4.5 g intravenously every 6 h). Carbapenem (i.e., meropenem 1 g intravenously every 8 h) and cephalosporin (i.e., ceftriaxone 2 g intravenously every 24 h and ceftazidime 2 g intravenously every 8 h) monotherapy regimens were prescribed equally (5 cases).

Of the 32 patients recruited in this study, only 22 had antimicrobial susceptibility results (Supplementary Table 2). Sixteen out of 22 patients underwent definitive therapy due to their antimicrobial susceptibility results. However, monotherapy antibiotics were still the most prescribed (Table 3). Carbapenem monotherapy was the most prescribed antibiotic drug (nine cases), followed by cephalosporin and beta-lactam/beta-lactamase inhibitors (five and four cases, respectively). Moreover, antibiotic regimens with colistin (300 mg intravenously immediately, then 150 mg intravenously every 12 h) were prescribed more as definitive therapy than empirical therapy (six cases vs. one case, respectively). Additionally, all colistin regimens were combined with meropenem.

Table 2 Antibiotic Regimens as the Empirical Therapy for the Infection of *Acinetobacter baumannii* in 32 Patients

Antibiotic Regimen		Number of Case
Monotherapy	Beta-lactam/Beta-lactamase inhibitor	7
	Cephalosporin	5
	Carbapenem	5
Combination therapy	Cephalosporin + Macrolide	4
	Carbapenem + Fluoroquinolone	3
	Cephalosporin + Metronidazole	2
	Carbapenem + Vancomycin	2
	Cephalosporin + Clindamycin	1
	Cephalosporin + Vancomycin + Clindamycin	1
	Carbapenem + Vancomycin + Fosfomycin	1
	Carbapenem + Fluoroquinolone + Beta-lactam/Beta-lactamase inhibitor + Colistin	1

Table 3 Antibiotic Regimens as the Definitive Therapy for the Infection of *Acinetobacter baumannii* in 32 Patients

Antibiotic Regimen		Number of Case
Monotherapy	Carbapenem	9
	Cephalosporin	5
	Beta-lactam/Beta-lactamase inhibitor	4
	Fluoroquinolone	1
Combination therapy	Colistin + Carbapenem	2
	Colistin + Carbapenem + Beta-lactam /Beta-lactamase inhibitor	3
	Cephalosporin + Macrolide	2
	Beta-lactam/Beta-lactamase inhibitor + Fluoroquinolone	1
	Carbapenem + Macrolide	1
	Carbapenem + Fluoroquinolone	1
	Carbapenem + Vancomycin + Fosfomycin	1
	Carbapenem + Vancomycin + Colistin	1
	Cephalosporin + Vancomycin + Clindamycin	1

Clinical Outcomes and Safety Profiles

Table 4 describes the clinical outcomes, which were assessed by doctors and the mortality rates of patients at the end of treatment. Of all 32 patients that received

Table 4 Clinical Cure and Mortality Rates of 32 Patients Receiving Antibiotic Regimens for the Treatment of *Acinetobacter baumannii* Infection

Antibiotic Regimen	Number of Case (%)	Number of Clinical Cure (%)	Number of Death (%)
All regimens	32 (100.0)	19 (45.9)	11 (43.4)
Monotherapy regimens			
Cephalosporin	5 (15.6)	5 (100.0)	0 (0.0)
Carbapenem	9 (28.1)	7 (77.8)	2 (22.2)
Beta-lactam/Beta-lactamase inhibitor	4 (12.5)	2 (50.0)	2 (50.0)
Combination therapy regimens with colistin			
Combination therapy regimens with carbapenem	6 (18.8)	1 (16.7)	4 (66.7)
Combination therapy regimens without colistin and carbapenem	9 (28.1)	1 (11.1)	7 (77.8)
Combination therapy regimens without colistin and carbapenem	4 (12.5)	4 (100.0)	0 (0.0)

Note: All combination regimens with colistin included meropenem, and then were counted twice.

antibiotics, 59.4% achieved clinical cure, while 34.4% died. Patients treated with cephalosporin and carbapenem monotherapy regimens had a 100% and 77.8% complete response rate, respectively, while patients treated with a beta-lactam/beta-lactamase inhibitor had a 50% response rate. Individual data on the patient characteristics, administered antibiotics, and clinical responses are shown in [Supplementary Table 3](#).

The combination antibiotic regimens included in this study were found to have low clinical cure rates with high mortality rates. Patients who received colistin regimens had a 66.7% mortality rate, and those who received meropenem regimens had a 77.8% mortality rate. Although the number of patients who received other combination therapy regimens (neither carbapenem nor colistin) and achieved clinical cure was high, the actual number of each regimen was too low to reflect the actual efficacy (one case per regimen).

Due to the limitations of retrospective methodology, together with the limited number of tests available in secondary hospitals, nephrotoxicity was the only safety variable collected in this study. The mean and standard deviation (SD) of BUN of 32 patients before and after antibiotic administration were 19.72±11.63 and 20.88 ±11.77 mg/dL, respectively. In addition, the mean and SD of serum creatinine of all patients were 2.98 ±3.35 mg/dL prior to treatment and 3.15±3.38 mg/dL at the end of treatment. No increase in BUN and serum creatinine was found in all six patients receiving colistin.

Discussion

Regimens of antibiotics to treat infections normally depend on the sensitivity of the infecting bacteria, and the sensitivity usually varies from area to area. According to a report by NARST in 2019, the prevalence of CRAB in upper southern Thailand was approximately 53%, the lowest of all areas in Thailand.⁶ Furthermore, antibiotic use in tertiary hospitals is different from primary and secondary hospitals. Unfortunately, not many studies, particularly in Thailand, have been performed in secondary and primary hospitals, so this is one of the first studies to focus on the treatment and prevalence of *Acinetobacter baumannii* outside tertiary hospitals.

The prescribed antibiotic regimens in this study, as expected, were different from those reported in previous studies in tertiary hospitals. Empirical therapy, mostly prescribed at Phang-Nga Hospital, was a beta-lactam/beta-lactamase inhibitor, while other hospitals preferred starting

with colistin⁷ and carbapenem.⁸ In addition, the most frequently prescribed definitive therapy at Phang-Nga Hospital was carbapenem, while previous studies mostly used beta-lactam/beta-lactamase inhibitors, carbapenem, and colistin as definitive therapies. This difference resulted from the different sensitivities of the *Acinetobacter* species in different areas.

A study by Puttilerpong et al reported that only 1–2% of *Acinetobacter baumannii* at King Chulalongkorn Memorial hospital were sensitive to cephalosporin.⁷ Likewise, Kanankaeng et al indicated that no *Acinetobacter baumannii* found at Maharat Nakhon Ratchasima hospital were sensitive to cephalosporin.⁹ Moreover, the sensitivity of *Acinetobacter baumannii* at Sunpasitthiprasong hospital to ceftriaxone and ceftazidime were 3% and 27.3%, respectively.¹⁰ Nevertheless, the results of this study indicate that up to 63.6% of *Acinetobacter baumannii* at Phang-Nga Hospital were still sensitive to ceftazidime. These sensitivity results are in agreement with the reported clinical outcomes.

The clinical cure rates of cephalosporin monotherapy (i.e., ceftazidime and ceftriaxone) and carbapenem monotherapy in this study were as high as 100% and 77.8%, respectively, while patients receiving carbapenem monotherapy had only 53.8%⁸ and 15.8%⁹ clinical response rates in other studies. Similarly, the clinical cure rate of beta-lactam/beta-lactamase inhibitor monotherapy in this study was higher than in a previous study (50% vs. 36.4%, respectively).⁸ However, this study found that patients that received combination therapy had a higher mortality rate than those on monotherapy. These results were in agreement with the study by Kanankaeng et al that reported no difference in the clinical outcomes between monotherapy and combination therapy.⁹ Moreover, patients who received antibiotic regimens with colistin did not have better clinical outcomes than without colistin, which was similar to the previously mentioned study.⁹ In addition, the inconsistent clinical efficacy of colistin has been reported in several studies.^{11–14}

Concerning the susceptibility results of 22 patients in this study, as shown in [Supplementary Table 2](#), most of the collected isolates were sensitive to ceftazidime but not ceftriaxone. Half of the patients were sensitive to ampicillin/sulbactam and piperacillin/tazobactam. In addition, less than 25% of the isolates were sensitive to ceftriaxone. These results indicate that patients suspected of having *Acinetobacter baumannii* infection at Phang-Nga Hospital should not be administered ceftriaxone monotherapy, but rather ceftazidime or meropenem should be considered.

Moreover, according to a six-year observational study of *Acinetobacter baumannii* resistance in Thailand by NARST, the resistance of bacteria to various types of antibiotics has increased.¹⁵ The antibiotics found to have more than 50% resistance included ceftazidime, aminoglycosides, and ciprofloxacin. For CRAB, up to 74% of the isolates in Thailand were resistant to meropenem, which is similar to that in Singapore and Vietnam.¹⁶ Likewise, a study in Malaysia reported that more than 50% of *Acinetobacter baumannii* were resistant to cephalosporins (cefotaxime, ceftazidime, and cefepime) and carbapenems (imipenem and meropenem).¹⁷ Although these results suggest a surge in resistance of *Acinetobacter baumannii* to many antibiotics, including ceftazidime and meropenem in Thailand and neighboring countries, the results in this study still support the use of ceftazidime in secondary or lower-level hospitals in Thailand.

As this study is a pilot study with a retrospective methodology, there are several limitations. First, the number of patients in this study was limited, especially compared with previous studies in tertiary or university hospitals. However, due to the low total number of inpatients at Phang-Nga Hospital and the location of this hospital between two tertiary hospitals, few cases of *Acinetobacter baumannii* infection were expected. Besides, as this study is a pilot study, more patients will be included in the future from other hospitals. Second, as we retrospectively reviewed patient medical charts, some variables could not be collected. As the data were originally collected for routine patient treatment, not research, some variables were not available. For example, microbiological tests after the treatment course are not routinely performed in secondary hospitals. Therefore, this study tried to avoid comparing patients within the study. Moreover, the causation of the clinical outcomes should not be extrapolated from the current results, as it could be misleading. Third, the patients in this study were only from Phang-Nga province, so it is not possible to extrapolate the results to other secondary hospitals in Thailand due to different antimicrobial susceptibilities. A more obvious trend of antibiotic resistance/sensitivity should be apparent when more patients from other secondary hospitals are included in the next phase of this study.

Conclusion

The main aim of this pilot study was to raise awareness of Antibiotic Smart Use in Thailand by investigating antibiotic regimens used to treat *Acinetobacter baumannii*

infections at a secondary hospital. The results indicate that more than 60% of *Acinetobacter baumannii* at Phang-Nga Hospital were sensitive to cephalosporin antibiotics, and monotherapy regimens of cephalosporin or carbapenem provided higher than a 50% clinical cure rate. The next phase of this study will collect patient data from other secondary hospitals in Thailand to examine the antibiotic regimens used to treat *Acinetobacter baumannii* infections in Thailand more thoroughly.

Disclosure

The authors report no conflicts of interest in this work.

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