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Treatment outcomes and their predictive factors in patients with *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Providencia* spp., I-indole-positive *Proteus* spp., and *Morganella* spp, bloodstream infection

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ABSTRACT

The present study examined the treatment outcomes and factors related to mortality in patients with *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Providencia* spp., I-indole-positive *Proteus* spp., and *Morganella* spp. (ESCPIM) bloodstream infections and determined the susceptibility of ESCPIM pathogens to antimicrobial compounds. This retrospective study was performed at a university hospital in Thailand, using records from March 2017 to December 2018. Fifty-six patients with ESCPIM bacteremia were included. Approximately, half the patient cohort (55.4%) was infected with *Enterobacter* spp. The in-hospital mortality rate was 23.2%. Of the 56 patients studied, 20 patients (35.7%) had received a carbapenem treatment regimen, whereas 36 patients (64.3%) were treated with non-carbapenem regimens. The mortality rates in the carbapenem and non-carbapenem treatment regimens were 30% and 19.4%, respectively, although this difference was not statistically significant. In multivariate analysis of factors related to treatment outcome, only mechanical ventilator use and intensive care unit (ICU) admission significantly predicted 30-day mortality. Piperacillin/tazobactam, carbapenems, and aminoglycosides were the antimicrobial agents with most activity against the ESCPIM isolates assayed in the present study. In conclusion, patients with ESCPIM septicemia showed an in-hospital mortality rate of approximately one in four. Mechanical ventilator use and ICU admission were significant predictors of mortality. Thus, these critical conditions have to be concerned to improve patient outcomes.

Keywords: AmpC β-lactamase, Bacteremia, Carbapenem, Enterobacterales

INTRODUCTION

Enterobacter spp., *Serratia* spp., *Citrobacter* spp., *Providencia* spp., indole-positive bacteria (*Proteus* spp.), and *Morganella* spp. (ESCPIM) bacteria are Gram-negative bacilli. These pathogens can cause invasive organ infections leading to prolonged hospitalization and unfavorable treatment outcomes.[1] Moreover, nosocomial ESCPIM infections often exhibit antibiotic resistance, especially against β-lactams that would be the treatment of choice against ESCPIM pathogens.[2] The main mechanism of resistance against β-lactams is the production of AmpC β-lactamase, which inactivates third-generation cephalosporins, cefoxitin, β-lactam/β-lactamase inhibitors (BLBIs) such as piperacillin/tazobactam, and aztreonam, with the exception of carbapenems and cefepime.[3] Therefore, the optimal choices for the treatment of ESCPIM pathogens have been carbapenems, cefepime, fluoroquinolones, and aminoglycosides.[1,4]

Carbapenem resistance is currently a major worldwide medical problem. In 2017, the World Health Organization listed carbapenem-resistant *Enterobacterales* as critical priority pathogens for which research into novel drugs or treatments is required.[5] Moreover, the antimicrobial stewardship program (ASP) is a coordinated program that promotes the appropriate use of antimicrobials to reduce microbial resistance. Among the various ASP strategies, de-escalation and the use of the narrowest-spectrum antibiotic play important roles in reducing antibiotic resistance.[6]

Thus, non-carbapenem antibiotics, such as cefepime, fluoroquinolones, extended-spectrum penicillins, and aminoglycosides, are suitable for treatment of ESCPIM bacterial infections, in line with the documented protocols to reduce antibiotic resistance. Supporting this strategy, past research indicated that there was no difference in mortality rate between non-carbapenem and carbapenem treatments.[7,8] Theoretically, even the use of third-generation cephalosporins confers a potential increase in the risk of treatment failure in infections due to chromosomally mediated AmpC-producing *Enterobacterales*.[9] However, clinical evidence has indicated that treatment with third-generation cephalosporins did not make a significant contribution to the poor outcomes in infection with *Enterobacter* spp., *Serratia* spp., or *Citrobacter* spp., compared with other antimicrobial agents.[10,11] Therefore, the use of non-carbapenem antibiotic treatments would favorably limit the occurrence of carbapenem resistance.

Patients infected with *Enterobacter* spp. or *Citrobacter* spp. had a mortality rate of 16–21%[11-13] depending on their prognostic factors, such as gender,[14] underlying diseases, severity of illness (as measured using the Acute Physiology and Chronic Health Evaluation II),[15] bacteremia,[16] septic shock,[14,17] and infection caused by strains carrying the bla_{TEM-1} gene encoding β-lactamase.[18] However, several previous studies have shown that prognostic factors in patients with ESCPIM infections remain a controversial issue. Moreover, the study of clinical outcomes and risk factors related to treatment outcome among patients with ESCPIM pathogen infections in Thailand has been scant.

Therefore, in the present study, we compared clinical outcomes in patients with ESCPIM bloodstream infection receiving either carbapenem or non-carbapenem treatments, focusing on mortality rate; further, we analyzed factors related to mortality. In addition, we determined the susceptibility rates and minimum inhibitory concentration (MIC) values for the available suite of antibiotics against ESCPIM isolates obtained from patients with bloodstream infection.

MATERIALS AND METHODS

The present study was conducted retrospectively using records of patients with ESCPIM bloodstream infection admitted to Phramongkutklao Hospital (a university hospital in Bangkok, Thailand) between March 2017 and December 2018. The aim of this study was to determine the mortality rate and identify predictive factors associated with clinical outcomes of patients with ESCPIM bloodstream infection. The inclusion criteria for ESCPIM bacteremia consisted of (1) Age ≥18 years; (2) blood culture results for the first isolate of ESCPIM; and (3) clinical signs of infection, such as at least two out of the four systemic inflammatory response syndrome items (body temperature >38°C or <36°C, respiratory rate >20 breaths/min, heart rate >90 beats/min, or leukocytosis <4000 or >12,000 cells/mL) with bloodstream infections. Exclusion criteria were transfers between hospitals, incomplete medical records, or treated patient unable to be followed up. This study was approved by the ethical review committee of the Royal Thai Army Medical Department (approval no. Q036h/61_Exp).

Data Collection

The data were collected from medical records, and treatment allocation was concealed by coding. The collected data included patient characteristics such as sex, age, comorbidities, duration of admission, ward, source of infections, mechanical ventilator use, the presence of central venous catheter or urinary catheter, antibiotic regimen (type and dosage of antibiotic), in-hospital mortality, and microbial susceptibility records (percentage of isolates showing antibiotic resistance).

In terms of clinical outcomes, in-hospital mortality was defined as death of a diagnosis of ESCPIM infection occurring during the hospital stay. For risk factors related to mortality, we included predictive factors documented in the previous studies such as gender,[14] underlying diseases, severity of illness,[15] and septic shock.[14,17] On the basis of a sample size for multivariate data analysis of at least 15 cases for each factor,[19] 60 participants are suitable for analysis.

Determination of MIC

All clinical ESCPIM isolates obtained from patients with bloodstream infection were included in antimicrobial susceptibility testing. The susceptibility of ESCPIM isolates to antimicrobial agents such as amikacin, ceftriaxone, ceftazidime, cefepime, ciprofloxacin, colistin, co-trimoxazole, ertapenem, gentamicin, imipenem, meropenem, piperacillin/tazobactam, and tigecycline was evaluated using automated susceptibility testing (Thermo Scientific™ Sensititre™ ARIS™ 2X Instrument) based on the broth microdilution method. The tested bacterial growth was determined using fluorescence measurement after 18–24 h of incubation depending on the species.

The percentage of susceptible isolates was calculated by comparing the MIC of the assayed antibiotics in each

ESCPIM strain against the Clinical and Laboratory Standards Institute (CLSI) breakpoints.[20] In the absence of available CLSI breakpoints, the European Committee on Antimicrobial Susceptibility Testing breakpoints were applied.[21]

Statistical Analysis

Descriptive statistics were used to describe the characteristics, clinical status, mortality rate, and treatment failure rate in patients with ESCPIM infections. Chi-square or Fisher's exact test statistics were used to analyze the relationship between discrete data. Kolmogorov–Smirnov Z test (median with interquartile range) or Student's t-test (mean with standard deviation) were used to compare the median or mean, respectively, between continuous data. All significant variables in univariate logistic regression analysis (considering significance at $\alpha = 0.1$) were included in the multivariate logistic regression analysis. Analysis and data interpretation were performed using SPSS at $\alpha = 0.05$ ($P < 0.05$) for statistical significance.

RESULTS

We identified 56 admitted patients with ESCPIM bloodstream infection during the study period from March 2017 to December 2018. The ESCPIM isolates obtained from blood cultures from these patients included 31 *Enterobacter* spp. isolates (55.4%), 5 *Serratia* spp. isolates (8.9%), 8 *Citrobacter* spp. isolates (14.3%), 2 *Providencia* spp. isolates (3.6%), 2 indole-positive *Proteus* spp. isolates (3.6%), and 8 *Morganella* spp. isolates (14.3%) [Table 1].

The mean (± SD) age among the 56 patients with ESCPIM bloodstream infection was 63.6 ± 23.2 years, and 36 participants (64.3%) were men. Twenty-one cases (37.5%) were admitted to the intensive care unit (ICU), and 17 cases (30.4%) received assisted ventilation with a mechanical ventilator. Clinical characteristics, source of infection, and antibiotic regimen are shown in Table 1.

Regarding clinical outcomes, the in-hospital mortality in patients with ESCPIM infection was 13 out of 56 cases (23.2%). Of the 13 deaths, 6 deaths were due to *Enterobacter* spp. infection; *Providencia* spp., *Citrobacter* spp., and *Serratia* spp. infections were responsible for two deaths each, and the remaining one death was due to *Morganella* spp. [Figure 1].

Of the 56 patients, 20 (35.7%) and 36 (64.3%) patients received carbapenem and non-carbapenem treatments, respectively. There were more men than women in both the carbapenem (60% men) and non-carbapenem (66.7% men) groups. The mean (± SD) age was 62.4 ± 24.4 years in the carbapenem group and 64.3 ± 22.9 years in the non-carbapenem group. Nine cases (45%) in the carbapenem group and 12 cases (33.3%) in the non-carbapenem group were admitted to the ICU. The in-hospital mortality rates for the carbapenem and non-carbapenem groups were 30% and 19.4%, respectively; this difference was not statistically significant. There were no significant differences between the carbapenem and non-carbapenem groups in any of the demographic characteristics measured in the present study [Table 2].

Univariate analysis of factors potentially affecting clinical outcome showed that patient ICU admission, mechanical ventilator use, central venous catheter use, and septic shock were significant predictors for in-hospital mortality. In multivariate analysis, only ICU admission (odds ratio [OR] 37.93, 95% confidence interval [CI] 3.46–416.43) and mechanical ventilator use (OR 6.66, 95% CI 1.06–41.98) were significant predictors of 30-day mortality [Table 3].

Table 1: Baseline and clinical characteristics in patients with *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Providencia* spp., indole-positive *Proteus* spp., or *Morganella* spp. (ESCPIM) bloodstream infection (n=56 cases)

Variables	Result
Age (year), mean±SD	63.6±23.2
Male, number (%)	36 (64.3)
Underlying diseases, number (%)	
Diabetes mellitus	26 (46.4)
Chronic kidney disease	17 (30.4)
Chronic obstructive pulmonary disease	2 (3.6)
Cancer	7 (12.5)
Intensive care unit admission, number (%)	21 (37.5)
Neutropenia, number (%)	1 (1.8)
Mechanical ventilator, number (%)	17 (30.4)
Central venous catheterization, number (%)	20 (35.7)
Urinary catheterization, number (%)	18 (32.1)
Septic shock, number (%)	22 (39.33)
Duration of hospitalization, mean±SD	42±50.6
Sources of infection, number (%)	
Urinary tract infection	14 (25.0)
Primary bacteremia	14 (25.0)
Lower respiratory tract infection	11 (19.6)
Intra-abdominal infection	9 (16.1)
Skin and soft tissue infection	4 (7.1)
Catheter-related infection	3 (5.4)
Bone and joint infection	1 (1.8)
Pathogens (ESCPIM)	
Enterobacter spp., number (%)	31 (55.4)
Serratia spp., number (%)	5 (8.9)
Citrobacter spp., number (%)	8 (14.3)
Providencia spp., number (%)	2 (3.6)
Indole positive *Proteaus* spp., number (%)	2 (3.6)
Morganella spp., number (%)	8 (14.3)
Antibiotics	
Carbapenems, number (%)	20 (35.7)
Third generation cephalosporins, number (%)	11 (19.6)
Cefepime, number (%)	4 (7.1)
Colistin, number (%)	2 (3.6)
Fluoroquinolones, number (%)	16 (28.6)
Others, number (%)	3 (5.4)

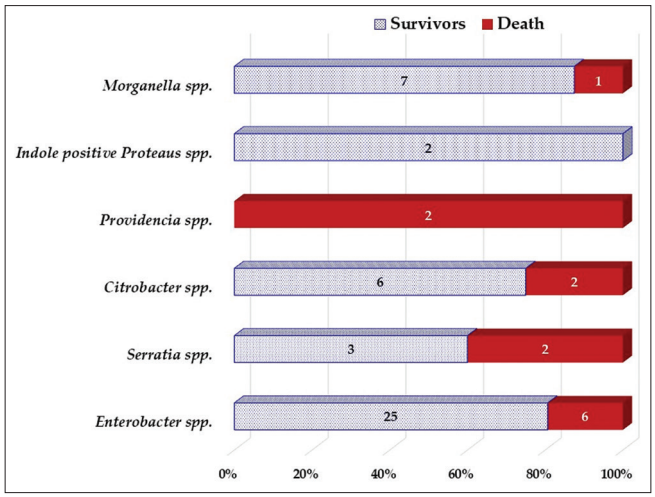

Figure 1: Mortality rates (red bar) in patients with *Enterobacter* spp., *Serratia* spp., *Citrobacter* spp., *Providencia* spp., indole-positive *Proteus* spp., or *Morganella* spp. bloodstream infections

Antimicrobial Susceptibility Testing

All ESCPIM isolates were universally resistant to ampicillin [Table 4]. ESCPIM isolates showed a susceptibility rate of >80% to piperacillin/tazobactam, carbapenems (ertapenem, meropenem, imipenem, and doripenem), aminoglycosides (gentamicin and amikacin), and colistin. The susceptibility of ESCPIM isolates to other antimicrobials is shown in Table 4.

DISCUSSION

This study evaluated the clinical outcome in patients with ESCPIM bloodstream infection. The observed mortality rate in this study (23.2%) was twice as high as that reported in other previous studies (10.6–13.1%).[22,23] The high death rate may be a result of the higher number of patients with severe illness, as indicated by septic shock and mechanical ventilator use, in the present study compared with that in previous studies.

Cefepime has been considered an effective carbapenem-sparing option for treatment of infections involving

Table 2: Baseline and clinical characteristics in patients with ESCPIM bloodstream infection who underwent carbapenem or non-carbapenem treatment regimens

Variables	Carbapenem group (*n*=20)	Non-carbapenem group (*n*=36)	*P*-value
Age (years), mean±SD	62.4±24.4	64.3±22.9	0.783
Male, number (%)	12 (60)	24 (66.7)	0.618
Underlying diseases, number (%)			
Chronic kidney disease	3 (15)	14 (38.9)	0.062
Chronic obstructive pulmonary disease	2 (10)	0 (0)	0.123
Cancer	5 (25)	2 (5.6)	0.084
Intensive care unit admission, number (%)	9 (45)	12 (33.3)	0.388
Neutropenia, number (%)	1 (5)	0 (0)	0.357
Mechanical ventilator, number (%)	7 (35)	10 (27.8)	0.573
Central venous catheterization, number (%)	8 (40)	12 (33.3)	0.618
Urinary catheterization, number (%)	5 (25)	13 (36.1)	0.394
Shock, number (%)	10 (50)	12 (33.3)	0.221
Enterobacter spp., number (%)	10 (50)	15 (41.7)	0.548
In-hospital mortality, number (%)	6 (30)	7 (19.4)	0.510

Table 3: Factors affecting in-hospital mortality in patients with ESCPIM bloodstream infection

Factors	Univariate analysis		Multivariate analysis	
	Odd ratio (95%CI)	*P*-value	Odd ratio (95%CI)	*P*-value
Age≥65 years	1.47 (0.39–5.55)	0.747		
Male	0.86 (0.24–3.09)	1.000		
Underlying diseases				
Chronic kidney disease	2.49 (0.69–9.04)	0.182		
Chronic obstructive	3.5 (0.20–60.21)	0.414		
Pulmonary disease				
Cancer	1.38 (0.24–8.13)	0.658		
Neutropenia	ND	1.000		
Intensive care unit stay	45.33 (5.19–396.36)	0.000	37.93 (3.46–416.43)	0.003
Mechanical ventilator	9.84 (2.41–40.16)	0.001	6.66 (1.06–41.98)	0.044
Central venous catheter	4.13 (1.13–15.18)	0.046	1.14 (0.17–7.50)	0.895
Urinary tract catheter	0.92 (0.24–3.51)	1.000		
Shock	3.314 (0.92–12.0)	0.061	1.26 (0.193–8.266)	0.807
Non-carbapenems use	0.56 (0.16–1.99)	0.510		
Enterobacter spp.	1.62 (0.47–5.64)	0.446		

Table 4: The susceptible rate of antibiotics against among ESCPIM pathogens (n=56 isolates)

Antibiotics	ESCPIM pathogens (isolates)						
	***Enterobacter* spp. (31)**	***Serratia* spp. (5)**	***Citrobacter* spp. (8)**	***Providencia* spp. (2)**	**Indole positive *Proteaus* spp. (2)**	***Morganella* spp. (8)**	**Total isolates (56)**
	Number (%) of antibiotic susceptible isolates						
Penicillin							
Ampicillin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Piperacillin/ tazobactam	25 (80.6)	5 (100)	8 (100)	2 (100)	2 (100)	8 (100)	50 (89.3)
Cephalosporins							
Ceftriaxone	16 (51.6)	3 (60)	7 (85.7)	2 (100)	2 (100)	6 (75)	36 (64.3)
Ceftazidime	17 (54.8)	3 (60)	7 (85.7)	2 (100)	2 (100)	7 (87.5)	38 (67.9)
Cefepime	21 (67.7)	4 (80)	7 (85.7)	2 (100)	2 (100)	7 (87.5)	43 (76.8)
Carbapenems							
Ertapenem	27 (87.1)	5 (100)	8 (100)	2 (100)	2 (100)	7 (87.5)	51 (91.1)
Meropenem	25 (80.6)	5 (100)	8 (100)	2 (100)	2 (100)	8 (100)	50 (89.3)
Imipenem	29 (93.5)	5 (100)	8 (100)	2 (100)	1 (50)	8 (100)	53 (94.6)
Doripenem	27 (87.1)	5 (100)	8 (100)	2 (100)	2 (100)	8 (100)	52 (92.9)
Aminoglycosides							
Amikacin	30 (96.8)	5 (100)	8 (100)	2 (100)	2 (100)	8 (100)	55 (98.20
Gentamicin	25 (80.6)	5 (100)	8 (100)	2 (100)	1 (50)	6 (75)	47 (83.9)
Others							
Ciprofloxacin	22 (71)	4 (80)	8 (100)	2 (100)	1 (50)	4 (50)	41 (73.2)
Co-trimoxazole	19 (61.3)	3 (60)	8 (100)	2 (100)	1 (50)	8 (100)	41 (73.2)
Colistin	26 (83.9)	1 (20)	7 (87.5)	2 (100)	2 (100)	8 (100)	46 (82.1)

AmpC-producing bacteria. However, the overall cefepime susceptibility rate among ESCPIM isolates in the present study was 76.4%. The lower cefepime susceptibility rate was caused by the presence of carbapenem-resistant strains that we found in *Enterobacter* spp. isolates (approximately 20%; Table 4). Thus, the use of cefepime is warranted. The isolates in the present study showed >80% susceptibilty rate to carbapenems, aminoglycosides, and piperacillin/ tazobactam; as such, these antimicrobials may be good options for treating ESCPIM infections. In addition, in a systematic review and meta-analysis by Harris *et al*.,[7] BLBIs or fluoroquinolones were non-inferior to carbapenems in relation to mortality among patients with bloodstream infections caused by AmpC β-lactamase-producing pathogens. However, the rationale for use of aminoglycosides was limited in cases of bacteremia secondary to urinary tract infections.[24]

Surprisingly, we identified the presence of colistin-resistant *Enterobacter* spp. isolates in the present study. We also found that only 20% of *Serratia* spp. isolates in the present study were susceptible to colistin; this was less suprizing as it is known that some *Proteus* spp., *Providencia* spp., and *Serratia* spp. are naturally resistant to colistin.[25] Resistance to colistin, the last-resort treatment for *Enterobacterales* infections, is becoming a major medical problem; it is known that colistin-resistant Gram-negative bacteria infections have been associated with an extremely high mortality rate.[26]

In our present study, we did not find any correlation between carbapenem treatment (compared with non-carbapenem treatment) and mortality rate among patients with ESCPIM infections. This finding was similar to that of a previous study by Harris *et al*.,[7] who reviewed studies of mortality in patients treated with carbapenems, BLBIs, fluoroquinolones, or cefepime. Harris *et al*. found that there was no different in mortality rate between non-carbapenem and carbapenem treatments in ESCPIM bacteremia. Thus, carbapenem-sparing regimens are useful for reducing carbapenem consumption in the treatment of AmpC-producing bacteria, resulting in diminished carbapenem resistance in *Enterobacterales*.

CONCLUSIONS

In the present study, we found that the only significant predictors of mortality rate in patients with ESCPIM infections were mechanical ventilator use and ICU admission. Our finding was similar to that in a study by Marcos *et al*.,[27] who revealed a relationship between mechanical ventilator use and mortality rate. The previous studies have indicated that septic shock is associated with death.[27,28] Although in the present study we identified a significant correlation (at $\alpha = 0.1$) between septic shock and mortality in univariate analysis, this correlation did not persist once adjusted for other factors in multivariate analysis. The lack of significance for this correlation in our analysis might result from the limitation of sample size.

The present study has several limitations. First, it is a single-center retrospective study with a small number of ESCPIM bacteremia cases, which may lack the statistical power to evaluate all previous identified factors related to mortality. Second, our clinical outcomes were from a medical school hospital, which might differ from those taken at other types of hospitals. Third, a number of participants in our study were treated with third-generation cephalosporins; the use of third-generation cephalosporins has the potential to increase the risk of treatment failure in infections due to chromosomally mediated AmpC-producing *Enterobacterales*.[9] Further studies with a larger number of participants and multiple centers are required to investigate the clinical outcomes and predictors for death in ESCPIM infection.

The conclusions in-hospital mortality rate for patients with ESCPIM bloodstream was approximately 25%. Carbapenems, aminoglycosides and, piperacillin/tazobactam may be good treatment options for ESCPIM infections due to high susceptibility rates. Mechanical ventilator use and ICU admission were predictors of mortality. Thus, these critical conditions have to be concerned to improve patient outcomes.

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