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Clinical outcomes and mortality risk factors among intensive care unit patients with bacteremia at a university hospital

Wichai Santimaleeworagun[1,2], Petch Wacharasint[3], Weerayuth Saelim[1,2], Juthathip Suphanklang[1,4], Kawin Duangmee[1], Narisa Ruenroengbun[1], Pachara Thiengkumdee[1], Sukhontha Ratchadawan[1], Duangspan Tewthao[1] and Thanathorn Kulkiatprasert[1]*

[1] Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand
[2] Pharmaceutical Initiative for Resistant Bacteria and Infectious Diseases Working Group (PIRBIG), Silpakorn University, Nakhon Pathom 73000, Thailand
[3] Division of Pulmonary and Critical Care, Department of Medicine, Phramongkutklao Hospital 10400, Thailand
[4] Silpakorn University Research Program (SURP), Silpakorn University, Nakhon Pathom 73000, Thailand

***Corresponding author**:
Weerayuth Saelim
saelim_w6@su.ac.th

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ABSTRACT

This study aimed to determine the prevalence and antimicrobial susceptibility of causative pathogens associated with 30-day mortality among intensive care unit (ICU) patients with bloodstream infections as well as to analyze clinical outcomes and risk factors. This retrospective study was conducted at Phramongkutklao Hospital, Thailand, between October 2017 and December 2018. The study included 142 patients with bloodstream infections caused by 193 isolated pathogens. Of the 142 patients, the clinical cure and death rates were reported to be 40.1% and 62.0%, respectively. Of the 193 isolated bacterial strains, 83.4% were Gram-negative: predominately *Klebsiella pneumoniae*, followed by *Acinetobacter baumannii*, and then *Pseudomonas aeruginosa* isolates. Gram-positive bacteria accounted for 16.6% of the total isolated bacterial strains: *Staphylococcus aureus* was the leading isolate, followed by coagulase-negative staphylococci and then *Enterococcus faecalis*. Most of the *A. baumannii* isolates (97.0%) were resistant to meropenem, but 57.7% of *P. aeruginosa* and 40.0% of *K. pneumoniae* were susceptible to meropenem. Through multivariate analysis, it was found that the significant factors for 30-day mortality were male gender, catheter-related bloodstream infection, and carbapenem-resistant Gram-negative infection. Due to the high 30-day mortality rate of almost two-thirds of the study groups, healthcare professionals are challenged to select an optimized treatment regimen for ICU patients with carbapenem-resistant gram-negative infection.

Keywords: bacteremia; death; causative pathogen

1. INTRODUCTION

Nosocomial infections frequently occur in intensive care units (ICUs) and can have severe outcomes, including multiple organ dysfunction syndrome, which is the most common cause of death, with a risk of central nervous system and cardiovascular failures (Mayr et al., 2006). Thus, an appropriate empiric antimicrobial therapy is

important to improve clinical outcomes and reduce the resistance of pathogens by carefully focused treatments and "antimicrobial stewardship" specific to each case (Campion and Scully, 2018).

The results from the European prevalence of infection in intensive care study in 17 western European countries revealed that the most common nosocomial infections occurring in ICUs affected the lower respiratory tract (64.7%), followed by urinary tract (17.6%), and bloodstream (12.0%), respectively (Vincent et al., 1995).

An Asian epidemiological study reported that 34.1% of the causative pathogens in ICUs were Gram-positive, including methicillin-susceptible *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), vancomycin-sensitive *Enterococci*, and vancomycin-resistant *Enterococci* (VRE). Gram-negative bacteria account for 74.3% of the cases, including *Pseudomonas* spp., *Klebsiella* spp., *Acinetobacter* spp., *Escherichia coli*, and *Enterobacter* spp. (Vincent et al., 2009).

Vincent et al. (2020) conducted a recent observational clinical study and investigated patients admitted to 1,150 ICUs in 88 countries. They found a high infection-induced mortality rate from antimicrobial-resistant microorganisms, including VRE, β-lactam-resistant *Klebsiella* spp., and carbapenem-resistant *Acinetobacter* spp. Thus, the prevalence of causative pathogens and their antimicrobial susceptibility are vital issues for antibiotic selection.

Good clinical outcomes depend on an appropriate antibacterial regimen. Fraser et al. (2006) demonstrated that an appropriate empiric antibiotic therapy for causative pathogens significantly reduces the 30-day mortality rate and length of hospital stay. There have been a few studies conducted in ICUs in Thailand that investigated clinical outcomes, risk factors for death, and etiologic bacteria.

Our retrospective study aimed to determine the prevalence and antimicrobial susceptibility of causative pathogens. In this study, the ICU patients with bloodstream infections and the clinical outcomes and risk factors associated with the 30-day mortality were evaluated.

2. MATERIALS AND METHODS

The medical records of patients with bloodstream infections who were admitted to the ICU at the Phramongkutklao Hospital (Bangkok, Thailand), which is a 1,200-bed teaching hospital, from October 2017 to December 2018 were retrospectively reviewed. The study protocol was approved by the Institutional Review Board of the Royal Thai Army Medical Department, Phramongkutklao Hospital (approval No. Q038h/61_Exp, 6 February 2019).

Eligible study participants were (1) 18 years of age or older; (2) the patients who had an ICU stay lasting over 48 h; and (3) the patients who had positive blood cultures for bacteria, with known or unknown origins, infecting the organs or systems, including the lungs (hospital-acquired pneumonia [HAP] or ventilator-associated pneumonia [VAP]), urinary tract, bloodstream (catheter-related bloodstream infection [CRBSI]), gastrointestinal tract (e.g., intra-abdominal infection), and integumentary system (e.g., skin and soft tissue infection), based on the definitions from the Centers for Disease Control and Prevention (CDC) (Centers for Disease Control and Prevention, United States, 2018). Patients who were referred to other hospitals or had incomplete data were excluded.

2.1 Data collection

The medical records of the patients were reviewed for gender, age, comorbidities, medical diagnosis, vital signs, sequential organ failure assessment (SOFA) score, mechanical ventilator use, and mortality assessment 30 days after the diagnosis of bloodstream infection. Antimicrobial treatment details included prescribed antimicrobials, dosing intervals, treatment duration, and antimicrobial susceptibility of causative pathogens.

2.2 Definition

The following clinical definitions were used: *clinical cure* indicates the improvement or elimination of signs or symptoms after three days of treatment based on the CDC definitions following infections in the organs or systems (e.g., improved clinical symptoms after antibiotic initiation, decreased sputum purulence, body temperature within the normal range (36-38°C), or white blood cell counts within the normal range (4,000-12,000 cells/mL) (Centers for Disease Control and Prevention, 2018). *Appropriate timing of antibiotics* is defined as antibiotic administration of at least 1 h after the diagnosis of infection. *Appropriate dosage regimen of antibiotics* indicates the recommended dose in clinical practice, which is adjusted for renal or hepatic function. *Appropriate choice of antibiotics* is defined as at least one active antibiotic agent covering the causative pathogen. The *30-day mortality* is defined as patients who died within 30 days after the diagnosis of bloodstream infection.

2.3 Antimicrobial susceptibility

Antimicrobial susceptibility testing (as a minimum inhibitory concentration [MIC] value) of bacterial isolates was conducted *via* broth microdilution (Thermo Scientific™ Sensititre™ ARIS™ 2X Instrument). Bacterial growth was determined *via* fluorescence measurement after a species-dependent incubation period. The MIC of the studied antibiotic was interpreted as the percentage of susceptible isolates using the susceptibility breakpoint of the Clinical and Laboratory Standards Institute (CLSI) (Clinical and Laboratory Standards Institute, 2019). If the CLSI breakpoints were unavailable, the European Committee on Antimicrobial Susceptibility Testing susceptibility breakpoint was adapted (The European Committee on Antimicrobial Susceptibility Testing, 2019).

2.4 Statistical analysis

All variables were analyzed using descriptive statistics to determine the mean or median of age and length of hospital stay and percentage of patient characteristics, 30-day mortality rate, antimicrobial use, mechanical ventilator use, and comorbidities to obtain antimicrobial susceptibility testing results. The Kolmogorov-Smirnov test can be used to test the normal distribution of continuous data for considering parametric or non-parametric statistics. Chi-squared test or Fisher's exact test (used as appropriate) was employed to analyze the discrete data. The parameters used in the adjusted model for the logistic regression analysis were significant variables ($\alpha = 0.1$) in univariate analysis to test the association between risk factors and 30-day mortality.

3. RESULTS AND DISCUSSION

A total of 142 patients with bloodstream infections: 75 males (52.8%) and 67 females (47.2%), with a median age of 69.5 years (interquartile range [IQR] 24.3) were identified. A total of 101 patients (71.1%) required the use of mechanical ventilator. Among the 142 patients, the most common comorbidities were hypertension (85 patients, 59.9%), followed by type 2 diabetes mellitus (55 patients, 38.7%), and dyslipidemia (53 patients, 37.3%), respectively. Most of the patients with bloodstream infections had pneumonia, either HAP or VAP. The median SOFA score was 8 (IQR 6). Table 1 presents the patients characteristics.

Table 1. Baseline characteristics of patients with bloodstream infections (n = 142)

Characteristics	Values
Male, number (%)	75 (52.8)
Age (years), median (IQR)	69.5 (24.3)
ICU wards, number (%)	
Medicinal ICU	113 (79.6)
Surgical ICU	12 (8.5)
Coronary care unit	12 (8.5)
Trauma ICU	3 (2.1)
Mechanical ventilator use, number (%)	101 (71.1)
Comorbidities, number (%)	
Dyslipidemia	53 (37.3)
Hypertension	85 (59.9)
Type 2 diabetes	55 (38.7)
Cancer	16 (11.3)
Atherosclerotic cardiovascular disease	42 (29.6)
Chronic kidney disease	40 (28.2)
Asthma or COPD	9 (6.3)
Cirrhosis	4 (2.8)
Principle diagnosis, number (%)	
Pneumonia (HAP or VAP)	48 (33.8)
Catheter-related bloodstream infection	30 (21.1)
Catheter-associated urinary tract infection	10 (7.0)
Intra-abdominal infection	12 (8.5)
Skin and soft tissue infection	8 (5.6)
Unspecified source	34 (23.9)
SOFA score (points), median (IQR)	8 (6)
Appropriate timing of antibiotics, number (%)	44 (31.0)
Appropriate dosage regimen of antibiotics, number (%)	116 (81.7)
Appropriate choice of antibiotics, number (%)	93 (65.5)
Resistant strains, number (%)	
Third generation cephalosporin resistance (ceftazidime)	72 (50.7)
Carbapenem resistance (meropenem)	57 (40.1)
Clinical outcomes, number (%)	
Clinical cure	57 (40.1)
30-day mortality	88 (62.0)

Note: *COPD*; chronic obstructive pulmonary disease, *HAP*; hospital-acquired pneumonia, *ICU*; intensive care unit, *SOFA*; sequential organ failure assessment, *VAP*; ventilator-associated pneumonia

3.1 Antimicrobial susceptibility

During the study period, 193 bacterial strains were isolated from 142 patients with bloodstream infections. Among all isolates, 161 bacterial strains were Gram-negative bacteria (83.4%). *K. pneumoniae* mostly found in Gram-negative bacteria group (24.8%), followed by *A. baumannii* (20.5%) and then *P. aeruginosa* (16.1%) isolates (Table 2).

Table 2. Prevalence of causative pathogens in study patients (n = 193)

Pathogens	Total number of organisms (%)
Gram positive bacteria (n=32)	
Staphylococcus aureus	15 (7.8)
Coagulase-negative *Staphylococci*	8 (4.1)
Enterococcus faecium	3 (1.6)
Enterococcus faecalis	4 (2.1)
Viridans group *streptococci*	1 (0.5)
Staphylococcus spp.	1 (0.5)
Gram negative bacteria (n=161)	
Klebsiella pneumoniae	40 (20.7)
Acinetobacter baumannii	33 (17.1)
Pseudomonas aeruginosa	26 (13.5)
Pseudomonas spp.	17 (8.8)
Escherichia coli	13 (6.7)
Stenotrophomonas maltophilia	10 (5.2)
Acinetobacter spp.	5 (2.6)
Enterobacter cloacae	4 (2.1)
Serratia marcescens	3 (1.6)
Proteus mirabilis	2 (1.0)
Proteus penneri	1 (0.5)
Proteus vulgaris	1 (0.5)
Klebsiella ozaenae	1 (0.5)
Citrobacter spp.	1 (0.5)
Enterobacter spp.	1 (0.5)
Morganella morganii	1 (0.5)
Providencia spp.	1 (0.5)
Flavobacterium spp.	1 (0.5)

A total of 32 isolates (16.6%) were Gram-positive, with *S. aureus* being the most frequent pathogen (46.9%), followed by coagulase-test negative staphylococci (25.0%) and then *E. faecalis* (12.5%).

In the antimicrobial susceptibility testing, *A. baumannii* isolates (93.9%) were resistant to carbapenems but susceptible to colistin (96.6%). Only 31.0% of the *A. baumannii* isolates were tigecycline-sensitive (breakpoint ≤ 0.5 μg/mL). *P. aeruginosa* isolates were susceptible to ceftazidime (65.4%), imipenem (42.3%), meropenem (57.7%), ciprofloxacin (61.5%), piperacillin/tazobactam (65.4%), and colistin (88.5%) (Table 3).

K. pneumoniae isolates were susceptible to several antimicrobials, such as ceftriaxone (22.5%), ertapenem (35.0%), imipenem (47.5%), meropenem (40.0%), ciprofloxacin (27.5%), amikacin (85.0%) and colistin (67.5%). *E. coli* isolates were resistant to ceftriaxone (75.0%) and ertapenem (36.7%) and had low susceptibility to ceftriaxone (23.1%), gentamicin (23.1%), and ciprofloxacin (7.7%).

MRSA is a cefoxitin-resistant *S. aureus* strain (66.6%), but it is universally susceptible to vancomycin and linezolid. A total of isolated *E. faecalis* were also susceptible to vancomycin. Inversely, only one of the three *E. faecium* isolates was susceptible to vancomycin.

3.2 Clinical outcomes and risk factors associated with the 30-day mortality

Among the 142 patients with bacteremia, the death rate was 62.0%, whereas the clinical cure rate was 40.1%. The univariate analysis results revealed that the statistically significant risk factors were male gender, cancer diagnosis, CRBSI, and infection resistant to meropenem (Table 4). After the multivariate analysis, only male gender (odd ratio (OR) 3.03, 95% confidence interval (CI) 1.30-7.04), CRBSI (OR 0.24, 95% CI 0.09-0.67), and carbapenem-resistant Gram-negative bacterial infection (OR 2.99, 95% CI 1.26-7.01) remained as significant predictors for death (Table 4).

Table 3. Antibiotic susceptibility rate (%) against causative pathogens found in studied patients

Antibiotics	Pathogens (isolates)						
	E. coli **(n=13)**	***K. pneumoniae*** **(n=40)**	***P. aeruginosa*** **(n=26)**	***A. baumannii*** **(n=33)**	***S. aureus*** **(n=15)**	***E. faecium*** **(n=3)**	***E. faecalis*** **(n=4)**
Penicillins							
Ampicillin	0.0	60.0	-	-	-	33.3	100.0
Piperacillin/ Tazobactam	46.2	30.0	65.4	12.1	-	-	-
Cephalosporins							
Ceftriaxone	23.1	22.5	-	3.0	-	-	-
Ceftazidime	30.8	22.5	65.4	12.1	-	-	-
Cefepime	23.1	25.0	80.8	12.1	-	-	-
Carbapenems							
Ertapenem	61.5	35.0	-	-	-	-	-
Meropenem	76.9	40.0	57.7	3.0	-	-	-
Imipenem	69.2	47.5	42.3	6.1	-	-	-
Aminoglycosides							
Amikacin	84.6	85.0	73.1	21.2	-	-	-
Gentamicin	23.1	70.0	65.4	18.2	73.3	-	-
Others							
Ciprofloxacin	7.7	27.5	61.5	15.6	40.0	33.3	50.0
Co-trimoxazole	38.5	30.0	-	27.3	-	-	-
Colistin	100.0	67.5	88.5	96.6	-	-	-
Tigecycline	100.0	100.0	-	31.0	100.0	66.7	100.0
Vancomycin	-	-	-	-	100.0	33.3	100.0
Linezolid	-	-	-	-	100.0	66.7	100.0
Cefoxitin	-	-	-	-	33.3	-	-

4. DISCUSSION

The most common causative pathogens of bacteremia in the ICU were found to be Gram-negative bacteria, including *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa*. Similarly, a previous study conducted in a provincial hospital in northeastern Thailand described the most common pathogens to be *P. aeruginosa* and *A. baumannii* (Kovitangkoon et al., 2017). One-third of *K. pneumoniae* isolates were colistin-resistant, and it was the most notable isolate in our institution. This colistin-resistant organism has been considered as a major concern in hospital outbreaks in several previous studies (Al Mayahi et al., 2019; Guducuoglu et al., 2018; and Mansour et al., 2017). We also recently reported the increasing number of *K. pneumoniae* isolates as the first rank of colistin-resistant Gram-negative bacteria in our setting (Santimaleeworagun et al., 2020). Thus, to prevent the increase in the rates of infection caused by this organism, surveillance and infection-control strategies are particularly important (Teerawattanapong et al., 2017). However, as previously described, there are a few studies on prevalence of causative pathogens among ICU-patients in Thailand, types of bacteria were possibly in different patterns depending on epidemiology, hospital environment, hospital level, and infection control strategy (Gupta et al., 2019). Thus, this issue has to be further studied.

The results of the antimicrobial susceptibility testing were compared with the 2018 data from the National Antimicrobial Resistance Surveillance Center Thailand (NARST). It is found that *A. baumannii* isolates had low susceptibility to meropenem (3%) when compared with NARST's antibiogram, which exhibited a high susceptibility rate (49.5%); however, the colistin-sensitive strains were similar (The National Antimicrobial Resistant Surveillance Thailand, 2018).

The percentage of carbapenem-susceptible *P. aeruginosa* was lower compared with that of the NARST's data; in this study, *K. pneumoniae* and *E. coli* also had lower susceptibility rates to antimicrobials compared with those in the NARST's antibiogram. We investigated the ICU setting of a single medical school hospital, whereas the average susceptibility in the NARST's antibiogram was calculated from 85 hospitals nationwide (The National Antimicrobial Resistant Surveillance Thailand, 2018). The university hospitals have a higher rate of resistant organisms compared with secondary-care hospitals (McCann et al., 2018).

The mortality rate in this study (62.0%) was higher than

that in a previous report (Khwannimit and Bhurayanontachai, 2009); the patients in this study had a median SOFA score of 8, which is suggested to be a mortality risk (Lie et al., 2018). Moreover, the high prevalence of carbapenem resistance among Gram-negative isolates in this study also contributed to the high mortality rate among the studied patients (Prawang et al., 2019). Such a high death rate was explained by the increase in the 30-day mortality rate by the carbapenem-resistant Gram-negative infection.

The findings were similar to those of the recent study by Vincent et al. (2020) that revealed that carbapenem-resistant *Klebsiella* is associated with a high risk of death. Surprisingly, CRBSI was an independent factor associated with the 30-day mortality. Only one report by Kim et al. (2019) indicated that CRBSI was identified as a decreased mortality risk factor in patients with carbapenem-resistant *A. baumannii* bacteremia. This was not supported by this study or those of others; thus, it needs further investigation.

The timing of antibiotic initiation is important in treating septic ICU patients, as reported in a previous study (Sterling et al., 2015). However, an association between early antibiotic treatment (<1 h) and mortality was not found in this study. This might be explained by the small sample size and lack of the available data due to retrospective review.

Table 4. Factors affecting the 30-day mortality in studied patients (n = 142)

Factors	Univariate analysis Odd ratio (95% CI)	*p*-value	Multivariate analysis[a] Adjusted odd ratio (95% CI)	*p*-value
Age ≥ 60 years	1.16 (0.57-2.38)	0.679		
Male	2.83 (1.41-5.71)	0.003	3.03 (1.30-7.04)	0.010
Underlying diseases				
Diabetes mellitus	0.68 (0.34-1.36)	0.27		
Hypertension	0.92 (0.46-1.84)	0.812		
Chronic kidney disease	1.20 (0.56-2.57)	0.642		
Asthma/COPD	1.24 (0.30-5.20)	1.000		
Cancer	4.92 (1.07-22.57)	0.026	5.43 (0.97-30.48)	0.055
ASCVD	1.33 (0.63-2.84)	0.455		
Principle diagnosis				
Pneumonia	0.84 (0.41-1.70)	0.619		
CRBSI	0.45 (0.20-1.02)	0.052	0.24 (0.09-0.67)	0.007
CA-UTI	0.59 (0.16-2.14)	0.505		
Intra-abdominal infection	1.94 (0.50-7.50)	0.536		
Skin and soft tissue infection	1.02 (0.24-4.47)	1.000		
SOFA score ≥5 points	1.35 (0.56-3.24)	0.498		
Carbapenem resistant-GNB	2.88 (1.32-6.30)	0.007	2.99 (1.26-7.10)	0.013
Appropriate of timing of antibiotics	1.17 (0.53-2.60)	0.703		
Appropriate of dosage regimen of antibiotics	0.66 (0.16-2.77)	0.570		
Appropriate chosen of antibiotics	0.86 (0.41-1.80)	0.686		
K. pneumoniae infection	1.05 (0.44-2.51)	0.906		
A. baumannii infection	1.88 (0.80-4.41)	0.146		
P. aeruginosa infection	0.74 (0.27-2.0)	0.548		
S. aureus infection	1.47 (0.36-5.94)	0.742		

Note: [a]All variables with *p*-value<0.1 in the univariate analysis were included in the multivariate regression model using the enter method.
ASCVD; Atherosclerotic cardiovascular disease, *CA-UTI*; Catheter-associated urinary tract infection, *COPD*; chronic obstructive pulmonary disease, *GNB*; Gram-negative bacteria, *SOFA*; sequential organ failure assessment

5. CONCLUSION

This study reported a high mortality rate of ICU patients with bacteremia in Thailand. Antibiotic choices are diminished due to antimicrobial-resistance, especially carbapenem-resistant Gram-negative bacteria. Thus, this factor must be considered to optimize treatment regimens for infected patients, particularly in ICU settings.

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