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Association between the appropriate antimicrobial therapy and clinical outcomes in patients with sepsis

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ABSTRACT

Sepsis is the leading cause of death in hospitals, but appropriate antimicrobial therapy can reduce the mortality rate and improve the clinical outcome. This prospective study analyzed the association between appropriate antimicrobial therapy and clinical outcomes in patients with sepsis or septic shock who visited at Siriraj Hospital from July to September 2016. A total of 200 patients were enrolled, 65% had sepsis and 35% had septic shock, while 48.5% were diagnosed with community-acquired infections. Appropriate antimicrobial therapy, in terms of the four-criteria of, (i) administration of antimicrobials within 1 h post-diagnosis, (ii) empirical treatment, (iii) loading dose, and (iv) dose adjustment in renal failure, was significantly associated with a resolved clinical outcome at 7 days post-diagnosis (dpd; $P = 0.044$) and decreased mortality rate at 28 dpd ($P = 0.034$). Completion all six-criteria of appropriate antimicrobial therapy (the above four plus (v) antimicrobial adjustment to match the culture results and (vi) selection of the correct solvent for administration) were significantly associated with a better clinical outcome at 7 dpd ($P = 0.018$) and decreased mortality rate at 28 dpd ($P = 0.02$). Sepsis patients who received appropriate antimicrobial therapy showed an improved clinical outcome and increased the survival rate.

Keywords: Antimicrobial, clinical outcome, emergency room, sepsis, septic shock

INTRODUCTION

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Organ dysfunction can be identified as an acute change in the total sequential organ failure assessment (SOFA) score of ≥2.[1] Nowadays, the SOFA score is the diagnostic tool used in clinical criteria to assess and evaluate organ dysfunction that has an associated risk of mortality.

Sepsis is one of the globally important public health problems and is a continuum of a disease process that can progress from initial localized infection to severe sepsis and septic shock, where severe sepsis and septic shock have a poor prognosis and a high mortality rate of approximately 34.3%[2] and 72%,[3] respectively. Moreover, sepsis can lead to prolonged hospitalization, where the annual cost of sepsis care has been estimated about $17 billion in the United States.[4]

The most important risk factors associated with sepsis are the underlying diseases, which include chronic lung disease, diabetes mellitus, chronic kidney disease, and myocardial infarction.[5,6] Moreover, patient's factors, such as alcohol drinking, smoking, neutropenia, and indwelling urinary catheter, are also associated with sepsis.[7]

Optimization of the management of sepsis, severe sepsis and septic shock, including the urgent and standard

treatment, has been associated with a lower mortality rate.[8] The appropriate antimicrobial treatment in terms of the empirical therapy[9] depends on the suspected site of infection, loading dose for the first dose,[10] adjustment of the dosage of antimicrobials depending on renal function, choosing the antimicrobial treatment with respect to the local microbial-susceptibility patterns, and time to administration of antimicrobials within 1 h post-diagnosis (1 hpd).[11]

However, no research has been performed to explore how these criteria are associated with clinical outcomes. The aim of this study was to describe the association between the appropriate antimicrobial therapy based on set criteria and the clinical outcomes in patients with sepsis.

MATERIALS AND METHODS

Study Design and Population

A single center, observational prospective study was conducted from July 1, 2016, to September 30, 2016. We enrolled the patients with sepsis or septic shock who were administered to the emergency room, Siriraj Hospital which is a tertiary care hospital with 2221 beds in Bangkok, Thailand. The study population consisted of 200 adult patients (aged >18-year-old) who were diagnosed with sepsis or septic shock and had received antimicrobial treatment at the emergency room. Exclusion criteria were being treated with antimicrobial therapy from other hospitals or being referred to other hospitals with sepsis symptoms, as well as end-stage underlying diseases receiving palliative care. This study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University. The ethics number was 356/2016 (EC3).

Data Collection and Definitions

Medical records of patients were reviewed. We collected demographic characteristics, underlying diseases, diagnosis, types and sources of infection, microbiological data, complications, laboratory results, clinical outcomes, and 28-day post-diagnosis (dpd) mortality rate data. Organ dysfunction was assessed using the SOFA score, where organ failure was defined as a SOFA score of more than three in each system. The definition of the four-criterion appropriate antimicrobial therapy (4-CAAT) consisted of (i) empirical treatment, (ii) loading level of the first dose, (iii) adjustment of the dose in renal failure, and (iv) administration of antimicrobials within 1 h. Similarly, the definition of the 6-CAAT included the same four criteria plus additionally the (v) antimicrobial adjustment according to the culture results and the (vi) correct choice of the solvent for administration. Resolved sepsis was defined as no abnormalities of the systemic inflammatory response syndrome (SIRS) for at least three criteria. As soon as, the patients were diagnosed with sepsis, severe sepsis or septic shock and received the initial antimicrobial treatment, they were assessed for appropriate antimicrobial treatment using the 4-CAAT approach and then assessed using the 6-CAAT at 72 hpd [Figure 1]. Clinical outcomes assessment at 72 hpd and 7 dpd were resolved sepsis or worse than the first diagnosis. Clinical outcomes assessment at 28 dpd was mortality rate.

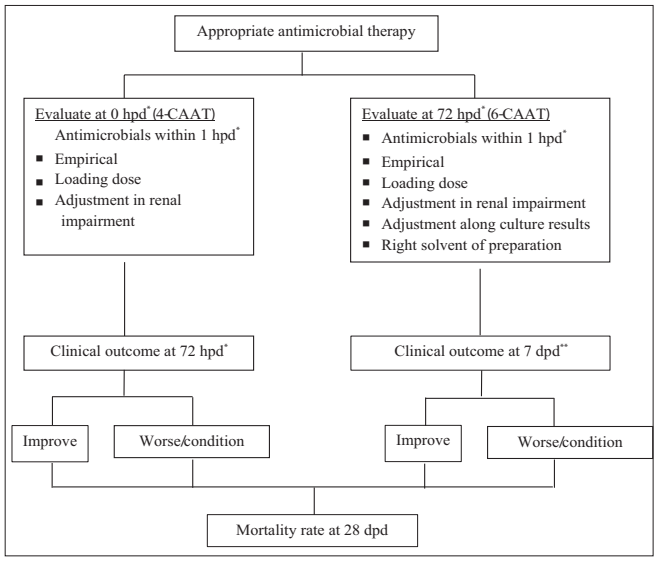

Figure 1: Schematic flow chart of this study

*hpd: Hour post-diagnosis, **dpd: Day post-diagnosis

Statistical Analyses

Statistical analyses were performed using SPSS version 22.0 (SPSS. Co., Ltd, Bangkok, Thailand). For the purposes of this article, the data were performed using the Chi-square test, Mann–Whitney U-test. Univariate and multivariate logistic regression analysis was used to determine risk factors for infection, clinical outcomes at 72-hpd and 28-day mortality.

RESULTS

A total of 200 patients with sepsis or septic shock were enrolled in this study. The mean age of the patients was 69.39 years with an almost equal gender ratio (49.5% male). Almost all of the patients resided in a family dwelling (95.5%), whereas 4.5% resided in a nursing home. The most common underlying factor was hypertension (55%) followed by diabetes mellitus (33.5%) and neurological disease (31%). During the 90 days before sepsis, 49.5% of the number of patients receiving any antimicrobial therapy with monotherapy or combination therapy. The most of prior monotherapy antimicrobials were beta-lactam antimicrobials. 130 patients (65%) presented with sepsis, of which most were classified with community-acquired infection (48.5%). The sources of infection were urinary (37.5%), respiratory (34%), and intra-abdominal (22%). The most frequent complication of sepsis was acute renal disease defined as a rapid fall in the rate of glomerular filtration, which manifests clinically as an abrupt and sustained increase in the serum levels of urea and creatinine[12] (30%) followed by hyponatremia (14%) and anemia (12.5%). The mean ± SD of SOFA score was 4.5 ± 2.92, while the mean of quick SOFA (qSOFA) score was 1.64 ± 0.85. Organ dysfunctions were found in 14.5% of the patients with sepsis, with acute kidney injury being the most common organ dysfunction. Most of patients received antimicrobial therapy with meropenem (29.5%) followed

Table 1: Demographic data of patients (n=200)

Variable	*n* (%)
General demographics	
Age (years) (mean+SD)	69.39±16.27
Male	99 (49.5)
Residence	
House	191 (95.5)
Nursing home	9 (4.5)
Underlying disease	
Hypertension	110 (55)
Diabetes mellitus	67 (33.5)
Neurological disease	62 (31)
Solid tumor	52 (26)
Renal disease	48 (24)
Dyslipidemia	48 (24)
Cardiovascular disease	47 (23.5)
Prior antimicrobials within 90 days	
No history to received prior antimicrobials within 90 days	101 (50.5)
History to received prior antimicrobials within 90 days	99 (49.5)
Monotherapy (n=42)	
Beta-lactams*	27 (13.5)
Fluoroquinolones	13 (6.5)
Macrolides	1 (0.5)
Sulfonamides	1 (0.5)
Combination therapy (n=57)	
2 drugs combination	
2 Beta-lactams	13 (6.5)
*Beta-lactams+Fluoroquinolones	9 (4.5)
*Beta-lactams+Other classes**	6 (3)
*Aminoglycosides+Glycopeptides	1 (0.5)
>3 drugs combination	
*2 Beta-lactams+1 or 2 other classes**	16 (8)
*Beta-lactams+2 or 3 Other classes**	6 (3)
3 Beta-lactams	5 (2.5)
*3 Beta-lactams+other classes**	1 (0.5)
Type of sepsis	
Sepsis	130 (65)
Septic shock	70 (35)
Type of infection***	
Community-acquired	97 (48.5)
Healthcare-associated	86 (43)
Hospital-acquired	17 (8.5)
Source of infection	
Urinary tract	75 (7.5)
Respiratory	68 (34)
Intra-abdomen	44 (22)
Bloodstream	18 (9)
Central nervous system	9 (4.5)
Skin and subcutaneous	3 (1.5)
Other	3 (1.5)
Unknown	5 (2.5)
Complication	
Acute renal disease	60 (30)
Hyponatremia	28 (14)
Anemia	25 (12.5)
Metabolic acidosis	22 (11)
Hypokalemia	19 (9.5)
Severity parameter (mean±SD)	
SOFA score	4.5±2.92
qSOFA score	1.64±0.85
Organ dysfunction with SOFA score	29 (14.5)
Antimicrobial therapy	
Monotherapy (n=149)	
Meropenem	59 (29.5)
Ceftriaxone	41 (20.5)
Piperacillin/tazobactam	38 (19)
Imipenem/cilastatin	5 (2.5)
Ciprofloxacin	2 (1)
Ampicillin	1 (0.5)
Ampicillin/sulbactam	1 (0.5)
Ceftazidime	1 (0.5)
Levofloxacin	1 (0.5)
Combination therapy (n=51)	
Meropenem+vancomycin	12 (6)
Ceftriaxone+clindamycin	10 (5)
Ceftriaxone+azithromycin	9 (4.5)
Ceftriaxone+metronidazole	8 (4)
Ceftriaxone+ampicillin	3 (1.5)
Ceftazidime+vancomycin	2 (1)
Ceftriaxone+amikacin	2 (1)
Ampicillin/sulbactam+metronidazole	1 (0.5)
Ceftriaxone+levofloxacin	1 (0.5)
Meropenem+amikacin	1 (0.5)
Piperacillin/tazobactam+azithromycin	1 (0.5)
Piperacillin/tazobactam+vancomycin	1 (0.5)

(Contd...)

*Beta-lactams: Penicillins, cephalosporins, carbapenems, **Other classes: Fluoroquinolones, glycopeptides, macrolides, aminoglycosides, nitroimidazole, sulfonamides, lincosamides, polymyxin B, phosphonic acid derivatives. ***Type of infection: Community-acquired is defined as infection within 48 h of hospital admission in patients without previous contact with healthcare service. Health-care-associated is defined as infection within 48 h of hospital admission in patients that had previous contact with health-care service within 1 year. Hospital-acquired is a localized or systemic condition that results from an adverse reaction to the presence of an infectious agent(s) or its toxin(s) and present 48 h or more after hospital admission and not incubating at hospital admission time.[13] SOFA: Sequential organ failure assessment

by ceftriaxone (20.5%) and piperacillin/tazobactam (19%), respectively [Table 1].

Microorganisms were identified from 171 different specimens. The most common associated pathogens were *Escherichia coli* (37.4%), methicillin-sensitive *Staphylococcus aureus* (11.7%), and *Klebsiella pneumoniae* (11.7%), and these three organisms were also the most common pathogens found in blood specimens [Table 2].

Nearly one-third of *E. coli* resisted to ceftriaxone and cefuroxime, and also a high number of *K. pneumoniae* resisted to cefuroxime (20%) and ceftriaxone (15%) [Table 3].

Among the 200 patients, 23 and 15 patients died within 72 hpd and 7 dpd, respectively. Comparing the appropriate antimicrobial therapy and clinical outcomes, the administration under the 4-CAAT tended to result in lower clinical outcomes of the worse or unchanged condition at 72 hpd than with an inappropriate antimicrobial therapy (36.1% vs. 63.9%; P = 0.055). In addition, patients treated under the 4-CAAT showed a significantly decreased level of worse or condition unchanged clinical outcomes at 7 dpd, compared to those with an inappropriate antimicrobial therapy (34.9% vs. 65.1%, P = 0.044), and a significantly decreased associated mortality rate (32.3% vs. 67.7%; P =0.034) at 28 dpd. The patients who were initiated on their antimicrobial treatment within 1 hpd had a significantly greater level of resolved clinical outcomes at 72 hpd than those that were not (58.6% vs. 41.4%, P = 0.021). Moreover, there were significant relationships between the 6-CAAT and the clinical outcome, where the worse or condition unchanged clinical outcome of patients was much lower at 7 dpd in those patients treated within the 6-CAAT than those who were not in the 6-CAAT (22.1% vs. 77.9%, P = 0.018). At 28 dpd, patients treated under the 6-CAAT were significantly associated with a low mortality rate (20% vs. 80%, P = 0.02) [Table 4].

Univariate and multivariate analysis for the risk factors associated with the clinical outcomes at 72 hpd is shown in

Table 2: Microorganisms isolated from samples of patients with sepsis and acute sepsis

Causative microorganism	*n* (%)				
	Blood	Urine	Sputum	Others	Total
Escherichia coli	35 (39.8)	21 (47.7)	-	8 (42)	64 (37.4)
Methicillin-sensitive *Staphylococcus aureus*	15 (17.1)	-	4 (20)	1 (5.3)	20 (11.7)
Klebsiella pneumoniae	11 (12.5)	6 (13.6)	2 (10)	1 (5.3)	20 (11.7)
Pseudomonas aeruginosa	3 (3.4)	2 (4.5)	8 (40)	1 (5.3)	14 (8.1)
Proteus mirabilis	5 (5.8)	5 (11.4)	-	1 (5.3)	11 (6.4)
Enterococcus spp.	2 (2.3)	7 (15.9)	-	-	9 (5.3)
Aeromonas veronii	1 (1.1)	-	1 (5)	2 (10.5)	4 (2.3)
Plesiomonas shigelloides	-	-	-	4 (21)	4 (2.3)
Enterobacter spp.	3 (3.4)	-	-	-	3 (1.8)
Streptococcus pyogenes	3 (3.4)	-	-	-	3 (1.8)
Acinetobacter baumannii	1 (1.1)	-	2 (10)	-	3 (1.8)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	1 (1.1)	-	2 (10)	-	3 (1.8)
Streptococcus Group F	2 (2.3)	-	-	-	2 (1.2)
Streptococcus Group G	1 (1.1)	-	-	1 (5.3)	2 (1.2)
Listeria spp.	2 (2.3)	-	-	-	2 (1.2)
Streptococcus pasteurianus	1 (1.1)	1 (2.3)	-	-	2 (1.2)
Burkholderia cepacia	-	-	1 (5)	-	1 (0.6)
Citrobacter spp.	-	1 (2.3)	-	-	1 (0.6)
Salmonella group C	1 (1.1)	-	-	-	1 (0.6)
Streptococcus agalactiae	-	1 (2.3)	-	-	1 (0.6)
Corynebacterium spp.	1 (1.1)	-	-	-	1 (0.6)
Total	88 (100)	44 (100)	20 (100)	19 (100)	171 (100)

Table 3: Cephalosporin nonsusceptible strains for *Escherichia coli* and *Klebsiella pneumoniae*

Causative microorganism	Total	Nonsusceptible					
		Cefepime	Cefotaxime	Cefoxitin	Ceftazidime	Ceftriaxone	Cefuroxime
Escherichia coli	64 (37.4)	11 (17.2)	3 (4.7)	1 (1.6)	2 (3.1)	20 (31.2)	20 (31.2)
Klebsiella pneumoniae	20 (11.7)	0	1 (5)	1 (5)	1 (5)	3 (15)	4 (20)

Tables 5 and 6, respectively. From the univariate analysis, the significant risk factors were a source of respiratory infection and events or complication, including aspiration pneumonia and hepatic encephalopathy.

The significant risk factors from the multivariate analysis were associated with the clinical outcomes at 72 hpd were a source of respiratory infection and hepatic encephalopathy of complication [Table 6].

The overall mortality rate of patients with sepsis was 32.5%. Univariate and multivariate analysis for the risk factors associated with the 28-dpd mortality is shown in Tables 6 and 7, respectively. From the univariate analysis, the significant underlying disease risk factor was a hepatic disease. Assessment of the SOFA score indicated that organ abnormalities of the central nervous and hepatic systems and organ failure (SOFA score >3 in each organ) of the renal and central nervous systems were significant. Patients with complications of metabolic acidosis and hepatic encephalopathy had a significantly higher mortality risk than patients without these complications. There was an increased significant risk factor among patients who received inappropriate antimicrobial therapy, with the failure to adjust the treatment following renal impairment, or administration of antimicrobial therapy outside the 4-CAAT or 6-CAAT [Table 7].

Table 4: The association between the appropriate antimicrobials and clinical outcome at 72 hpd and 7 dpd

Treatment	Clinical outcomes at; *n* (%)								
	72 hpd			7 dpd			28 dpd		
	Resolve	Worse or condition unchanged	*P*-value	Resolve	Worse or condition unchanged	*P*-value	Survive	Death	*P*-value
4-CAAT									
Antimicrobials within 1 hpd									
Appropriate	74 (65.5)	51 (58.6)	0.021						
Inappropriate	39 (34.5)	36 (41.4)							
Empirical antimicrobial									
Appropriate	93 (82.3)	77 (88.5)	0.176						
Inappropriate	20 (17.7)	10 (11.5)							
Loading dose									
Appropriate	103 (91.2)	80 (92)	0.980						
Inappropriate	10 (8.8)	7 (8)							
Adjustment in renal impairment									
Appropriate	46 (40.7)	42 (48.3)	0.376						
Inappropriate	15 (13.3)	19 (21.8)							
Normal renal function	52 (46)	26 (29.9)							
Complete with all of 4-CAAT									
Appropriate	51 (49.5)	35 (36.1)	0.055	56 (49.1)	30 (34.9)	0.044	65 (48.1)	21 (32.3)	0.034
Inappropriate	52 (50.5)	62 (63.9)		58 (50.9)	56 (65.1)		70 (51.9)	44 (67.7)	
6-CAAT									
Adjustment along culture results (n=161)									
Appropriate	-	-	-	97 (97)	58 (95.1)	0.818			
Inappropriate				3 (3)	3 (4.9)				
Right solvent and administration (n=161)									
Appropriate	-	-	-	91 (91)	53 (86.9)	0.446			
Inappropriate				9 (9)	8 (13.1)				
Complete with all 6-CAAT	-	-	-						
Appropriate				43 (37.7)	19 (22.1)	0.018	49 (36.3)	13 (20)	0.020
Inappropriate				71 (62.3)	67 (77.9)		86 (63.7)	52 (80)	

72 hpd: 72 h post-diagnosis, 7 dpd: 7 days post-diagnosis

Table 5: Univariate analysis of factors associated with the clinical outcomes at 72 h post-diagnosis

Factor	Clinical outcomes at 72 hpd; *n* (%)	OR (95% CI)	*P*-value
Underlying disease			
Renal disease	48 (24)	0.57 (0.30–1.10)	0.089
Liver disease	24 (12)	0.51 (0.22–1.20)	0.123
Hematologic disease	19 (9.5)	2.32 (0.81–6.71)	0.121
Benign prostatic hyperplasia	9 (4.5)	2.81 (0.57–13.86)	0.205
Osteoporosis	7 (3.5)	0.29 (0.06–1.56)	0.151
Source of infection			
Respiratory	68 (34)	0.35 (0.19–0.64)	<0.001
Events and complication			
Urinary tract infection	41 (20.5)	1.64 (0.8–3.35)	0.178
Metabolic acidosis	22 (11)	0.49 (0.2–1.21)	0.123
Hypokalemia	19 (9.5)	2.32 (0.8-6.71)	0.121
Hepatic encephalopathy	14 (7)	0.28 (0.09–0.93)	0.038
Aspiration pneumonia	12 (6)	0.24 (0.06–0.90)	0.035
Hypernatremia	8 (4)	0.24 (0.05–1.24)	0.088
Upper gastrointestinal bleeding	5 (2.5)	0.19 (0.02–1.69)	0.135
Hypoglycemia	5 (2.5)	0.19 (0.02–1.69)	0.135
Inappropriate antimicrobials therapy (at least one choice inappropriate)			
4-CAAT	85 (42.5)	1.65 (0.93–2.93)	0.086

Table 6: Multivariate analysis of factors associated with the clinical outcomes at 72 hpd

Factors	Clinical outcomes at 72 hpd; *n* (%)	OR (95% CI)	*P*-value
Source of infection			
Respiratory	68 (34)	0.36 (0.19–0.67)	0.001
Events and complication			
Hepatic encephalopathy	14 (7)	0.22 (0.06–0.74)	0.014
Aspiration pneumonia	12 (6)	0.31 (0.08–1.24)	0.098

72 hpd: 72 h post-diagnosis

Multivariate analysis of the risk factors that were significantly associated with the 28-dpd mortality risk revealed that respiratory and intra-abdominal infections were key sources, while renal and central nervous system failures were the main associated organ failure risks. The 28-dpd risk-associated complications were electrolyte imbalance, consisting of hyperkalemia, and hypernatremia. Evaluation of the patients' SOFA scores showed that central nervous and hepatic system abnormalities were associated with the 28-dpd mortality, which is the same as in the univariate analysis. There was a significant relationship between the inappropriate adjustment of antimicrobial therapy and 28-dpd mortality [Table 8].

DISCUSSION

This is a prospective study of antimicrobial treatment administered under the 4- and 6-CAAT in patients with sepsis, which is different to previous studies that examined treatment under the administration of antimicrobials within 1 h, empirical treatment, loading level of the first dose or adjustment of the dose in renal failure.[14] The most common underlying diseases were hypertension (55%) and diabetes mellitus (33.5%). These data are compatible with the prospective study in a tertiary and university hospital by Worapratya *et al*.[15] Acute renal failure was previously found to be the principal complication risk factor in patients with septic shock,[16] where acute renal failure with septic shock increased the mortality rate three-fold in both genders compared to patients with normal renal function. However, complications associated with the 28-dpd mortality risk in this study, as analyzed by multivariate logistic regression, showed instead hyperkalemia and hypernatremia as the risks. Recent research has shown that increased potassium levels of 6–6.5 and >6.5 mmol/L were associated with an increased mortality rate of 2.8- and three-fold, respectively.[17] Patients with sepsis develop hypernatremia due to abnormal serum sodium levels due to the increased reuptake of sodium leading to an increased serum concentration of sodium.[18]

In this study, sepsis was a more common diagnosis on administration than septic shock, which is different from a recent study in the same hospital,[2] where the septic shock was higher than sepsis. This is because this hospital now treats patients with antimicrobials as directed by the Siriraj Hospital's clinical practice guideline, which improves the

Table 7: Univariate analysis of factors associated with the 28-dpd mortality

Factor	28-dpd mortality (%)	OR (95% CI)	*P*-value
Gender			
Male	35 (17.5)	0.77 (0.43–1.40)	0.394
Culture results	42 (21)	1.51 (0.82–2.73)	0.190
Gram negative bacteria			
Pseudomonas aeruginosa	7 (3.5)	2.60 (0.84–8.06)	0.099
Gram-positive bacteria			
Enterococcus spp.	5 (2.5)	2.73 (0.71–10.53)	0.145
Underlying disease			
Hepatic disease	13 (6.5)	2.82 (1.19–6.70)	0.019
Diabetes mellitus	26 (13)	1.53 (0.83–2.83)	0.178
More than one source of infection	11 (5.5)	1.76 (0.75–4.13)	0.193
Source of infection			
Respiratory	28 (14)	1.80 (0.97–3.32)	0.061
Urinary tract	20 (10)	0.65 (0.35–1.21)	0.174
Intra-abdominal	18 (9)	1.61 (0.80–3.21)	0.180
SOFA score			
Central nervous system (SOFA >0)	50 (25)	3.10 (1.59–6.04)	0.023
Hepatic system (SOFA >0)	23 (11.5)	2.26 (1.12–4.55)	0.001
Organ failure			
(SOFA >3 in each organ)	19 (9.5)	5.16 (2.24–11.92)	<0.001
Type of organ failure			
Renal system	12 (6)	3.59 (1.39–9.30)	0.008
Central nervous system	9 (4.5)	21.54 (2.67–174.01)	0.004
qSOFA score	65 (32.5)	1.99 (1.36–2.92)	<0.001
Events and complication			
Metabolic acidosis	13 (6.5)	3.50 (1.41–8.69)	0.007
Hepatic encephalopathy	10 (5)	5.96 (1.79–19.80)	0.004
Hyperkalemia	7 (3.5)	2.60 (0.84–8.06)	0.099
Hypernatremia	5 (2.5)	3.67 (0.85–15.84)	0.082
Inappropriate antimicrobials therapy (at least one choice inappropriate)			
Adjustment in renal impairment	29 (14.5)	2.27 (1.02–5.00)	0.016
4-CAAT	44 (22)	1.96 (1.04–3.57)	0.035
6-CAAT	52 (26)	2.27 (1.12–4.55)	0.021

CI: Confidence interval, CAAT: Criterion appropriate antimicrobial therapy, SOFA: Sequential organ failure assessment, QSOFA: Quick SOFA, 28-dpd: 28 days post-diagnosis

management of infected patients with antimicrobial therapy and decreases the severity of the disease. In addition, in this study, patients had acquired their sepsis from the community almost as frequently as health-care-associated, in contrast to a recent study that reported hospital- and health-care-associated sepsis as the most prevalent followed by community-acquired. The lower hospital-acquired sepsis in this study reflects the quick diagnosis and improved management of patients now in practice at this hospital to increase the quality of life and survival rate in patients with sepsis.

Our study found that Gram-negative bacteria were a causative pathogen of sepsis more frequently than Gram-positive bacteria, which was the same as in other studies in Thailand. Gram-negative bacteria were associated with a high mortality rate in septic patients. In our setting, a high number of *E. coli* and *K. pneumoniae* resisted to third-generation cephalosporin. As a result, carbapenem and piperacillin-tazobactam were considered preferred empiric therapy for serious *Enterobacteriaceae* infections such as sepsis or septic shock patients in tertiary care hospital.

Following analysis of a retrospective cohort, it was reported that initiation of appropriate antimicrobial therapy within 1 hpd was associated with a resolved clinical outcome at 72 hpd and a significantly decreased subsequent mortality

Table 8: Multivariate analysis of factors associated with 28-dpd mortality

Factors	28-dpd mortality (%)	OR (95% CI)	*P*-value
Culture result	42 (21)	1.51 (0.70–2.28)	0.295
Gram-negative bacteria			
Pseudomonas aeruginosa	7 (3.5)	2.60 (0.84–8.06)	0.099
Gram-positive bacteria			
Enterococcus spp.	5 (2.5)	2.65 (0.68–10.35)	0.161
Underlying disease			
Hepatic disease	13 (6.5)	1.20 (0.35–4.10)	0.767
Diabetes mellitus	26 (13)	1.50 (0.60–3.73)	0.382
Source of infection more than one	11 (5.5)	1.57 (0.65–3.81)	0.314
Source of infection			
Respiratory	28 (14)	2.28 (1.67–4.45)	0.016
Urinary tract	20 (10)	0.99 (0.47–2.07)	0.972
Intra-abdominal	18 (9)	2.21 (1.04-4.69)	0.039
SOFA score			
Central nervous system (SOFA >0)	50 (25)	1.72 (1.26–2.34)	0.001
Hepatic system (SOFA >0)	23 (11.5)	1.70 (1.17–2.48)	0.006
Organ system failure	19 (9.5)	1.26 (0.09–17.66)	0.862
Type of organ failure			
Renal system	12 (6)	3.66 (1.20–11.14)	0.022
Central nervous system	9 (4.5)	12.15 (1.40–105.29)	0.023
Complication			
Metabolic acidosis	13 (6.5)	2.15 (0.62-7.50)	0.230
Hepatic encephalopathy	10 (5)	1.76 (0.32–9.60)	0.512
Hyperkalemia	7 (3.5)	5.10 (1.23–21.20)	0.025
Hypernatremia	5 (2.5)	9.32 (1.46–59.50)	0.018
Inappropriate antimicrobials therapy (at least 1 choice inappropriate)			
Adjustment in renal impairment	29 (14.5)	2.28 (0.11–0.63)	0.049
4-CAAT	44 (22)	1.21 (0.45–3.26)	0.809
6-CAAT	52 (26)	2.08 (0.72–5.88)	0.211

CI: Confidence interval, CAAT: Criterion appropriate antimicrobial therapy, SOFA: Sequential organ failure assessment, 28-dpd: 28 days post-diagnosis

rate.[11] Furthermore, appropriate antimicrobial therapy under 4-CAAT significantly decreased the worse or unchanged condition clinical outcome at 7 dpd and decreased the mortality rate at 28 dpd. Initiation of the appropriate antimicrobial therapy under 6-CAAT was associated with a significantly decreased worse or unchanged condition clinical outcome at 7 dpd and decreased the mortality rate at 28 dpd. Thus, the appropriate antimicrobial therapy under the 4-CAAT led to a good prognosis, safe clinical outcome and decreased mortality rate, while under the 6-CAAT were similar clinical outcomes as under 4-CAAT plus a decreased adverse drug reaction from medication error and a more rational antimicrobial use.

The SOFA score is an assessment tool to predict the mortality in groups of patients with sepsis and is not different from the acute physiology and chronic health evaluation II scoring system in terms of specificity and accuracy rate for predicting the mortality outcome of critically ill patients.[19] The SOFA of the mortality rate in patients with sepsis or septic shock in this study revealed that central nervous system abnormalities (SOFA >0), hepatic system abnormalities (SOFA >0), and organ failure (SOFA >3 in each organ) were associated with the 28-dpd mortality. Accordingly, the SOFA score was suitable for predicting the prognosis of patients with sepsis.

The qSOFA score provides simple bedside criteria to identify adult patients with suspected infection. The results of this study indicated that qSOFA was associated with 28-dpd mortality. Nevertheless, a previous comparison of qSOFA and SOFA for predicting mortality, using an area under the receiver operator curve (AUROC), concluded that qSOFA was lower than SOFA (AUROC of 0.666 vs. 0.729).[20] Moreover, a comparison of qSOFA with SIRS criteria revealed that qSOFA was essentially the same as SIRS (AUROC of 0.66 vs. 0.65).[21,22] Accordingly, the SOFA score was better than the qSOFA score for predicting hospital mortality among patients with suspected sepsis, whereas qSOFA and SIRS were similar.

The principal limitation of our study is that it involved only subjects from a single center, and so limits the applicability to broader geographic interpretation. We enrolled patients with sepsis, severe sepsis or septic shock that received initial treatment at the emergency room, where most patients had comorbidities that might lead to increased mortality rates.

CONCLUSION

The implementation of treatment under the 6-CAAT was associated with a decreased mortality rate, decreased medication error, and increased rational antimicrobial use. Risk factors of an underlying disease and complications were associated with an increased hospital mortality rate. Consequently, patients with sepsis should be closely monitored and treated with appropriate antimicrobial therapy to increase the effectiveness of treatment and the safety of clinical outcomes.

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CONFLICTS OF INTEREST

All authors declared no conflicts of interest.

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