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Clinical manifestations, causative pathogens and treatment outcomes of patients with bacterial meningitis at a general hospital in eastern Thailand

Natenoi Chalee[1], Wichai Santimaleeworagun[2,3], Kawin Duangmee[2] and Juthathip Suphanklang[2,4]*

[1] Department of Medicine, Sa Kaeo Crown Prince Hospital, Sa Kaeo 27000, Thailand
[2] Department of Pharmacy, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand
[3] Antibiotic Optimization and Patient Care Project by Pharmaceutical Initiative for Resistant Bacteria and Infectious Diseases Working Group (PIRBIG)
[4] Silpakorn University Research and development group in Pharmaceutical care (SURP)

***Corresponding author**: Juthathip Suphanklang suphanklang_j@su.ac.th*

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ABSTRACT

Bacterial meningitis is a severe infection with significant morbidity and mortality. This study aimed to analyze causative pathogens, empirical therapy, antibiotic susceptibility, neurological sequelae and mortality rate in patients with bacterial meningitis. The study design was a retrospective, descriptive study. Patient eligibility criteria were the following: individuals diagnosed with bacterial meningitis according to the International Classification of Diseases (ICD)-10 codes from January 2014 to December 2017 at Sa Kaeo Crown Prince Hospital. A total of 99 patients with bacterial meningitis were identified, and 29% exhibited the classic triad (fever, drowsiness and neck stiffness). The causative pathogens were detected from blood or cerebrospinal fluid (CSF) in 40% and 6.1% of patients, respectively. The most common pathogens were *Streptococcus* spp. (10 patients), followed by *Streptococcus suis* (7 patients) and group D streptococcus (7 patients). Empirical therapy with monotherapy was mainly either ceftriaxone or cefotaxime (69.7%); however, the cephalosporin-resistant strain was 20.8%. Clinical outcomes included the 14-day mortality rate and neurological sequelae in 3% and 26.3% of patients, respectively. Pneumonia, septic shock and low CSF glucose concentration were significantly associated with unfavorable outcomes. Consequently, the most causative pathogen was *Streptococcus* spp., which was the third-generation cephalosporin-resistant strain. Third-generation cephalosporins plus vancomycin should be considered as an empirical therapy regimen.

Keywords: bacterial meningitis; *Streptococcus*; monotherapy; combination; neurological sequelae

1. INTRODUCTION

Bacterial meningitis is a low-incidence infectious disease (Fitch and van de Beek, 2007; van de Beek et al., 2004); however, it has a mortality rate as high as 15% to 20% (Khwannimit et al., 2004; van de Beek et al., 2004). Urgent and precise diagnosis is therefore warranted. The causative pathogens involved are different depending on

the setting. For example, *Streptococcus pneumoniae, Neisseria meningitides* and *Listeria monocytogenes* are common pathogens in community-acquired bacterial meningitis (CABM) (Chotmongkol and Techoruangwiwat, 2000; Khwannimit et al., 2004). In Thailand, the incidence of acute bacterial meningitis was examined at King Chulalongkorn Memorial Hospital. The most common causative pathogen was *S. pneumoniae* (30%), followed by *S. agalactiae* (28%) and *S. suis* (15%) (Opartpunyasarn and Suwanpimolkul, 2019). Conversely, Gram-negative bacilli, including *Acinetobacter baumann*ii and *Pseudomonas aeruginosa*, and Gram-positive cocci, including coagulase-negative staphylococci and *Staphylococcus aureus*, are common pathogens in nosocomial meningitis (NM) and are predisposing factors within 2 weeks of neurosurgery (Khwannimit et al., 2004; Kurtaran et al., 2018). Risk factors that increased the mortality rate in patients with bacterial meningitis were diabetes mellitus, cirrhosis, immunosuppressive agents (corticosteroids or immunosuppressants), head trauma, otitis media, cerebrospinal fluid (CSF) leakage and sinusitis (Chotmongkol and Techoruangwiwat, 2000; Fuentes-Antras et al., 2019). In addition, human immunodeficiency virus (HIV)-associated bacterial meningitis is associated with higher mortality, especially in pneumococcal meningitis (Tenforde et al., 2019). Therefore, the identification of risk factors is an important strategy to prevent unfavorable clinical outcomes in patients with bacterial meningitis.

The choice of antibiotics for empirical therapy depends on the causative pathogens, age and comorbidities, but microbiological culture combined with either CSF or blood and antibiotic susceptibility tests are nonetheless essential for documenting therapy (Tunkel et al., 2004; van de Beek et al., 2016). Data from King Chulalongkorn Memorial Hospital was published stating that only 35% of isolated *Streptococcus pneumoniae* were penicillin-sensitive (Dejsirilert et al., 2009), therefore implying that treatment failure might occur. Moreover, the mortality rate has been rising from NM because of resistant pathogens, such as methicillin-resistant *Staphylococcus aureus*, methicillin-resistant *Staphylococcus epidermidis* (Kurtaran et al., 2018) and multi-drug-resistant *Acinetobacter baumannii* (MDR-AB) (Kourbeti et al., 2015; Kurtaran et al., 2018). Therefore, combination therapy is required (Chusri et al., 2018). Despite the absence of drug-resistant strains in the early phase of neonatal meningitis, reports published in the late phase (Chang et al., 2003), necessitated the use of combination therapy (Satar et al., 2018). As previously known, third-generation cephalosporins remained the first-line agents for CABM. However, vancomycin might serve as an adjunctive drug to cephalosporins as an empirical therapy (Tunkel et al., 2004). Furthermore, the clinical study of vancomycin has been limited in Thailand.

During the pathogenesis of bacterial meningitis, the invasive pathogens directly infect the subarachnoid space and brain parenchyma resulting in severe inflammation as a consequence of cytokine release (Tauber et al., 1985; Mook-Kanamori et al., 2011). CABM from some pathogens can result in neurological sequelae caused by a severe inflammatory response (De Gans et al., 2002; Brouwer et al., 2015). Accordingly, it is important to recognise that neurological sequelae of bacterial meningitis can be improved with modulation of the inflammatory response, e.g., with dexamethasone (Tunkel et al., 2004; Tauber et al., 1985).

The purpose of this study was to analyze the incidence of bacterial meningitis, antibiotic susceptibility, clinical outcomes, implementation of corticosteroids use and the factors associated with unfavorable clinical outcomes. These results may serve to guide healthcare professionals as to the appropriate management of, and empirical therapy regimens in, patients with bacterial meningitis.

2. MATERIALS AND METHODS

We performed a descriptive, retrospective review of inpatient medical records of patients with bacterial meningitis from 1 January 2014, through 31 December 2017, at Sa Kaeo Crown Prince Hospital, a 388-bed general hospital.

Inclusion criteria were as follows. Patients diagnosed with bacterial meningitis according to the International Classification of Diseases (ICD)-10 codes (G00 to G00.9) with clinical symptoms of bacterial meningitis such as fever (body temperature >38°C), neck stiffness, drowsiness, headache (van de Beek et al., 2004) and one of the following criteria (Tunkel et al., 2004): (1) Positive bacterial CSF culture, (2) Positive bacterial blood culture, or (3) Abnormal CSF profiles (low glucose concentration [glucose level <40 mg/dL or CSF-to-serum glucose ratio <0.4], increased polymorphonuclear neutrophils (PMNs) [80%-99%], or absolute white cell count in the CSF [1000-5000 cells/mm^3] or high protein concentration [>100 mg/dL]). Exclusion criteria were the following: non-bacterial meningitis, an incomplete medical record and referred patients whose clinical outcome was unknown.

Data collection included three major components: 1) Baseline characteristics, such as age, gender, comorbidities, clinical presentations, level of consciousness, microbiological culture and CSF profile; 2) empirical therapy regimen and 3) clinical outcomes regarding unfavorable clinical outcomes. These outcomes were categorized into the following four dimensions: (1) non-responders, (2) hospitalization longer than 14 days, (3) neurological sequelae and (4) 14-day mortality rate. A non-responder was a patient who was referred by another hospital for further treatment. Neurological sequelae were focal signs in the neurologic examination and abnormal neuroimaging on the computed tomography (CT) scan. CT brain abnormalities that showed the complications of meningitis included cerebral infarction, subdural effusion, cerebral oedema, hydrocephalus, empyema and ventriculitis. Moreover, hearing problems evaluated by an otolaryngologist were collected and categorized as focal neurological deficits after evaluation. Furthermore, the factors associated with unfavorable clinical outcomes were also analyzed.

For empirical therapy, an appropriate antibiotic was selected. The definition of an appropriate antibiotic in this study was an antibiotic whose spectrum covered the causative pathogens with an appropriate dose in meningitis treatment after diagnosis.

Descriptive statistics were used to examine the frequency and percentage for categorical and continuous data analysis. Factors affecting clinical outcomes were analyzed using Fisher's exact and Chi-square tests with a significant level at a p-value <0.05. The study protocol was

approved by the ethics committee of Sa Kaeo Crown Prince Hospital (S007q/61).

3. RESULTS AND DISCUSSION

3.1 Baseline characteristics

A total of 99 patients with bacterial meningitis were identified, of whom 59 were male (59.6%). Their ages ranged from one month to 87 years old (median age was 41.3±22.7 years old). The majority of patients had CABM (89 patients), followed by NM (5 patients) and neonatal meningitis (5 patients), as shown in Table 1. The most common comorbidity was an immunocompromized state, seen in 13 patients, of whom 7 were HIV-positive.

Positive bacterial cultures from CSF were found in 6 patients (6.1%) and from blood specimens in 40 patients (40.4%). CSF glucose <40 mg/dL was reported in 55.8% of patients. Similarly, 56% of patients had low CSF-to-serum glucose ratios. Besides, increased PMNs (80%-99%) was found in 40% of patients and 62% had high protein concentrations (>100 mg/dL).

3.2 Clinical presentations

The classic triad of bacterial meningitis consists of fever, headache and neck stiffness. The classic triad was reported in 29% of patients, of whom 37.7% presented fever, 57.6% presented headache and 55.6% presented neck stiffness. Other symptoms were also reported (29.3% as an alteration of consciousness, 17.2% as respiratory failure, 13.1% as a seizure and 9.1% as septic shock). However, the Glasgow Coma Scale (GCS) score was categorized as mild in 54.5% of patients.

Table 1. Baseline characteristics, clinical presentations, and laboratory tests in patients with bacterial meningitis (n = 99)

Baseline characteristic	Patients with bacterial meningitis	
	N	(%)
Age (less than 1 month to 87 years)		
Neonate	5	5.1
>1 month - <18 years	11	11.1
18-50 years	46	46.5
>50 years	37	37.4
Male	59	59.6
Risk factors (n = 99)		
Immunocompromized state*	13	13.1
Anemia	11	11.1
Tuberculosis	10	10.1
Diabetic mellitus	10	10.1
Alcohol use	8	8.1
Liver disease	6	6.1
Post neurosurgery	3	3.0
Clinical presentations (n = 99)		
Fever	73	73.7
Headache	57	57.6
Neck stiffness	55	55.6
Alteration of consciousness	29	29.3
Acute respiratory failure	17	17.2
Seizure	13	13.1
Shock	9	9.1
Glasgow coma scale score (n = 77)		
13-15 points (mild)	54	70.1
9-12 points (moderate)	16	20.8
3-8 points (severe)	7	9.1
Positive bacterial culture in CSF (n = 6)		
Streptococcus pneumoniae	2	33.3
Group D streptococcus	2	33.3
Streptococcus agalactiae	1	16.7
Streptococcus spp.	1	16.7
Positive bacterial culture in blood	40	40.4
CSF profile		
White cell counts in CSF (cell/mm^3); median (range); n = 97	400 (1-14,080)	
Total protein in CSF (mg/dL); median (range); n = 95	121 (10-1,336)	
Glucose in CSF (mg/dL); median (range); n = 95	38 (0-124)	
Glucose in CSF lower than 40 mg/dL; n = 95	53	55.8
Glucose in CSF lower than 10 mg/dL; n = 95	16	16.8
CSF-to-serum glucose ratio <0.4; n = 75	42	56
Types of bacterial meningitis		
Community acquired bacterial meningitis	89	89.9
Hospital acquired meningitis	5	5.1
Neonatal bacterial meningitis	5	5.1

Note: CSF cerebrospinal fluid

*HIV infection or AIDS, receiving immunosuppressive therapy, or after transplantation

3.3 Causative pathogens, antibiotic susceptibility and treatment

Forty patients had positive bacterial cultures from blood specimens (40.4%). Table 2 shows the causative pathogens according to the age and antibiotic susceptibility. The most common causative pathogen was *Streptococcus* spp. (seen in 10 patients in which other streptococcal species were not identified), followed by *Streptococcus pneumoniae* (7 patients) and group D streptococcus (7 patients). Focusing on antimicrobial susceptibility testing, only 29 out of 40 isolates were additionally tested, 22 of 29 (75.9%) were susceptible to third-generation cephalosporins; however, the intermediate results were found in one isolate of *Streptococcus* spp. and two isolates of group D streptococci. Cefotaxime-resistant *Streptococcus* spp. were also isolated from 2 patients. Furthermore, 16 patients (100%) that performed the vancomycin susceptibility test were 'susceptible'.

Gram-negative pathogens were reported in 2 of the 4 patients with neonatal meningitis. Nevertheless, only 1 of the 5 patients with NM had Gram-positive pathogens, which were cefotaxime and a vancomycin-sensitive strain.

For empirical therapy, 69.7% of patients received monotherapy with third-generation cephalosporins, of which 58.6% and 10.1% were ceftriaxone and cefotaxime, respectively; however, 3 of the 5 patients with NM received ceftazidime monotherapy and only one patient with neonatal meningitis received cefotaxime monotherapy. Combination therapy was considered in 27 patients (27.3%) (Table 3). Most participants (93.9%) received an appropriate antibiotic, but dexamethasone was prescribed to 12.1%.

Table 2. Causative pathogens of bacterial meningitis according to the age and antibiotic susceptibility

Causative pathogens	Number (N = 40)	By age*				Antibiotic susceptibility					
		GR.1	GR.2	GR.3	GR.4	Cefotaxime (n = 24)			Vancomycin (n = 11)		
						S	I	R	S	I	R
Streptococcus spp.**	10	-	3	1	6	5	1	2	-	-	-
Streptococcus suis	7	-	-	1	6	6	-	-	6	-	-
Group D streptococci	7	-	-	4	3	3	2	-	3	-	-
Streptococcus pneumoniae	6	-	3	1	2	-	-	-	2	-	-
Streptococcus agalactiae	6	-	-	4	2	4	-	-	-	-	-
Group A streptococci	2	-	1	1	-	1	-	-	-	-	-
Gram-negative bacilli	2	2	-	-	-	-	-	-	-	-	-

Note: *GR.1 (Group 1) = isolated from neonatal meningitis, GR.2 (Group 2) = isolated from aged >1 month - <18 years, GR.3 (Group 3) = isolated from age 18-50 years, and GR.4 (Group 4) = isolated from age >50 years

**_Streptococcus_ spp. was not identified with any other Streptococcal species

Table 3. Empirical therapy in patients with bacterial meningitis

Empirical therapy	Patients with bacterial meningitis	
	Number	Percentage
Community-acquired bacterial meningitis	90	90.9
Monotherapy	68	68.7
Ceftriaxone	58	58.6
Cefotaxime	10	10.1
Combination	22	22.2
Ceftriaxone + ampicillin	8	8.1
Ceftriaxone + vancomycin	3	3.0
Ceftriaxone + doxycycline	3	3.0
Ceftriaxone + ceftazidime	2	2.0
Others	6	6.1
Hospital-acquired bacterial meningitis	5	5.1
Monotherapy	3	3.0
Ceftazidime	3	3.0
Combination	2	2.0
Meropenem + ceftazidime	1	1.0
Meropenem + fosfomycin	1	1.0
Neonatal bacterial meningitis	4	4.0
Monotherapy	1	1.0
Cefotaxime	1	1.0
Combination	3	3.0
Ampicillin + gentamicin	1	1.0
Cefotaxime + ampicillin	1	1.0
Cefotaxime + cloxacillin + gentamicin	1	1.0

3.4 Clinical outcomes

Three of the 99 patients (3.0%) died during hospitalization. Among the survivors, 70 patients (70.7%) were cured without neurological sequelae. Twenty-six patients (27.7%) appeared to have neurological sequelae. The most frequently reported signs and symptoms of neurological sequelae were persistent seizure (39.4%), followed by hearing loss (27.3%) and the eighth cranial nerve palsy (12.1%). There were 18 of 99 patients in which a brain CT scan was performed, particularly in patients with suspected neurological complication. A brain CT scan of these patients revealed cerebral infarction, hydrocephalus, subdural effusion and brain abscess (in 57.9%, 10.5%, 10.5% and 10.5% of patients, respectively) as shown in Table 4.

Table 4. Neurological sequelae

Signs and symptoms of neurological sequelae (n=26)	Number of frequencies (n = 33)	Percentage	Neurological sequelae on a brain CT scan (n=18)	Number of frequencies (n = 21)	Percentage
Seizure	13	39.4	Cerebral infarction	11	57.9
Hearing loss	9	27.3	Hydrocephalus	2	10.5
Cranial nerve 8th palsy	4	12.1	Subdural effusion	2	10.5
Cranial nerve 3rd palsy	3	9.1	Brain abscess	2	10.5
Hemiparesis	2	6.1	Cerebral edema	1	5.3
Spasticity	1	3.0	Focal cerebritis	1	5.3
Ataxia	1	3.0	Others*	2	10.5

Note: *Intracerebral hemorrhage (old lesions)

3.5 Unfavorable clinical outcomes and risk factors

The mortality rate and neurological sequelae were 3.2% and 27.7%, respectively. Non-responders were found in 11.1% of unfavorable clinical outcomes and 63.6% were hospitalized for more than 14 days.

Nearly one-fourth of patients were over 60 years of age, but such patients were not associated with any unfavorable clinical outcomes, similar to patients with a GCS rating of 12 points or less.

Pneumonia was associated with an increased mortality rate (odds ratio [OR] = 43.5; 95% confidence interval [CI]: 3.23-586.43) and non-responders (OR = 10.63; 95% CI: 1.83-61.56). Similarly, septic shock was also associated with non-responders (OR = 34; 95% CI: 6.51-177.67), but low glucose concentrations in CSF were associated with neurological sequelae (OR = 3.36; 95% CI: 1.20-9.44). Moreover, the difference between unfavorable clinical outcomes was non-significant with empirical therapy with combination and monotherapy both similar to patients who received dexamethasone (Table 5).

Table 5. Risk factors of unfavorable clinical outcomes

Risk factors	Number of patients	Unfavorable clinical outcome; OR (95% CI)			
		Mortality rate in 14 days (n = 3)	Neurological sequelae (n = 26)	Non-responder (n = 11)	Hospitalization >14 days (n = 63)
Age >60 years	22	7.58 (0.65-88.10)	0.74 (0.24-2.27)	2.22 (0.59-8.43)	1.00 (0.37-2.68)
Male	59	1.43 (0.13-16.39)	1.90 (0.73-4.93)	3.42 (0.70-16.76)	0.75 (0.32-1.75)
Comorbidity	42	0.61 (0.05-6.97)	1.41 (0.57-3.49)	0.47 (0.12-1.90)	2.20 (0.93-5.23)
Glasgow coma scale ≤12	25	0.96 (0.91-1.01)	2.21 (0.34-14.39)	3.60 (0.59-22.14)	1.40 (0.25-7.69)
Septic shock	9	NA	1.83 (0.20-5.96)	34 (6.51-177.67)	0.42 (0.11-1.68)
Pneumonia	6	43.5 (3.23-586.43)	NA	10.63 (1.83-61.56)	1.15 (0.20-6.63)
CSF culture positive	6	NA	2.91 (0.55-15.46)	1.66 (0.24-1.34)	0.55 (0.11-2.88)
CSF glucose <40 mg/dL	52	0.40 (0.04-4.55)	3.36 (1.20-9.44)	1.21 (0.32-4.61)	0.56 (0.61-4.02)
CSF-to-serum glucose ratio <0.4	41	0.38 (0.03-4.33)	1.29 (0.46-3.68)	0.61 (0.15-2.48)	1.56 (0.61-4.02)
Dexamethasone use	12	NA	1.64 (0.44-6.13)	0.7 (0.08-6.01)	1.83 (0.46-7.26)
Combination of antibiotic	27	1.48 (0.13-17.07)	1.94 (0.72-5.22)	1.62 (0.43-6.03)	0.77 (0.31-1.92)

Note: NA, data not available

3.6. Discussion

Bacterial meningitis is a severe infectious disease resulting in morbidity and mortality to patients. The deaths that occurred in our study only manifested in patients older than 50 years. This study showed only a 3% mortality rate which is lower than previous studies conducted between 2000 to 2004 (which reported a mortality rate of about 21%-34%; Lu et al., 2000; van de Beek et al., 2004; Santimaleeworagun et al., 2019). The reasons might include the fact that we found low proportions of risk factors that increased mortality rates, such as an alteration of consciousness, respiratory failure, CSF glucose concentrations lower than 10 mg/dL and seizures in adult patients with bacterial meningitis (Lovera and Arbo, 2005; Lu et al., 2001; van de Beek et al., 2004). These two studies included only adult patients. Nonetheless, we found that 5 patients with neonatal meningitis survived. Risk factors related to higher mortality rate were neonatal seizures, septic shock and CSF with positive bacterial culture (Feldmann, 1997), whereas septic shock was not found. Thus, we did not find the leading cause of mortality in our study.

Patient HIV infection and neurosurgery were the risk factors that conformed to previous studies (De Maria Ugalde-Mejia et al., 2018; Isea-Pena et al., 2013). However, underestimation was concerned due to the retrospective design of this study. Furthermore, HIV screening tests could be examined in our study, particularly in suspected cases of HIV infection.

Central nervous system infections can activate the immune system to secrete inflammatory mediators resulting in neurological sequelae due to a severe inflammatory response. Corticosteroids (e.g. dexamethasone) were useful medications in this regard (Tauber et al., 1985), especially in *Streptococcus pneumoniae* (De Gans et al., 2002; Tauber et al., 1985) and *Haemophilus influenzae* (Brouwer et al., 2015) infections. The results showed that only 12 of 99 patients (12.1%) received dexamethasone; neurological sequelae therefore occurred in 27.7% of the total. Another pneumococcal meningitis study in which only one of 16 participants (6.25%) received dexamethasone reported neurological sequelae in about 62.5% of the total (Suphanklang et al., 2017). Nevertheless, the benefits of corticosteroids remain unclear in this study because of small amounts of encapsulated bacteria (6.1%), e.g. *Streptococcus pneumoniae*, which were the main cause of neurological sequelae (Sadarangani, 2018).

The leading cause of high mortality in bacterial meningitis is cerebral infarction (Schut et al., 2012). Our study found 57.9% (a level as high as in the study by Suphanklang et al., 2017 which reported 60%) (Suphanklang et al., 2017). Cerebral infarction is associated with an alteration of consciousness and an age of 50 years old or above according to both studies; however, the recent study reported 29.3% and 37.4%, respectively. In our setting, brain CT scan was not routine procedure for all patients except for those whose clinical outcomes deteriorated or in which neurological complications were suspected. Therefore, our results were quite different from the previous studies, which performed CT scan in all participants. Brain abscess is another rare complication that accounted for less than 1% of patients (van de Beek et al., 2006) and our study found it in two of 21 patients who had a brain CT scan. Furthermore, focal cerebritis, another cause of brain abscess, was also found in only one case.

For patients older than 50 years, the most common causative pathogens were *Streptococcus* spp. and *Streptococcus suis,* similar to the study of Tonsanoi, which investigated hospitals around Sa Kaeo province before May 2016 (Tonsanoi, 2018). They classified microbes by conventional biochemical tests, which identified only *Streptococcus agalactiae*, group D streptococcus and *Streptococcus pneumoniae*. In contrast, Viridans group streptococci and *Streptococcus suis* were reported regarding *Streptococcus spp.* After May 2016, Vitek®2 compact automated identification was applied. After this implementation, *Streptococcus suis* was reported (Tonsanoi, 2018). A published study from northern Thailand reported that 70% of the early isolated pathogens had been determined to be viridans group streptococci and then the later pathogens were identified as *Streptococcus suis* (Fongcom et al., 2009; Fongcom et al., 2002).

The clinical practice guideline of the Infectious Diseases Society of America recommends the combination of vancomycin plus a third-generation cephalosporin for empirical therapy in patients with CABM (Tunkel et al., 2004). With our findings, patients principally received empirical monotherapy with third-generation cephalosporins (68.7%) and the causative pathogen was a cefotaxime-sensitive strain in approximately 79.2% of patients. This study revealed that empirical regimens with monotherapy ineffectively covered over 80% of causative pathogens in patients with CABM to ensure a preferable outcome. In the case of *Streptococcus* spp. and group D streptococcus, they were labelled as 'intermediate' and 'resistant'. Combination therapy with vancomycin and third-generation cephalosporins should be considered. Several studies have been published demonstrating the advantages of appropriate empirical antibiotic: for example, the decreased morbidity and mortality rate (Aronin et al., 1998; Fang et al., 2000).

In developed countries, ceftriaxone was recommended in combination with vancomycin (van de Beek et al., 2006). However, WHO guidelines recommended that ceftriaxone be the first-line treatment for bacterial meningitis in the African region because of the low prevalence of ceftriaxone non-susceptible *S. pneumoniae* strains (World Health Organization, 2007). In addition, due to the rarity of ceftriaxone-resistant *H. influenzae* and *N. meningitidis*, ceftriaxone is still the therapeutic choice for the area having the low prevalence of ceftriaxone resistance especially, in the lower-middle-income countries (World Health Organization, 2007; Prasad et al., 2007; Nathan et al., 2005). However, close monitoring of ceftriaxone-resistant *S. pneumoniae* strains must be performed in order to promptly change the more appropriate empirical therapy.

Causative pathogens of neonatal meningitis were *Escherichia coli* and group B streptococcus in prior studies, and they were isolated from maternal vagina and anus (Chang et al., 2003; Chang et al., 2014). Nevertheless, Gram-negative bacilli in this study were found in 2 of the 5 patients with neonatal meningitis. Practice guidelines for the management of bacterial meningitis recommended ampicillin with cefotaxime or aminoglycosides in neonatal meningitis to cover *Listeria monocytogenes* (Tunkel et al., 2004); however, empirical therapy with this combination was used in only one patient (25%).

Statistically significant risk factors for unfavorable clinical outcomes were septic shock, pneumonia and CSF glucose levels lower than 40 mg/dL. Pneumonia was associated with an increased mortality rate and non-responders. Nevertheless, interpretation of this result might be difficult because of the wide confidence interval because of smaller numbers of patients. In the previous study, pneumonia was not associated with unfavorable clinical outcomes; however, a GCS score of less than four points was used, which might account for the difference from the present study (van de Beek et al., 2004).

There are a few limitations to our study. Only one-third of patients had antibiotic susceptibility results owing to 60% negative cultures. Indeed, we found that around 40% of cultures were positive, which is similar to previous studies (Santimaleeworagun et al., 2019). *Streptococcus* spp. were the most common causative pathogens in this study; although the eating behaviour of populations in Sa Kaeo was raw pork, consumers were aware that *Streptococcus suis* had been reported (Tonsanoi, 2018). In addition, an automated bacterial identification tool was used after May 2016 that affected our results. Further studies are required to evaluate the epidemiology of causative pathogens of bacterial meningitis.

4. CONCLUSION

The most common causative pathogen of bacterial meningitis was *Streptococcus* spp. This study also reported the cephalosporin-resistant strains. Empirical therapy with the combination of either ceftriaxone or cefotaxime with vancomycin should be considered in such patients. However, the antibiotic susceptibility test was essential because the appropriate antibiotic decreased the mortality rate and prevented neurological sequelae.

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