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Prevalence of causative bacteria and clinical outcomes among patients with meningitis at a regional central hospital in Thailand

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ABSTRACT

This study aimed to identify causative bacteria and to investigate the outcomes of treatment and the appropriate empirical regimen among patients with bacterial meningitis. Patients with bacterial meningitis admitted at Ratchaburi Hospital during January 2012 to December 2016 were included. Of two hundred and eight patients, 76 cases of them with known causative pathogens were included. Fifty-five cases were males (72.4%) and 55.2% of patients were aged 2-50 years. Sixty three out of 76 patients with meningitis (82.9%) were community acquired (CA-) bacterial meningitis. The most frequently found isolated pathogens in 63 CA-bacterial meningitis cases were *S. agalactiae* followed by *S. pneumoniae*. While *A. baumannii* and *K. pneumoniae* were the top-two isolated organisms among 13 hospital acquired cases. The rates of in-hospital mortality among 76 cases were 18.4%. The third generation cephalosporins plus vancomycin was the most active agent against bacteria (87.3%) isolated from CA-bacterial meningitis whereas carbapenems plus vancomycin remain an effective choice against bacteria (84.6%) isolated from patients with hospital acquired meningitis. However, the most common of causative pathogens were a Gram-positive bacteria in community setting and Gram-negative bacteria in hospital setting. The appropriate empirical regimen against bacteria in both setting have to be further investigated.

Keywords: causative bacteria; clinical outcome; meningitis; mortality

1. INTRODUCTION

Bacterial meningitis is an important central nervous system infection causing morbidity or mortality (Heckenberg et al., 2014). The global burden of diseases, injuries, and risk factors study provides a comprehensive assessment of cause-specific mortality and years of life lost (YLLs) in 195 countries in 2017. They found that patients with meningitis have a high number of age-standardized death rate (per 100,000) and age-standardized YLL rate (per 100,000) at 4.0 and 280.5 compared with other infectious diseases (G. B. D. Causes of Death Collaborators, 2018).

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In Thailand, according to surveillance data in 2018 from Center of Epidemiological Information (2018), Bureau of Epidemiology, Ministry of Public Health, 1,638 patients with meningitis were nationwide reported with the rate of 2.48 per 100,000 people. As a high impact of disease on patient outcome, the early treatment with appropriate regimen covering causative bacteria could reduce the unfavorable outcome in patients with meningitis (Dzupova et al., 2009).

There are only few studies of causative bacterial meningitis in Thailand. Khwannimit and Chayakul (2004) investigated the causative pathogen among patients with community-acquired bacterial meningitis (CA-bacterial meningitis) from 1982 to 2001. The most common pathogen was *Streptococcus pneumoniae* followed by *Streptococcus* spp. and *Klebsiella pneumoniae*, respectively. The overall mortality rate of bacterial meningitis was 15.5%. Similarly to Chotmongkol and Techoruangwiwat (2000) studying on CA-bacterial meningitis in adults, they found that *S. pneumoniae* remained the most common pathogens, followed by *Streptococcus* spp. and *Escherichia coli*, respectively. However, the death rate was high as twice as from previous study (35%).

As two previous described, the consistent data still be variation and the epidemiologic data had been investigated before 2001. Moreover, there was only an etiologic study of hospital acquired bacterial meningitis (HA-bacterial meningitis) in Thailand. Therefore, the purpose of this study was to investigate the causative bacteria in CA-bacterial meningitis and HA-bacterial meningitis and also investigate the outcomes of treatment and the appropriate empirical regimen among them.

2. MATERIALS AND METHODS

We retrospectively reviewed the data of patients with bacterial meningitis admitted at Ratchaburi Hospital, 855-bed tertiary hospital in Western Thailand, during January 2012 and December 2016. The protocol was approved by the institutional review board of Faculty of Pharmacy, Silpakorn University and Ratchaburi Hospital with a waiver for informed consent.

2.1 Participants

This study was to identify the causative bacteria among patients with meningitis. Patients were included in the study if, an ICD-10 code representing the meningitis or meningoencephalitis such as A01.0, A02.2, A20.3, A22.8, A27.8, A32.1, A39.0, A50.4, A51.4, A52.1, A54.8, A69.2, G00, G00.0, G00.1, G00.2, G00.3, G00.8, G00.9, G01, GO3, G03.1, G03.2, G03.8, G03.9, G04 and G04.2. Patients had causative pathogen other than bacteria (viral, tuberculosis and parasite), treatment was not be able to follow-up, or patients with incomplete medical records were excluded.

2.2 Definition

Of clinical outcome definitions; *Clinical improvement* was defined as a normal body temperature and other vital signs and no meningeal signs or having CSF with normal glucose levels, leukocyte cell count or protein level. *Treatment failure* was defined as a recurrence of symptoms, a need to revise antimicrobial therapy or death during hospitalization. *Appropriate empirical regimen* meant treatment with at least one active antimicrobial agent according to antimicrobial susceptibility of causative bacteria. Patients with *hospital acquired meningitis* was defined as meningitis that occurred during hospitalization or within 1 week after hospital discharge.

2.3 Data collection

Patient data were reviewed, via database and medical records from medical record unit, for clinical information, including age, sex, underlying diseases, sign and symptom prior to admission, antimicrobial regimens (date of start, dosage, administration and duration), antimicrobial susceptibility, length of hospital stay, culture positive rate in CSF and/or blood culture, and clinical outcomes.

2.4 Statistical analysis

Descriptive statistics were used for etiologic classification, culture positive rate in CSF culture, mortality and treatment failure rates among patients with bacterial meningitis. Chi-square or Fisher's exact test statistics was analyzed the relationship between the discrete factors and clinical outcomes. Analysis and data interpretation were processed via R program at α=0.05 for statistical significance.

3. RESULTS

A total of 208 patients were diagnosed to have bacterial meningitis during the study period. Of those, 76 patients (36.5%) could be identified the pathogen in CSF and/or blood culture. Among 76 meningitis cases with known causative bacteria, 72.4% were male, 55.2% of patients were aged 2-50 years, followed by 30.3% were aged ≥50 years. Sixty three out of 76 patients (82.9%) were CA-bacterial meningitis (Table 1).

The clinical presentation prior to admission of the 76 patients with meningitis included 23 cases (30.3%) of fever and 18 cases (23.7%) of drowsiness. Fifteen out of 76 patients (19.7%) had a confusion. Thirteen (17.1%) and nine cases (11.8%) of nausea/ vomiting and seizure were reported, respectively. The CSF findings are listed in Table 1.

Of causative pathogens in CSF and/or blood culture, the isolated 77 organisms in 76 patients with meningitis were obtained (Table 2). Of them, the majority were Gram-positive bacteria (64.9%). The top-four pathogens included *S. agalactiae* (19.5%), *S. pneumoniae* (13%), *E. coli* (10.4%) and coagulase-negative S*taphylococci* (10.4%). For 63 CA-bacterial meningitis cases, the most frequently found isolated pathogens were *S. agalactiae* followed by *S. pneumoniae* and coagulase-negative S*taphylococci*; while *A. baumannii*, *K. pneumoniae*, *E. coli* and coagulase-negative S*taphylococci* were the top-four isolated organisms among thirteen HA-bacterial meningitis cases (Table 2). The pathogens solely isolated from CSF specimen are listed in Table 3.

With clinical outcomes among 76 patients with meningitis, the rates of in-hospital mortality and treatment failure were 18.4% and 1.3%, respectively. According to the type of meningitis, CA-bacterial meningitis cases (n=63) vs. HA-bacterial meningitis cases (n=13) had comparable in-hospital mortality rates of 19.0% and 15.4%, respectively (p=1.000). However, death rate of those with Gram-negative infection (26%) was higher than that of patients infected with Gram-positive bacteria (14.0%; p=0.216).

According to antimicrobial regimens in each setting, the majority of CA-bacterial meningitis patients (n=50, 79.4%) received the third generation cephalosporins as empirical therapy, followed by vancomycin + the third generation cephalosporins (7.9%). Whereas the most selected regimen in HA-meningitis patients was also the third generation cephalosporins (66.7%).

To investigate the appropriate empirical regimen based on the antimicrobial susceptibility of the isolated organisms from CSF and /or blood specimen, the third generation cephalosporins plus vancomycin was the most active agent against bacteria (87.3%) isolated from CA-bacterial meningitis patients whereas the third generation cephalosporins monotherapy might cover the causative bacteria approximately 77.8%. The carbapenems plus vancomycin remain an effective choice to cover bacteria (84.6%) isolated from HA-bacterial meningitis cases.

However, there is no significant in-hospital mortality rate between the patients with (18.2%) and without appropriate empirical regimen (20.0%) for bacterial meningitis treatment.

Table 1 Demographic and laboratory profiles of patients with bacterial meningitis (N=76)

Parameters	Bacterial meningitis
Gender: Male; number (%)	55 (72.4%)
Age	
≤ 1 month	6 (7.9%)
1-24 months	5 (6.6%)
2-50 years	42 (55.2%)
≥50 years	23 (30.3%)
Underlying diseases	
Presence	22 (10.6%)
Absence	186 (89.4%)
Number (%) of underlying diseases	
Hypertension	12 (5.8%)
Diabetes mellitus	9 (4.3%)
Tuberculosis	5 (2.4%)
Glucose-6-phosphate dehydrogenase deficiency	1 (0.5%)
Dyslipidemia	1 (0.5%)
Cerebrovascular diseases	1 (0.5%)
HIV infection	1 (0.5%)
Hepatitis C virus infection	1 (0.5%)
Clinical presentation prior to admission	
Fever	23 (30.3%)
Nausea/vomiting	13 (17.1%)
Drowsiness	18 (23.7%)
Headache	10 (13.2%)
Confusion	15 (19.7%)
Seizure	9 (11.8%)
Stiffness of neck	7 (9.2%)
Muscle weakness	3 (3.9%)
CSF profile	
White cell count (x 10^9/L); median (range)	318 (1-7500)
Total protein (g/dL); median (range)	240 (24-2500)
Glucose (g/dL); median (range)	28.5 (0-176)
Gram strain and bacterial culture	
CSF Gram strain positive only	**2 (2.6%)**
CSF culture positive	**41 (53.9%)**
CSF culture positive only	25
CSF and blood culture positive	16
Blood culture positive only	**33 (43.4%)**

Table 1 Demographic and laboratory profiles of patients with bacterial meningitis (N=76) (Continued)

Parameters	Bacterial meningitis
Type of meningitis	
Community setting	63 (82.9%)
Hospital setting	13 (17.1%)
Duration of hospitalization; median (interquartile range); day	15 (8-22)

Note: CSF, cerebrospinal fluid

Table 2 The seventy seven causative bacteria among 76 meningitis patients categorized by setting (community or hospital) and age group

Community (n=63 cases)	**63 isolates**
Age	
≤ 1 month	**4 isolates**
Coagulase-negative staphylococci (CoNS)	3
Escherichia coli	1
1-24 months	**4 isolates**
Escherichia coli	2
Haemophilus influenzae	1
Klebsiella pneumoniae (non-susceptible 3rd generation cephalosporin)	1
2-50 years	**33 isolates**
Streptococcus pneumoniae	8
Streptococcus agalactiae	5
Streptococci (alpha-haemolysis)	4
Streptococci spp.	3
Streptococcus pyogenes	2
Streptococcus suis	1
Viridans group streptococci	1
Coagulase-negative staphylococci (CoNS)	2
Escherichia coli	2
Escherichia coli (non-susceptible 3rd generation cephalosporin)	1
Haemophilus influenzae	1
Klebsiella pneumoniae	1
Klebsiella pneumoniae (non-susceptible 3rd generation cephalosporin)	1
Salmonella group D	1
≥50 years	**22 isolates**
Streptococcus agalactiae	10
Streptococcus pneumoniae	2
Streptococci (alpha-haemolysis)	2

Table 2 The seventy seven causative bacteria among 76 meningitis patients categorized by setting (community or hospital) and age group (Continued)

Community (n=63 cases)	**63 isolates**
Streptococci spp.	2
Coagulase-negative staphylococci (CoNS)	2
Acinetobacter baumannii	2
Klebsiella pneumoniae	1
Salmonella group B	1
Hospital (n=13 cases)	**14 isolates**
Post-neurosurgery (4 cases)	**5 isolates**
Acinetobacter baumannii (MDR-strains)	2
Acinetobacter baumannii	1
Klebsiella pneumoniae (non-susceptible 3rd generation cephalosporin)	1
Enterobacter spp. (non-susceptible 3rd generation cephalosporin)	1
Non-post-neurosurgery (9 cases)	**9 isolates**
Age ≤ 1 month (2 cases)	
Haemophilus influenzae	1
Staphylococcus epidermidis	1
Age 1-24 months (1 case)	
Escherichia coli	1
Age ≥ 2 years (6 cases)	
Klebsiella pneumoniae	1
Klebsiella pneumoniae (non-susceptible 3rd generation cephalosporin)	1
Escherichia coli (non-susceptible 3rd generation cephalosporin)	1
Pseudomonas aeruginosa	1
Streptococci (alpha-haemolysis)	1
Coagulase-negative staphylococci (CoNS)	1

Table 3 The 43 bacteria found in cerebrospinal fluid culture among 42 meningitis patients

Pathogens	**Number of isolates**
Streptococcus pneumoniae	5
Streptococcus agalactiae	6
Streptococci (alpha-haemolysis)	5
Streptococci spp.	3
Streptococcus pyogenes	1
Streptococcus suis	1
Coagulase-negative staphylococci (CoNS)	2
Haemophilus influenzae	2
Klebsiella pneumoniae	2
Klebsiella pneumoniae (non-susceptible 3rd generation cephalosporin)	2
Escherichia coli	6
Salmonella group B	1
Acinetobacter baumannii	3
Acinetobacter baumannii (MDR-strain)	2
Pseudomonas aeruginosa (MDR-strain)	1
Enterobacter spp.	1

4. DISCUSSION

Of 208 cases diagnosed with bacterial meningitis, CSF or blood cultures were successfully obtained in 76 patients resulting in 77 isolated organisms. Among 76 cases of bacterial meningitis, we found more patients infected with Gram-positive bacteria than with Gram-negative cases. Additionally, the first two most found organisms were *S. agalactiae* and *S. pneumoniae* in CA-bacterial meningitis patients; while *A. baumannii*, *K. pneumoniae*, *E. coli* and coagulase-negative *Staphylococci* were the fourth most identified organisms for HA-bacterial meningitis cases, respectively. To our knowledge, our study not only show the causative bacteria in CA- and HA-bacterial meningitis patients investigated after year 2001 but also indicate the prevalence of *S. agalactiae* as a predominant pathogen that caused bacterial meningitis in persons aged >20 years.

Etiologic pathogens for CA-bacterial meningitis are Gram-positive bacteria, especially *S. agalactiae* and *S. pneumoniae* and Gram-negative bacteria, specifically *E. coli* and *K. pneumoniae*. As expected, we also found causative bacteria similar to those in several reports in Thailand. Khwannimit and Chayakul (2004) studied the causative agents among patients with CA-bacterial meningitis patients at a tertiary care teaching hospital in the south of Thailand from 1982 to 2001. They found that nearly 30% and 16% of cases were caused by *S. pneumoniae* and *K. pneumoniae*, respectively. Our finding of causative pathogens were also found in a study by Chotmongkol and Techoruangwiwat (2000) in a medical school hospital in the north-eastern part of Thailand during 1984-1998. They found that *S. pneumoniae* was the most common organism followed by *E. coli,* Non A, B, D *Streptococci* and *K. pneumoniae*. Another study by Sribussara and Rusmeechan (2007) on the etiology of meningitis at a provincial medical school hospital during 1998-2003 revealed that *Streptococcus* spp. was the number-one cause. At present, previous studies and our present study revealed that bacterial pathogens of CA-bacterial meningitis were common.

Focusing on the causative bacteria varied by age group in the present study, *E. coli* was the most common bacterial meningitis in children group whereas *S. pneumoniae* was found in adult group. Our findings were similar to the recent systematic review and meta-analysis by Oordt-Speets et al. (2018) showing *E. coli* and *S. pneumoniae* were mostly found as etiologic bacteria in children and adult, respectively.

However, *S. agalactiae* as not predominately identified in previous studies of CA-bacterial meningitis in Thailand was found in our finding, specifically almost all persons aged >20 years. Our findings are consistent with the global trends described elsewhere. Phares et al. (2008) performed the epidemiologic study of invasive group B Streptococcal disease in the United States during 1999-2005. They found that among persons aged 15 through 64 years, disease incidence increased from 3.4 per 100,000 population in 1999 to 5.0 per 100,000 in 2005. Similarly, among adults 65 years or older, incidence increased from 21.5 per 100,000 to 26.0 per 100,000 or approximately a relative increase of 20%. A changing trend was also seen in Abat et al. (2014) study. They found an increasing trend of the number of invasive group B Streptococcal diseases between 2008 and 2013; with a 1.5-fold rise was observed among patients older than 15 years. However, direct evidence of changing trend in Thailand is lacking.

Of HA-bacterial meningitis, our finding is similar to Khwannimit et al. (2004) study revealing Gram-negative bacilli as common organisms, especially *Acinetobacter* spp. However, it is fact that, a considerable discrepancy in the prevalence of individual pathogenic bacteria among various levels of healthcare institutes was of concern. This discrepancy emphasizes the importance of the tailor-made antimicrobial selection approach. Continuous studies on the hospital acquired meningitis should be encouraged in individual setting.

Bacterial meningitis is a severe infection and is associated with morbidity and mortality (Suphanklang et al., 2017). In this study, we recorded a mortality rate of 18.4%, which is similar to that reported in previous study (Khwannimit and Chayakul, 2004). Moreover, our finding of high mortality rate (26%) among patients with Gram-negative bacterial infection was consistent with the result of death from 31% to 48% (Sribussara and Rusmeechan, 2007; Chusri et al., 2018).

With our findings, we could not detect the different mortality rate between the patients with and without appropriate empirical treatment due to the small sample size. However, there were the previous studies indicating the appropriate empirical regimen is necessary for reducing the unfavorable outcomes (Lu et al., 2002; Køster-Rasmussen et al., 2008). Based on our finding and the recommendation from Infectious Diseases Society of America (IDSA), the third generation cephalosporins plus vancomycin and meropenem plus vancomycin remained the most active regimens for CA-bacterial meningitis and HA-bacterial meningitis patients, respectively (Tunkel et al., 2004).

Although we gathered data covering 5 years at a single tertiary hospital, only 77 meningitis isolates were identified. A multicenter study conducted in tertiary hospitals across Thailand is needed to further investigate the severity of the condition.

5. CONCLUSION

This study has illustrated the pattern of causative pathogens for community and hospital setting in a regional hospital comparable to that in a medical school hospital. Additionally, *S. agalactiae* meningitis have to be closely monitor as emerging pathogen. For the HA-meningitis, the individual pattern of causative pathogens is a strategy to improve the quality of meningitis treatment.

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