BACTERIAL MENINGITIS: ETIOLOGIES, DRUG SUSCEPTIBILITIES AND MORTALITY RATE AT A UNIVERSITY HOSPITAL IN THAILAND

Pornchai Opartpunyasarn[1,2] and Gompol Suwanpimolkul[1, 3]

[1] Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, The Thai Red Cross Society, Bangkok; [2] Department of Medicine, Chulabhorn Hospital, Bangkok, [3]Emerging Infectious Diseases Clinical Center, The Thai Red Cross Society, Bangkok, Thailand

Abstract. Bacterial meningitis is a serious medical problem that requires appropriate, prompt treatment. Empiric antibiotic treatment should be guided by the epidemiology and drug susceptibility patterns. Therefore, it is vital to monitor changes in their patterns over time. In this study, we aimed to determine the organisms and their drug susceptibilities and outcomes of meningitis patients at the study hospital in order to guide future empiric treatment of meningitis patients until the culture results are available. We also aimed to identify factors associated with mortality in these patients to guide mortality prevention studies in the future. We conducted this retrospective study by reviewing the records of patients aged ≥ 16 years diagnosed as having acute bacterial meningitis at King Chulalongkorn University Hospital during June 2006-June 2014. Subjects with head trauma or cranial surgery were excluded from the study. A total of 66 subjects were identified as having acute bacterial meningitis during the study period. The median age of subjects was 47 years; 60% of subjects were males. The most common etiological organism was *Streptococcus pneumoniae* (30%), followed by *S. agalactiae* (28%), *S. suis* (15%), *Klebsiella pneumoniae* (13%), *S. bovis* (11%), *S. oralis* (2%) and *Escherichia coli* (2%). Twenty-nine percent of *S. pneumoniae* strains were resistant to penicillin, no *S. agalactiae* strains were resistant to penicillin and 14% of *S. suis* strains were resistant to penicillin. However, all *Streptococcus* species in this study were sensitive to cefotaxime. The mortality rate among study subjects was 15%. On univariate analysis, a Glasgow Coma Scale (GCS) score ≤ 10 was significantly (p=0.03) associated with mortality. Infections due to *K. pneumoniae* and *S. pneumoniae* had mortality rates of 33% and 29%, respectively. There were no deaths among subjects infected with *S. suis* or *S. bovis*. Among study subjects, the most common organism isolated was *S. pneumoniae* which had a high mortality rate, a relatively high percentage of isolates resistant to penicillin, but all isolates were sensitive to cefotaxime. Cefotaxime should be considered for empiric treatment of patients presenting with acute bacterial meningitis at the study hospital until culture results are obtained. Subjects with a GCS score ≤ 10 should be monitored closely due to high risk for mortality.

Keywords: bacterial meningitis, etiology, drug susceptibility, mortality rate

Correspondence: Gompol Suwanpimolkul, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, The Thai Red Cross Society, 1873 Rama 4 Road, Pathumwan, Bangkok 10330, Thailand.
Tel +66 (0) 2256 4578-9; Fax: +66 (0) 82256 4000-3419; E-mail: sgompol@gmail.com

INTRODUCTION

Acute bacterial meningitis is associated with morbidity and mortality. One study from Thailand reported the mortality rate of acute bacterial meningitis to be 34% (Chotmongkol and Techoruangwiwat, 2000) and another to be 15.5% (Khwannimit *et al*, 2004). Acute bacterial meningitis requires prompt diagnosis and correct treatment. It is important for physicians who treat these cases to be aware of the most common etiological organisms and their antimicrobial susceptibilities to select appropriate empiric treatment until culture results come back. The most common causes of acute bacterial meningitis in adults aged ≥ 18 years in the United States were reported to be *Streptococcus pneumoniae, Neisseria meningitidis* and *S. agalactiae* (Thigpen *et al*, 2011), comprising 90% of cases in that study. In Thailand, studies of acute bacterial meningitis cases aged ≥ 15 years (Chotmongkol and Techoruangwiwat, 2000; Khwannimit *et al*, 2004) reported the following as the most commonly isolated etiological organisms: *S. pneumoniae, Streptococcus* spp, *Escherichia coli* and *Klebsiella pneumoniae*; however, *Neisseria meningitidis* comprised only 1% of cases. Twenty-nine point four percent of *S. pneumoniae* isolates in one study from Asia were found to be penicillin resistant *S. pneumoniae* (PRSP) (Song *et al*, 2004). Cephalosporin-resistant *S. pneumoniae* (CRSP) isolates were reported to comprise 4.1% of isolates from Asia (Song *et al*, 2004) compared to 15% of isolates in a study from the United States (Whitney *et al*, 2000). The current recommendation for empiric treatment of acute bacterial meningitis in adult patients aged < 50 years is a third generation cephalosporin combined with vancomycin (Tunkel *et al*, 2004). However, there is the concern about development of vancomycin resistance.

The aim of our study was to retrospectively determine the organisms, their drug susceptibilities, outcomes and factors associated with death among adult patients with acute bacterial meningitis treated at King Chulalongkorn Memorial Hospital (KCMH) in order to guide empiric treatment and inform future studies regarding mortality prevention in the study population.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of all patients aged ≥ 16 years with acute bacterial meningitis treated at KCMH during June 2006-June 2014, including patients initially treated at other hospitals and transferred to our hospital for treatment. Patients with a recent history of head trauma or cranial surgery were excluded from our study. Acute bacterial meningitis was diagnosed based on having signs and symptoms consistent with acute bacterial meningitis (fever, headache, vomiting, altered consciousness and neck stiffness) and one of the following: having a positive cerebrospinal fluid (CSF) culture and/or positive blood culture, a positive CSF Gram stain for bacteria or CSF neutrophilic pleocytosis of at least 100 neutrophils per cubic millimeter ($0.1x10^9$ per liter) with a low glucose level and a high protein level. Mortality due to acute bacterial meningitis was defined as death due to meningitis or its complications, not from a preexisting illness or death after bacteriologic cure or clinical recovery from meningitis.

The study was approved by the ethics committee and the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Statistical analysis

Clinical characteristics of the patients were compared between those

Table 1
Characteristics of study subjects.

	Total (*N*=66) *n* (%)	Survived (*n*=56) *n* (%)	Died (*n* =10) *n* (%)	*p*-value
Age in years, median (range)	47 (37-61)	45 (34-61)	57.5 (45-63)	0.12
Male	40 (61)	35 (63)	5 (50)	0.46
Bacteria (*n*=47)				
E. coli	1 (2)	1 (3)	0 (0)	
K. pneumoniae	6 (13)	4 (10)	2 (25)	
S. agalactiae	13 (28)	11 (28)	2 (25)	
S. bovis	5 (11)	5 (13)	0 (0)	
S. oralis	1 (2)	1 (3)	0 (0)	
S. pneumoniae	14 (30)	10 (26)	4 (50)	
S. suis	7 (15)	7 (18)	0 (0)	
S. pneumoniae				0.17
Non-*S. pneumoniae*	33 (70)	29 (74)	4 (50)	
S. pneumoniae	14 (30)	10 (26)	4 (50)	
Drug resistance for *S.pneumoniae*				
Median MIC for penicillin (range)	0.023 (0.012-0.38)	0.02 (0.012-0.023)	0.214 (0.03-0.44)	0.25
Median MIC for cefotaxime (range)	0.028 (0.016-0.125)	0.02 (0.016-0.032)	0.125 (0.069-0.158)	0.56
Underlying diseases				
No	28 (42)	24 (43)	4 (40)	
Chronic lung disease	2 (3)	2 (4)	0 (0)	
Chronic steroid use	3 (5)	3 (5)	0 (0)	
DM	7 (11)	6 (11)	1 (10)	
Epilepsy	1 (2)	1 (2)	0 (0)	
Hematologic cancer	1 (2)	0 (0)	1 (10)	
HT, DLP	10 (15)	9 (16)	1 (10)	
Liver disease	7 (11)	6 (11)	1 (10)	
Old TB	2 (3)	1 (2)	1 (10)	
Solid organ cancer	3 (5)	2 (4)	1 (10)	
Thalassemia	2 (3)	2 (4)	0 (0)	
HIV positive	7 (11)	6 (11)	1 (10)	0.72
Correct empiric ATB given	47 (71)	39 (70)	8 (80)	0.71
Median GCS score (range)	13.5 (10-15)	14.5 (11-15)	10 (7-12)	0.01

N, total number; *n*, number; MIC, minimal inhibitory concentration; DM, diabetes mellitus; HT, hypertension; DLP, dyslipidemia; TB, tuberculosis; HIV, human immunodeficiency virus; ATB, antibiotic(s); GCS, Glasgow Coma Scale.

who survived and those who died using the Wilcoxon rank sum test for continuous variables and the chi-square test for categorical variables. Logistic regression analysis was performed to determine factors associated with mortality.

RESULTS

During the study period, 95 patients were diagnosed with having bacterial meningitis according to the medical records. Thirteen of these patients did not meet the criteria for diagnosing acute bacterial meningitis and 16 patients had a history of traumatic head injury or cranial surgery. Thus, 66 patients were included in this study; 60% were males. The clinical characteristics of study subjects are shown in Table 1. Twenty-seven patients presented during 2006-2010 and 39 patients presented during 2010-2014. The lengths of time from symptom onset to presentation are shown in Table 2. Subjects with *S. pneumoniae* and *S. agalactiae* as etiological organisms had a median time to presentation of 1 day. Subjects with *S. bovis* had a median time to presentation of 5 days (Fig 1).

CSF and bacteriological findings

CSF samples were obtained by lumbar puncture from all patients. Bacteria were detected on culture of CSF or blood in 47 patients (71%). Of these, the Gram stain of the CSF was positive for bacteria in 26 cases (55%). *S. pneumoniae* was the most common organism isolated (30%), followed by *S. agalactiae* (28%) and *S. suis* (15%), of whom 3 of 7 *S. suis* infected patients gave a history of pig contact or ingestion. *Neisseria meningitidis, Listeria monocytogenes* and *Haemophilus influenzae* were not isolated in this study. The causative organisms isolated are shown in Table 3.

Drug susceptibilities

Of the 14 *S. pneumoniae* isolates, 4 (29%) were penicillin-resistant *S. pneumoniae* (PRSP). All 14 *S. pneumoniae* isolates were

Table 2
Duration in days from symptom onset to presention for medical care by organism.

Organism	*n*	Mean	SD	Min	p25	Median	p75	Max
Total	47	2.3	1.9	0.13	1	2	3	9
E.coli	1	5.0						
K.pneumoniae	6	3.0	2.2	1	1	3	3	7
S.agalactiae	13	1.8	1.3	0.38	1	1	2	5
S.bovis	5	4.6	2.1	2	3	5	6	7
S.oralis	1	0.3						
S.pneumoniae	14	1.5	1.3	0.17	1	1	2	5
S.suis	7	2.6	1.8	1	1	2	4	6
S.pneumoniae	14	1.5	1.3	0.17	1	1	2	5
Non S.pneumoniae	33	2.6	2.0	0.25	1	2	3	7

Significantly different ($p = 0.03$) median time for presentation for medical care by subjected infected with *S.pneumoniae* and non *S.pneumoniae* (p=0.03)

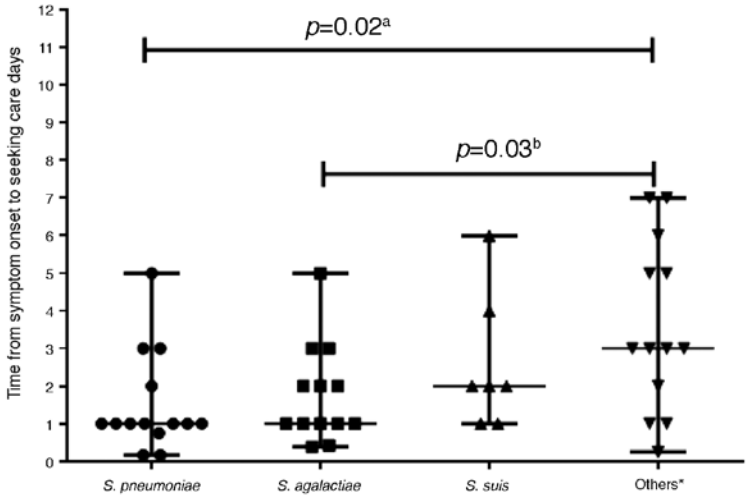

Fig 1-Comparison of the median number of days from symptom onset to presentation for medical cake by isolate.

[a]Comparison of the median number of days from symptom onset to seeking medical care between subjects with *S. pneumoniae* infection and those with other types of infections.

[b]Comparison of the median number of days from symptom onset to seeking medical care between subjects with *S. galactiae* infection and other types of infections.

Table 3
Characteristics of organisms isolated from study subjects.

Organisms	No. of patients (%)	Penicillin non-susceptibility (%)	Cefotaxime non-susceptibility	Mortality rate (No.)
Streptococcus pneumoniae	14 (30)	4 (29) [a]	0	29% (4)
Streptococcus agalactiae	13 (28)	0	0	15% (2)
Streptococcus suis	7 (15)	1 (14) [b]	0	0
Klebsiella pneumoniae	6 (13)	N/A	N/A	33% (2)
Streptococcus bovis	5 (11)	1 (20) [b]	0	0
Streptococcus oralis	1 (2)	0	0	0
Escherichia coli	1 (2)	N/A	N/A	0

[a]Penicillin-resistant, [b]Penicillin-intermediate.

sensitive to cefotaxime. One *S. suis* isolate was intermediately sensitive to penicillin. All 13 *S. agalactiae* isolates were sensitive to penicillin. The drug susceptibilities of the isolates are shown in Table 3.

Mortality

In this study, 10 patients died from bacterial meningitis (15% mortality). The organisms with greater mortality were *Klebsiella pneumoniae* (2 out of 6 cases,

Table 4
Factors associated with mortality.

Risk factors	Univariate analysis		
	Odds ratio	95%CI	*p*-value
Age > 50 years	2.70	0.68 - 10.71	0.16
Female	1.67	0.43 - 6.45	0.46
S. pneumoniae	2.90	0.61 - 13.82	0.18
HIV-positive	0.93	0.1 - 8.64	0.95
Comorbidity	1.13	0.29 - 4.43	0.87
GCS ≤ 10	4.96	1.21 - 20.3	0.03

CI, confidence interval; HIV, human immunodeficiency virus; GCS, Glasglow Coma Scale.

33%), *S. pneumoniae* (4 out of 14 cases, 29%) and *S. agalactiae* (2 out of 13 cases, 15%). The mortality rates by organism are shown in Table 3. On univariate analysis, a GCS score ≤ 10 was significantly (p=0.03) associated with mortality (Table 4).

DISCUSSION

In our study, *S. pneumoniae* was the most common isolated organism, followed by *S. agalactiae* and *S. suis* and *K. pneumoniae*. *S. pneumoniae* isolates comprised 30% of organisms isolated, similar to 28% from Khon Kaen University (Chotmongkol and Techoruangwiwat, 2000) and 23% from Songklanagarind hospital (Khwannimit *et al*, 2004). There were no cases of *N. meningitidis, L. monocytogenes* or *H. influenzae* in our study, unlike a study from the United States (Thigpen *et al*, 2011). This suggests a different epidemiology for acute bacterial meningitis in Thailand than in the United States.

In our study, the time from symptom onset to presentation varied by etiological organism, with subjects infected with *S. pneumoniae* or *S. agalactiae* presenting earlier than subjects with *S. bovis*. This suggests subjects presenting later may be more likely to have an infection caused by *S. bovis*. However, this is not sufficient information to influence empiric antibiotic use.

Twenty-nine percent of *S. pneumoniae* isolates were PRSP, higher than a previous study from Songklanagarind hospital of 17.6% (Khwannimit *et al*, 2004). All the isolates were sensitive to cefotaxime suggesting a third generation cephalosporin alone can be used for empiric treatment of community-acquired acute bacterial meningitis at the study institution. Based on our results, vancomycin does not need to be used for empiric treatment of acute bacterial meningitis at the study institution if the case is community acquired and there is no recent history of antibiotic use.

In our study, 15% of subjects died due to acute bacterial meningitis, which is lower than the 34% mortality rate reported from Khon Kaen University (Chotmongkol and Techoruangwiwat, 2000) but is similar to the 15.5% mortality rate reported from Songklanagarind hospital (Khwannimit *et al*, 2004).

In our study, higher mortality was

significantly associated with a GCS score ≤ 10. Subjects with a low GCS need to be monitored more carefully.

In our study, we evaluated the epidemiology of acute bacterial meningitis at the study institution. Our study had some limitations. This study was retrospective so may have missing data. We did not determine long term sequelae in these subjects. Our results are only applicable to the study institution. A prospective study that is multi-center in design is needed to better evaluate the epidemiology of acute bacterial meningitis in Thailand.

In summary, the most common etiological organisms of community-acquired acute bacterial meningitis in our study were *S. pneumoniae, S. agalactiae* and *S. suis.* Some of the isolates were penicillin-resistant *S. pneumoniae* (PRSP) but all isolates were sensitive to third generation cephalosporins. The mortality rate was significantly higher among subjects with a GCS score ≤ 10.

We conclude a third generation cephalosporin can be used as a single empiric antibiotic to treat community-acquired acute bacterial meningitis at the study institution. Subjects with a low GCS score should be monitored more closely due to a high risk for mortality.

ACKNOWLEDGEMENTS

Statistical analysis was conducted with the assistance of Jiratchaya Sophonphan.

REFERENCES

Chotmongkol V, Techoruangwiwat C. Community acquired bacterial meningitis in adults. *Southeast Asian J Trop Med Public Health* 2000; 31: 506-8.

Khwannimit B, Chayakul P, Geater A. Acute bacterial meningitis in adults: a 20 year review. *Southeast Asian J Trop Med Public Health* 2004; 35: 886-92.

Song JH, Jung SI, Ko KS, *et al*. High prevalence of antimicrobial resistance among clinical *Streptococcus pneumoniae* isolates in Asia (an ANSORP study). *Antimicrob Agents Chemother* 2004; 48: 2101.

Thigpen MC, Whitney CG, Messonnier NE, *et al*; Emerging Infections Programs Network. Bacterial meningitis in the United States, 1998-2007. *N Engl J Med* 2011; 364: 2016-25.

Tunkel AR, Hartman BJ, Kaplan SL, *et al*. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 2004; 39: 1267-84.

Whitney CG, Farley MM, Hadler J, *et al*. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. *N Engl J Med* 2000; 343: 1917-24.