PNEUMOCOCCAL MENINGITIS AT A THAI HOSPITAL OVER A 10-YEAR PERIOD: CLINICAL OUTCOMES, SEROTYPES, AND ANTIMICROBIAL SUSCEPTIBILITY PATTERNS

Juthathip Suphanklang[1,2], Wichai Santimaleeworagun[1,3], Sudaluck Thunyaharn[4] and Jantima Traipattanakul[5]

[1]Department of Pharmacy, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom; [2]College of Pharmacotherapy Thailand, Pharmacy Council, Nonthaburi; [3]Antibiotic Renaissance Project and Antibiotic Optimization and Patient Care Project by Pharmaceutical Initiative for Resistant Bacteria and Infectious Diseases Working Group (PIRBIG); [4]Faculty of Medical Technology, Nakhonratchasima College, Nakhon Ratchasima; [5]Division of Infectious Disease, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand

Abstract. Pneumococcal meningitis causes high rates of morbidity and mortality and requires appropriate antimicrobials. We retrospectively reviewed cases of pneumococcal meningitis presenting to a 1,200-bed tertiary care hospital in Bangkok, Thailand to determine the clinical outcomes, etiological serotypes and antimicrobial susceptibility patterns over a 10 year period in order to inform future management and empiric antimicrobial protocols and determine if available pneumococcal vaccines cover the isolates causing disease. Antibiotic susceptibility testing against penicillin, ceftriaxone, cefotaxime, levofloxacin, fosfomycin and vancomycin were determined by Epsilometer test (E test) strips. Capsular serotyping was observed by microscopic examination. One hundred twenty-two cases of invasive pneumococcal disease were identified during the study period based on a positive blood culture for *Streptococcus pneumoniae*. Of these, 16 (13%) had meningitis, of which 6 (37.5%) died and 10 (62.5%) developed neurological complication. Ten isolates (62.5%) were resistant to penicillin. All isolates were susceptible to cefotaxime and ceftriaxone. The most common serotype was 23F (4 strains). In our study, pneumococcal meningitis was associated with high rates of mortality and morbidity. Penicillin is not recommended for empiric therapy due to resistance. Ceftriaxone and cefotaxime are the recommended treatment for pneumococcal meningitis based on our study results. The most common serotype was 23F that is covered by the available vaccines used in Thailand.

Keywords: pneumococcal meningitis, serotype, clinical outcome, antimicrobial susceptibility

Correspondence: Wichai Santimaleeworagun
Department of Pharmacy, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand.
Tel +66 (0) 34 255 800; Fax +66 (0) 34 255 801
E-mail: swichai1234@gmail.com

INTRODUCTION

Streptococcus pneumoniae, a gram-positive diplococcus bacterium, is the leading cause of upper and lower respiratory tract infections and invasive pneumococcal

disease (IPD), such as bacteremia, meningitis, and meningoencephalitis (Konradsen and Kaltoft, 2002). The neurological sequelae causing by *S. pneumoniae* was involved in the subarachnoid space and brain parenchyma triggered the release of cytokines thus resulting in severe inflammation. (Mook-Kanamori *et al*, 2011). In Thailand, the incidence of IPD is estimated to be around 17/100,000 persons/year (Netsawang *et al*, 2010). One study from Thailand found 15% of IPD cases were pneumococcal meningitis (Suwanpakdee *et al*, 2010). Since pneumococcal meningitis has a high morbidity and mortality rates, early use of appropriate empiric antimicrobials is important (Bennett *et al*, 1992; Leelarasamee *et al*, 1999; O'Brien *et al*, 2009). However, the treatment of *S. pneumoniae* meningitis has become a challenge because of the emergence of multidrug-resistant *S. pneumoniae*.

The prevalence of penicillin non-susceptible *S. pneumoniae* (PNSSP) ranges from 25% to >50% in the United States [penicillin minimal inhibitory concentration (MIC) cut off of ≤0.06 mg/l] (Appelbaum, 2002) and has been reported to be higher in some countries in Europe and Asia (Schito *et al*, 2000; Song *et al*, 2004). According to National Antimicrobial Resistance Surveillance Thailand (NARST) data for 2016 collected from 55 hospitals, *S. pneumoniae* isolates obtained from sterile sites were found to be resistant to tetracycline, trimethoprim-sulfamethoxazole, erythromycin, and a combination of penicillin and tetracycline, with resistance rates of 72.5%, 54.1%, 32.3%, 30.5%, and 29.3%, respectively; however, vancomycin and levofloxacin maintained excellent activity (NARST, 2016). Between 1998 and 2009, only two studies focused on the MIC of penicillin against strains of *S. pneumoniae* causing meningitis in Thailand (Netsawang *et al*, 2010; Kim *et al*, 2012). One study reported 30% of 106 children with invasive pneumococcal disease had meningitis; resistance to cefotaxime and ceftriaxone were reported in 8.2% and 12.3% of cases, respectively (Netsawang *et al*, 2010). However, neither the study by Kim *et al* (2012) nor Netsawang *et al* (2010) determined the pneumococcal capsular serotype. Pneumococcal infections differ by serotype in severity, invasiveness and lethality (Grabenstein and Musey, 2014).

Due to this lack of data regarding serotypes and antibiotic sensitivities of *S. pneumoniae* isolates causing meningitis, we aimed to determine the serotypes and antibiotic sensitivities of *S. pneumoniae* causing meningitis at a tertiary care hospital in Bangkok, Thailand. We did this in order to inform empiric management of these cases and to evaluate if available pneumococcal vaccines cover the serotypes causing disease.

MATERIALS AND METHODS

We retrospectively reviewed the charts of patients hospitalized with invasive pneumococcal disease (IPD) who had a positive culture for *S. pneumoniae* during January 2006 - December 2015 at Phramongkutklao Hospital, a 1,200-bed tertiary care hospital in Bangkok, Thailand.

Inclusion criteria were: 1) having a blood and/or cerebral spinal fluid (CSF) culture positive for *S. pneumoniae*; 2) having the 3 following signs of fever, mental status change and signs of meningeal irritations; and 3) having CSF with decreased glucose levels, increased leukocytes with predominantly polymorphonuclear leukocytes and an elevated protein level. Exclusion criteria were having a positive blood culture but none of the 3 preceding signs.

Data collection

In addition to the above inclusion criteria, other data obtained from the patient charts included patient demographies, clinical presentation prior to admission, treatment outcomes, history of underlying disease, history of being treated in the intensive care unit, history of mechanical ventilator use, history of shock, hepatic function, renal function, history of being immunocompromised, antimicrobial regimens used (dosage, route, and duration), and length of hospital stay, Glasgow Coma Scale score, CSF exam results, antimicrobial susceptibilities and clinical outcome.

The following definitions were used for our study: presumptive treatment success was considered as a cure or clinical improvement. A cure was defined as both clinical improvement and microbiological clearing (culture negative after treatment). Clinical improvement was defined as a normal body temperature and other vital signs, a normal white blood cell count and no meningeal signs. Treatment failure was defined as a recurrence of symptoms, a need to revise antimicrobial therapy or death during hospitalization. Appropriate antimicrobial therapy was defined as administration of one or more antimicrobial agents to which the isolate was sensitive on susceptibility testing at a dosage used in clinical practice.

Antimicrobial susceptibility testing

All isolates were identified as *S. pneumoniae* based on the results of standard testing: biochemistry, colony morphology, hemolysis pattern on blood agar, ethylhydrocupreine hydrochloride disk (optochin) susceptibility and bile solubility. Antimicrobial susceptibility testing was performed using the disk diffusion test following the Clinical and Laboratory Standards Institute 2016 guidelines (CLSI, 2016). To determine the minimum inhibitory concentration (MIC) of penicillin, cefotaxime, ceftriaxone, levofloxacin, fosfomycin, and vancomycin, Epsilometer test (E-test) strips were used after plating isolates on Mueller-Hinton agar supplemented with 5% sheep blood and then incubating for 18-20 hours at 35°C in 5% CO_2.

Capsular serotype determination

The isolate serotypes were determined based on capsular swelling (Quellung reaction) observed microscopically after treating isolates with antisera prepared by the Statens Serum Institute (Copenhagen, Denmark). This assay was conducted at the National Reference Laboratory, National Institute of Health, Nonthaburi, Thailand.

Ethical considerations

This study protocol was approved by the institutional review board of the Royal Thai Army Medical Department and Phramongkutklao Hospital (No. Q015h/59).

RESULTS

A total of 122 patients had IPD, of whom 16 (13.1%) met the inclusion criteria; 69% were male. Fifty percent of patients were aged 2-60 years; and 31.3% were aged >60 years.

Clinical presentation prior to admission

Of the 16 cases included in the study, 14 had typical manifestations of meningoencephalitis, 14 (88%) had altered consciousness and 13 (81%) had acute respiratory failure requiring intensive care unit admission. Nine subjects had a seizure; of these 2 developed status epilepticus. Eight subjects had fever (>38.5°C) and headache. Six subjects had a septic shock (Table 1). One subjects developed disseminated intravascular coagulation.

Table 1
Demographic profile, laboratory results, clinical presentation and clinical outcome of patients with pneumococcal meningitis (*N*=16).

Variables	Number (%)
Demographic profile	
Age in years	
<2	3 (19)
2-60	8 (50)
>60	5 (31)
Underlying diseases	
Chronic disease[a]	10 (63)
Traumatic brain injury	3 (19)
CSF rhinorrhea	3 (19)
Post-neurosurgery	2 (13)
Malignancy	2 (13)
Diabetic mellitus	2 (13)
Splenectomy	1 (6)
HIV infection	1 (6)
Alcoholism	1 (6)
Clinical presentation	
Fever >38.5ºC	8 (50)
Alteration of consciousness	14 (88)
Seizure	9 (56)
Headache	8 (50)
Stiff neck	9 (56)
Septic shock	6 (38)
Acute respiratory failure	13 (81)
Glascow Coma Score	
13-15 points (mild)	3 (19)
9-12 points (moderate)	4 (25)
3-8 points (severe)	9 (56)
CSF results	
White cell count (x 10^9/l), median (range)	0.38 (0.01-27.6)
Total protein (mg/dl), median (range)	709 (15-1,593)
Glucose (mg/dl), median (range)	5 (0-64)
CSF-to-serum glucose ratio <0.4	12 (75)
Positive culture for *S. pneumoniae*	4 (25)
Clinical outcome	
Mortality	6 (38)
Cured without complications	2 (13)
Cured with complications	8 (50)
Seizure	5/8 (63)
Increased CSF pressure	3/8 (38)
Cranial nerve palsy	3/8 (38)
Hemiparesis	1/8 (13)

[a]Chronic diseases: chronic lung diseases, liver diseases, renal diseases, heart diseases. CSF, cerebrospinal fluid.

Table 1 also shows the results of CSF examination among study subjects. The median of white cell count, total protein and glucose were 0.38 x10^9/l, 709 mg/dl and 5 mg/dl, respectively. Twelve subjects (75%) had a CSF-to-serum glucose ratio <0.4.

Clinical outcomes

Ten subjects received combination antibiotics therapy as empirical treatment. Empiric treatment was initiated immediately upon diagnosis based on the clinical presentation and CSF findings (median time from hospital admission to antibiotic administration = 2.3 hours). Six patients were treated with monotherapy of whom 3 received an inappropriate non-meningitis dosage of cephalosporin. Six subjects died during hospitalization. Of the 10 survivors, 9 recovered relatively rapidly, while one required prolonged intubation and tracheostomy.

Neurologic complications were evaluated using brain computed tomography. Ten patients (63%) appeared to have neurological complication. The most common neurological complication were hydrocephalus (7 cases) and cerebral infarction (6 cases). Cerebritis was seen in 3 cases (Table2).

Antimicrobial susceptibility

Susceptibility testing was performed in all 16 cases. All the strains were susceptible to cefotaxime, levofloxacin, linezolid, and vancomycin on the disk diffusion test.

The MIC was determined in 10 of the isolates (Table 3). Thirty-six percent of isolates were susceptible to penicillin (MIC50: 0.158 mg/l) and 100% were susceptible to cefotaxime (MIC50: 0.125 mg/l), respectively.

Capsular serotyping

Ten isolates were identified to serotype (Table 4). The most commonly isolated serotypes were 23F (*n*=4) and 6C (*n*=2). Only one isolate was found for each of the following serotypes: 3, 6A, 6B, and 23A.

Table 2
Neurological complications of pneumococcal meningitis (*N*=10).

Neurological complications	Frequency
Hydrocephalus	7
Cerebral infarction	6
Cerebritis	3
Subdural collection or empyema	2
Brain abscess	1

DISCUSSION

Pneumococcal meningitis causes high rates of morbidity and mortality. In our study, the mortality rate was 37.5%, similar to that reported by previous studies (Lu *et al*, 2001; Kambire *et al*, 2016). In our study, 88% of subjects had altered consciousness, 81% had acute respiratory failure, 75% had a CSF-to-serum glucose ratio <0.4 and 56% had seizure upon presentation to the hospital, which are known to be poor prognostic factors (Lu *et al*, 2001; Lovera and Arbo, 2005). The mortality rate in our study (38%) was much higher than that reported in a previous study (17.5%)(Lim *et al*, 2017). This could be because the initial inappropriate antibiotic regimen rate in our study (19%) was much higher than in the study with the lower mortality (4%) (Lim *et al*, 2017).

The rate of neurological sequelae due to bacterial meningitis can be reduced by corticosteroid use along with antibiotic treatment (Tauber *et al*, 1985). However, only 1 subject in our study received dexa-

Table 3
Antimicrobial susceptibilities of 10 *Streptococcus pneumoniae* isolated from patients with meningitis.

Antimicrobials	Minimum inhibitory concentration (mg/l)		Susceptibility cut-off level (mg/l)	% Susceptible
	MIC50[a]	MIC range		
Penicillin*	0.1575	0.008-1	≤0.06	36
Cefotaxime*	0.125	0.008-0.38	≤0.5	100
Ceftriaxone	0.1575	0.006-0.38	≤0.5	100
Levofloxacin	0.75	0.38-1	≤2	100
Vancomycin	0.19	0.094-0.38	≤1	100
Fosfomycin	24	6-32	≤32	100

[a]MIC 50, the lowest concentration of antimicrobial at which 50% of the isolates are inhibited.
*Penicillin and cefotaxime susceptibilities test using 14 isolates.

Table 4
Serotypes of pneumococcal meningitis isolates according to the presence of PNSSP and age group (*N*=10).

Capsular serotypes	Age of patients (years)			Drug resistance		Serotype component of vaccines			
	<2	2-60	>60	PSSP	PNSSP	PCV10	PCV13	PCV15	PCV23
3	-	-	1	-	1	√	√	√	√
6A	-	-	1	1	-	´	√	√	´
6B	1	-	-	-	1	√	√	√	√
6C	1	-	1	-	2	´	´	´	´
23A	-	1	-	-	1	´	´	´	´
23F	-	2	2	2	2	√	√	√	√

PCV, pneumococcal conjugate vaccine; PSSP, penicillin susceptible *S. pneumoniae*; PNSSP, penicillin non-susceptible *S. pneumonia*; PCV 10, serotypes coverage; 1, 4, 5, 6B, 7F, 9V, 10C, 18C, 19F and 23F; PCV13, serotypes coverage; 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F; PCV15, serotypes coverage; 1, 3, 4, 5, 6A, 6B, 7F, 9V, 10C, 18C, 19A, 19F, 22F, 23F, 33F; PCV23, serotypes coverage; 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F.

methasone and only one patient received adjunctive dexamethasone.

A previous study reported cerebral infarction among 25% of adults with bacterial meningitis, resulting in a 32% mortality rate (Schut *et al*, 2012). Another previous study (Lucas *et al*, 2013) reported higher infarction rate of 56% which was similar to our study (60%). The higher infarction rate in our study could be due to our subjects being aged >50 years. A decreased level of consciousness, parameters of systemic inflammation, and infection with *S. pneumoniae* were also reported to be factors predicting the development of cerebral infarction (Weisfelt *et al*, 2006;

Roine *et al*, 2008). A brain abscess is a rare complication of community-acquired pneumococcal meningitis, occurring in <1% of all meningitis complications (Van de Beek *et al*, 2006; Weisfelt *et al*, 2006). However, in our study, 3 patients developed cerebritis and cerebral abscess formation. This is also likely due to inappropriate treatment in our cohort.

The World Health Organization (WHO, 2017) announced penicillin non-susceptible *S. pneumoniae* (PNSSP) is one of the 12 most important resistant bacterial problems globally for which an urgent need for new treatments exists. In our study, 36% of isolates were PSSP, similar to a report by National Antimicrobial Resistance Surveillance Thailand (NARST, 2016). Our results show penicillin G is no longer recommended for empiric treatment of pneumococcal meningitis.

In our study, 100% of the isolates were susceptible to ceftriaxone and cefotaxime. Srifuengfung *et al* (2014) found 10% of PNSSP isolates obtained from patients with IPD were resistant to ceftriaxone, particularly serotypes 6B and 19A. In our study, only one isolate of 6B and no isolate of 19A were seen. These discordant results indicate MIC determination is important.

Vancomycin is an alternative treatment for patients allergic to beta-lactams, along with levofloxacin and fosfomycin. Levofloxacin has satisfactory CSF penetration (Scotton *et al*, 2001; Pea *et al*, 2003). High dose fosfomycin can also penetrate the CSF (Kuhnen *et al*, 1987). However, there is little clinical data regarding the use of levofloxacin in the treatment of meningitis and it is unclear what is the appropriate dosage. One study reported 2 cases of pneumococcal meningitis treated successfully with levofloxacin (Scotton *et al*, 2001). One previous study reported fosfomycin can be used in combination with ampicillin or gentamicin to treat meningitis (10 of 12 patients treated successfully) (Sicilia *et al*, 1977) and another study reported fosfomycin can be used in combination with penicillin, ampicillin or chloramphenicol to treat meningitis (Sicilia *et al*, 1981); however those are very old studies and new susceptibility testing is needed.

The most common serotype detected in our study was 23F, unlike the results from the Netherlands (7F) (Dias *et al*, 2016) or a report from 4 African countries (Type 1) (Gessner *et al*, 2010). In our study, 20% of isolates were serotype 6C and 10% were serotype 23A, neither of which is covered by the pneumococcal vaccine (PCV) available in Thailand. In our study, serotype 23F was associated with a 50% mortality. A study from South Africa also reported serotype 23F was associated with 55.7% mortality (Cohen *et al*, 2015).

Pneumococcal meningitis cases in our study were very rare at the study hospital: only 16 cases in 10 years. A multicenter study of hospitals throughout Thailand is warranted to determine the true prevalence of this disease.

In conclusion, meningococcal meningitis was rare, penicillin G is not appropriate empiric treatment. Third-generation cephalosporins do appear to be appropriate first line empiric treatment of community-acquired pneumococcal meningitis. There is insufficient data to determine if levofloxacin or fosfomycin can be used to treat pneumococcal meningitis. Further studies are needed to determine this. Due to the rarity of the infection, it is unclear if a new pneumococcal vaccine covering other strains is warranted. Further studies are needed to determine this.

ACKNOWLEDGEMENTS

We would like to thank Assoc Prof Nalin Payakachat for the manuscript editing.

REFERENCES

Appelbaum PC. Resistance among *Streptococcus pneumoniae*: implications for drug selection. *Clin Infect Dis* 2002; 34: 1613-20.

Bennett NM, Buffington J, LaForce FM. Pneumococcal bacteremia in Monroe County, New York. *Am J Public Health* 1992; 82: 1513-6.

Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicorbial susceptibility tesing. Twenty-sixth Informational Supplement M100-S26. Wayne: CLSI, 2016.

Cohen C, Naidoo N, Meiring S, *et al*. *Streptococcus pneumoniae* serotypes and mortality in adults and adolescents in South Africa: analysis of national surveillance data, 2003 - 2008. *PLOS One* 2015; 10: e0140185.

Dias SP, Brouwer MC, Bijlsma MW, van der Ende A, van de Beek D. Sex-based differences in pneumococcal serotype distribution in adults with pneumococcal meningitis. *J Infect* 2016; 73: 616-9.

Gessner BD, Mueller JE, Yaro S. African meningitis belt pneumococcal disease epidemiology indicates a need for an effective serotype 1 containing vaccine, including for older children and adults. *BMC Infect Dis* 2010; 10: 22.

Grabenstein JD, Musey L.K. Differences in serious clinical outcomes of infection caused by specific pneumococcal serotypes among adults. *Vaccine* 2014; 32: 2399-405.

Kambire D, Soeters HM, Ouedraogo-Traore R, *et al*. Nationwide trends in bacterial meningitis before the introduction of 13-valent pneumococcal conjugate vaccine-Burkina Faso, 2011-2013. *PLOS One* 2016; 11: e0166384.

Kim SH, Song JH, Chung DR, *et al*. Changing trends in antimicrobial resistance and serotypes of *Streptococcus pneumoniae* isolates in Asian countries: an Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. *Antimicrob Agents Chemother* 2012; 56: 1418-26.

Konradsen HB, Kaltoft MS. Invasive pneumococcal infections in Denmark from 1995 to 1999: epidemiology, serotypes, and resistance. *Clin Diagn Lab Immunol* 2002; 9: 358-65.

Kuhnen E, Pfeifer G, Frenkel C. Penetration of fosfomycin into cerebrospinal fluid across non-inflamed and inflamed meninges. *Infection* 1987; 15: 422-4.

Leelarasamee A, Dhiraputra C, Hunnangkul S. Severe pneumococcal infection at a Thai hospital. *Int J Infect Dis* 1999; 3: 147-52.

Lim S, Chung DR, Kim YS, *et al*. Predictive risk factors for *Listeria monocytogenes* meningitis compared to pneumococcal meningitis: a multicenter case-control study. *Infection* 2017; 45: 67-74.

Lovera D, Arbo A. Risk factors for mortality in Paraguayan children with pneumococcal bacterial meningitis. *Trop Med Int Health* 2005; 10: 1235-41.

Lu CH, Chang WN, Chang HW. Streptococcal meningitis in adults: therapeutic outcomes and prognostic factors. *Clin Neurol Neurosurg* 2001; 103: 137-42.

Lucas MJ, Brouwer MC, van de beek D. Delayed cerebral thrombosis in bacterial meningitis: a prospective cohort study. *Intensive Care Med* 2013; 39(5): 866-71.

Mook-Kanamori BB, Geldhoff M, van der Poll T, van de Beek D. Pathogenesis and pathophysiology of pneumococcal meningitis. *Clin Microbiol Rev* 2011; 24: 557-91.

National Antimicrobial Resistance Surveillance Center (NARST), National Institute of Health, Ministry of Public Health, Thailand. Antibiogram 2016. Nonthaburi: NARST, 2016. [Cited 2017 Apr 27]. Available from: URL: http://narst.dmsc.moph.go.th/antibiograms.html/

Netsawang S, Punpanich W, Treeratweerapong V, Chotpitayasunondh, T. Invasive pneumococcal infection in urban Thai children: a 10-year review. *J Med Assoc Thai* 2010; 93 (Suppl 5): S6-12.

O'Brien KL, Wolfson LJ, Watt JP, *et al.* Pneumococcal Global Burden of Disease Study. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. *Lancet* 2009; 374: 893-902.

Pea F, Pavan F, Nascimben E, *et al.* Levofloxacin disposition in cerebrospinal fluid in patients with external ventriculostomy. *Antimicrob Agents Chemother* 2003; 47: 3104-8.

Roine I, Peltola H, Fernandez J, *et al*. Influence of admission findings on death and neurological outcome from childhood bacterial meningitis. *Clin Infect Dis* 2008; 46: 1248-52.

Schito GC, Debbia EA, Marchese A. The evolving threat of antibiotic resistance in Europe: new data from the Alexander Project. *J Antimicrob Chemother* 2000; 46 (Suppl T1): 3-9.

Schut ES, Lucas MJ, Brouwer MC, Vergouwen MD, van der Ende A, van de Beek D. Cerebral infarction in adults with bacterial meningitis. *Neurocrit Care* 2012; 16: 421-7.

Scotton PG, Pea F, Giobbia M, Baraldo M, Vaglia A, Furlanut M. Cerebrospinal fluid penetration of levofloxacin in patients with spontaneous acute bacterial meningitis. *Clin Infect Dis* 2001; 33: e109-11.

Sicilia T, Estevez E, Rodriguez A. Fosfomycin penetration into the cerebrospinal fluid of patients with bacterial meningitis. *Chemotherapy* 1981; 27: 405-13.

Sicilia T, Fadon A, Rodriguez A, Soto, J. Fosfomycin in pneumococcal meningitis. *Chemotherapy* 1977; 23 (Suppl 1): 429-40.

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: 2101-7.

Srifeungfung S, Phongsamart W, Tribuddharat C, *et al*. Serotype distribution and antibiotic susceptibility of invasive *Streptococcus pneumoniae* isolates in patients aged 50 years or older in Thailand. *Hum Vaccin Immunother* 2014; 10: 40-4.

Suwanpakdee D, Samakoses R, Sirinavin S, *et al*. Invasive pneumococcal disease in Phramongkutklao Hospital 2004-2008: clinical data, serotype distribution and antimicrobial resistance patterns. *J Med Assoc Thai* 2010; 93 (Suppl 5): S40-5.

Tauber MG, Khayam-Bashi H, Sande MA. Effects of ampicillin and corticosteroids on brain water content, cerebrospinal fluid pressure, and cerebrospinal fluid lactate levels in experimental pneumococcal meningitis. *J Infect Dis* 1985; 151: 528-34.

Van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. Community-acquired bacterial meningitis in adults. *N Engl J Med* 2006; 354: 44-53.

Weisfelt M, van de Beek D, Spanjaard L, Reitsma JB, de Gans J. Clinical features, complications, and outcome in adults with pneumococcal meningitis: a prospective case series. *Lancet Neurol* 2006; 5: 123-9.

World Health Organization (WHO). WHO publishes list of bacteria for which new antibiotics are urgently needed. Geneva: WHO, 2017. [Cited 2017 Apr 27]. Available from: URL: http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/