ACUTE BACTERIAL MENINGITIS IN ADULTS : A 20 YEAR REVIEW

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Abstract. During the period Jaunuary 1982 to December 2001 (20 years), a retrospective study in patients 15 years or older with acute bacterial meningitis who were admitted to Songklanagarind Hospital was carried out. There were 180 episodes in 161 cases of acute bacterial meningitis with an increasing incidence of disease during the study. Fifty-nine percent of episodes were nosocomial infection. The classic triad of acute bacterial meningitis was found in 54% of cases. The most common pathogen was *Streptococcus pneumoniae* (11.7%) in which 19% of these strain were penicillin-resistant. Gram-negative bacilli were common organisms in nosocomial meningitis (32.1%). Twenty-five patients died from meningitis with a mortality rate of 15.5%. Risk factors for mortality older age were than 60 years, HIV infection, impaired mental status and shock .

INTRODUCTION

Acute bacterial meningitis still has a high morbidity and mortality. In many previous studies, mortality rates were 20-27% (Durand *et al*, 1993; Sigurdardottir *et al*, 1997; Chotmongkol and Techoruangwiwat, 2000; Tang *et al*,1999; Hussein and Shafran, 2000) but increased to 40-50% in older adults (Gorse *et al*, 2000; Choi, 2001).

Epidemiological data of baterial meningitis in signs, symptoms, predisposing factors, microorganisms, and risk factors for death vary with time, geography, and patient age. *Streptococcus pneumoniae* is the most common causative organism in community-acquired bacterial meningitis in all studies (Durand *et al*, 1993; Sigurdardottir *et al*,1997; Tang *et al*, 1999; Chotmongkol and Techoruangwiwat, 2000; Hussein and Shafran, 2000). During the past three decades, penicillin-resistant *Streptococcus pneumoniae* (PRSP) has been rapidly increasing in many parts of the world. Data from ANSORP study revealed PRSP in 16.7% from CSF specimens (Song *et al*, 1999). In the United States, 36% of cases of pneumococcal meningitis were caused by PRSP and high resistance was found in 14% of cases (Schuchat *et al*, 1997). The increasing incidence of nosocomial bacterial meningitis is associated with an increase in neurosurgery and neurointervention (Tang *et al*, 1999). The most common nosocomial pathogens are gram-negative bacilli, *Staphylococcus aureus* and coagulase-negative staphylococci (Durand *et al*, 1993; Tang *et al*, 1999). The mortality rate in nosocomial meningitis is about 35% higher than in community-acquired meningitis (Durand *et al*, 1993).

In Thailand, there have been a few reports of acute bacterial meningitis (Chotpitayasunondh, 1994; Chotmongkol and Techoruangwiwat, 2000). However, there have been no data about community-acquired and nosocomial bacterial meningitis in adults. The purpose of this study was to compare clinical manifestations, predisposing factors, etiologic microorganisms and mortality rates in community-acquired and nosocomial bacterial meningitis; evaluate risk factors for death in acute bacterial meningitis and examine the incidence of PRSP meningitis.

MATERIALS AND METHODS

We reviewed the medical records of all patients, 15 years of age or older, in whom acute bacterial meningitis was diagnosed at Songklanagarind Hospital from January 1,1982 to December 31, 2001.

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The diagnosis of community-acquired bacterial meningitis was based on a compatible clinical picture, such as fever, headache, neck stiffness and impiared mental status plus one of the following (Duran *et al*, 1993; Sigurdardottir *et al*, 1997; Hussein and Shafran, 2000) : (1) positive cerebrospinal fluid (CSF) culture, (2) positive blood culture, positive CSF Gram stain and/or CSF antigen test, or (3) CSF neutrophilic pleocytosis defined as absolute neutrophils ≥ 100 cells/mm^3 or ≥ 50 cells/mm^3 in an immunocompromized host with a decreased glucose level, and an increased protein concentration despite a negative culture of the CSF and blood, where the results of the CSF Gram stain and antigen were negative. Infection was considered nosocomial if the diagnosis was made after more than 48 hours of hospitalization or within one week of discharge from the hospital (Garner *et al*, 1988; Durand *et al*, 1993). Coagulase-negative staphylococci isolated from CSF was considered as an etiologic agent only if it was found repeatedly or if it was cultured from the tip of an indwelling neurological device.

Viral, fungal, mycobacterial, and drug induced meningitis were excluded. Suspected cases subsequently proven to be secondary to intracranial or epidural abscess were also excluded.

Definition of clinical feature in this study: seizure was classified as meningitis only when it occurred within 24 hours of admission or with the diagnosis of meningitis. Focal neurological deficits and cranial nerve palsy were classified as meningitis related only if it was not due to a preexisting illness. Shock was defined as a blood pressure below 90/60 mmHg, or a urine output of less than 20 cc/hour or where a vasopressor was needed for more than 4 hours when the event occurred within 24 hours of admission or with the diagnosis of meningitis. Immunocompromized hosts were defined as patients with HIV infection or patients who either used prednisolone more than 30 mg/day for at least 2 weeks or immunosuppression within 1 month prior to admission with a diagnosis of meningitis. Mortality was classified as a meningitis related if death was due to meningitis or its complications, but not if it was due to a preexisting serious illness after biological cure and clinical recovery from meningitis.

Statistical analysis used the chi-square, Fisher's exact test and logistic regression models to determine the clinical characteristic, mortality rate and risk factors for mortality with acute bacterial meningitis.

RESULTS

There were 180 episodes of acute bacterial meningitis occurred in 161 patients over the 20 years period 1982-2001. One hundred forty-five patients (90%) had a single episode of meningitis, 16 patients (10%) had more than one episode of acute bacterial meningitis, 74 episodes (41.1%) were community-acquired meningitis and nosocomial meningitis occured in 106 episodes (58.9%). There were 114 (71.2%) men and 46 (28.8%) women with aged 15 to 80 years (mean ± SD, 40.6± 17.4 years).

The incidence of acute bacterial meningitis was significantly higher in the last 10 years of the study. There were 37 episodes from 1982 to 1991 and 143 episodes from1992 to 2001 (p=0.006) (Fig 1).

Clinical manifestations

The classic triad of symptoms (fever, neck stiffness, and impaired mental status) was present in 62.5% and 44.8% of episodes of community-acquired and nosocomial bacterial meningitis (average 54% in all episodes), respectively, but all had at least one of these findings. Fifty-two episodes (70.3%) of community-acquired meningi-

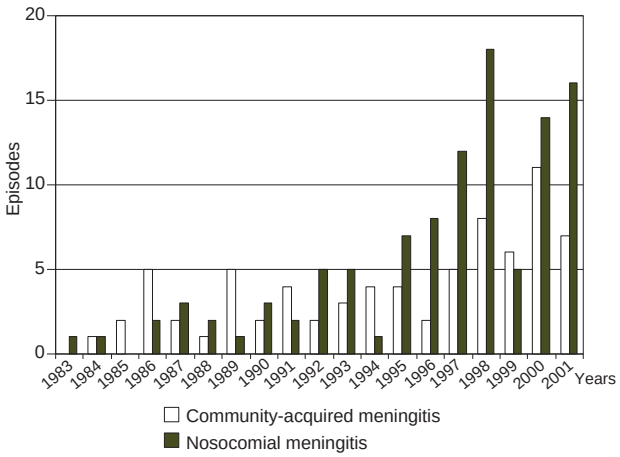

Fig 1–Incidence of acute bacterial meningitis in adults from 1982-2001.

tis had a change in mental status, of whom 3 episodes had coma and did not respond to stimuli. The patients with community-acquired meningitis had clinical symptoms of headache, focal neurological deficits, cranial nerve palsys, and vomiting more often than patients with nosocomial bacterial meningitis (Table 1). Seizure occurred in 8.9% of episodes of meningitis, which were focal in 6.3%, generalized in 81.3% and not characterized in 12.5%.

Focal neurological deficits occurred only in 4 patients with community acquired meningitis. One had left hemiplegia and a CT scan of the brain revealed a hypodense lesion in the frontoparietal lobe. One had left hemiplegia and hemiparesis grade I, with a normal CT scan of the brain. Another had cerebellar signs. Focal neurological deficits persisted until discharge in all patients.

Five patients with community-acquired meningitis had cranial nerve palsy. Two patients had facial nerve palsy; one had CN 3,4,6 palsy suspected of having a cavernous sinus thrombophlebitis; one had facial palsy and deafness; and 2 had only deafness. In 2 patients with deafness, the meningitis were caused by beta-hemolytic *Streptococcus* group A.

Predisposing factors

The frequency of 14 predisposing factors for acute bacterial meningitis are shown in Table 2. In community-acquired meningitis, the frequency of alcoholism, chronic otitis media, and HIV infection were significantly higher than in patients with nosocomial meningitis. Neurosurgery and neurointervention were significantly higher in patients with nosocomial infection.

Neurosurgery performed in nosocomial meningitis patients included craniotomy with clot removal (15.1%), craniotomy with tumor removal (14.2%), craniotomy with aneurysm clipping (8.5%), craniotomy with repair of dura (1.9%) and other surgery (7.6%). Neurointervention procedures done in nosocomial meningitis patients were classified as ventriculostomy (25.5%), VP shunt (14.2%), lumbar drainage (1.9%), and ICP monitoring (0.9%). A VP shunt procedure was done in only one was community-acquired meningitis patient.

Cerebrospinal fluid findings

CSF samples were available from lumbar puncture in 142 episodes (79%), ventriculostomy (12.8%), VP shunt (2.2%), lumbar drainage (1.7%), and other (4.4%). The opening pressure was recorded in 78 episodes (55%) with range from 4-60 cmH_2O (mean 24.7 cmH_2O). The remaining CSF parameters are outlined in Table 3. Ninety-seven percent of CSF samples had more than 100 WBC/mm^3 (mean 4,442±216 cells/mm^3). Sixty-three point eight percent of samples displayed a neutrophil predominance of more than 80% (mean 82±17%). CSF bacterial antigen was

Table 1
Clinical manifestations of acute bacterial meningitis.

Clinical	Community-acquired meningitis	Nosocomial meningitis	p-value
	Episodes (%)		
Fever	72/74 (97.3)	105/106 (99.1)	0.364
Headache	60/66 (90.9)	49/64 (76.6)	0.026
Impaired mental status	52/74 (70.3)	75/105 (71.4)	0.876
Neck stiffness	65/72 (90.3)	50/59 (84.8)	0.336
Seizure	8/73 (10.9)	8/106 (7.6)	0.432
Focal neurological deficit	4/69 (5.8)	0/106 (0)	0.036
Cranial nerve palsy	5/73 (6.9)	1/100 (1)	0.038
Papilledema	2/49 (4.1)	1/31 (3.2)	0.844
Vomiting	32/60 (53.3)	21/82 (25.6)	0.001
Shock	4/74 (5.4)	2/106 (1.9)	0.190

Table 2
Predisposing factors in acute bacterial meningitis.

Factors	Community-acquired meningitis 74 episodes (%)	Nosocomial meningitis 106 episodes (%)	p-value
Diabetes mellitus	8/74 (10.8)	7/106 (6.6)	0.315
Alcoholism	9/67 (13.4)	3/75 (4)	0.044
Cirrhosis	3/24 (12.5)	2/30 (6.7)	0.462
Acute otitis media	2/46 (4.4)	1/44 (2.3)	0.584
Chronic otitis media	5/46 (10.9)	0/42 (0)	0.028
Sinusitis	1/25 (4)	4/30 (13.3)	0.231
CSF leakage	14/74 (18.9)	24/105 (22.9)	0.562
Post-neurosurgery	1/74 (1.4)	50/106 (47.2)	0.000
Post-neurointervention	8/74 (10.8)	45/106 (42.5)	0.000
Immunocompromized	5/74 (6.8)	5/105 (4.8)	0.567
HIV infection	8/38 (21.1)	0/86 (0)	0.000
Malignancy	9/74 (12.2)	14/106 (13.2)	0.836
Pneumonia	4/74 (5.4)	12/106 (11.3)	0.170
Head injury	13/74 (20.3)	33/106 (31.1)	0.259
During 1 month	6/74 (8.1)	19/106 (17.9)	0.169
More than 1 month	7/74 (12.2)	14/106 (13.2)	0.836
None of 14 factors	18/74 (24.3)	7/106 (6.6)	0.001

Table 3
Initial cerebrospinal fluid analysis in acute bacterial meningitis.

CSF finding	Community-acquired meningitis (%)	Nosocomial meningitis (%)
Opening pressure (cmH_20)		
0-18	32	32.2
19-30	44	50
>30	24	17.8
White blood cell ($cells/mm^3$)		
0-100	4.1	1.9
101-5,000	75.3	78.1
5,001-10,000	13.7	6.7
>10,000	6.9	13.3
PMN (%)		
20-80	42.5	31.7
>80	57.5	68.3
Protein (mg/dl)		
0-50	2.8	2.9
51-200	22.5	38.5
201-500	46.5	45.2
>500	28.2	13.5
Glucose <40 mg%	71.6	65.7
CSF/blood glucose <0.4	86.3	76.2
CSF culture positive	60.3	60.6
CSF Gram stain positive	46	40
Hemoculture positive	45.7	17.7

performed in 22 episodes. There were only two positive results, one *S. pneumoniae* antigen (1 of 16 samples) and one *Haemophilus inluenzae* antigen (1 of 6 samples).

Blood culture was positive in patients with community-acquired meningitis significantly more than patients with nosocomial meningitis (45.7% *vs* 17.7%, p=0.006).

Bacteriological findings

Streptococcus pneumoniae was the most common organism overall (causing 11.7% of the 180 episodes). The relative frequency of the causative organism in acute bacterial meningitis is shown in Table 4. In the community-acquired meningitis group the three most common organisms were *S. pneumoniae* (20.3%), *Streptococcus* spp (20.3%) and *Klebsiella pneumoniae* (12.2%). There was one case of *H. influenzae* meningitis but *Neisseria meningitidis* and *Listeria monocytogenes* were not found in this study. In contrast, nosocomial bacterial meningitis 34 episodes (32.1%) were caused by gram-negative bacilli and the most common organisms in this group were *Acinetobacter* spp (10.4%), *K. pneumoniae* (8.3%) and coagulse-negative staphylococcus (8.3%).

There were four episodes (19%) caused by

Table 4
Microorganisms causing acute bacterial meningitis.

Organism	Community-acquired meningitis (episodes)	Nosocomial meningitis (episodes)
S. pneumoniae	17	4
β-*Streptococcus* gr A	4	0
α-*Streptococcus* not gr D	3	3
Enterococcus	3	3
Other *Streptococcus*[a]	5	3
S. aureus	4	8
Coagulase-negative *Staphylococcus*	2	9
K. pneumoniae	9	9
P. aeruginosa	1	8
Acinetobacter spp	0	11
Salmonella	2	0
H. influenzae	1	0
Other gram-negative bacilli[b]	5	6
Other gram-positive[c]	0	2
Mixed bacterial spp[d]	0	3
Culture negative	18	37
Total	74	106

[a]Other *Streptococcus*: β-*Streptococcus* not gr A,B,D (1/1), Microaerophilic streptococci (2/0), Gamma *Streptococcus* not gr D and *Streptococcus* gr B (1/0), α-*Streptococcus* not pneumoniae (1/0) and α-*Streptococcus* group D not enterococci (0/1).
[b]Other gram-negative bacilli: *E. coli* (1/1), *Enterobacter* (2/2), *Citrobacter* (1/2), *Providencia* (0/1), *unidentify* (1/0).
[c]Mixed bacterial spp: *Proteus mirabilis* + *K. pneumoniae*, α-*Streptococcus* group D not enterococci + *Salmonella* gr B, and S. epidermidis + Enterobacter (0/1)
[d]Other gram-positive: *Bacillus* and unidentify (0/1).

penicillin-resistant *S. pneumoniae* (PRSP) and 3 episodes were community-acquired meningitis. All episodes occurred in the last 5 years of study. Highly penicillin-resistant *S. pneumoniae* was found in 2 episodes (one had penicillin MIC ≥ 2 μg/ml, cefotaxime MIC 0.5 μg/ml and another had penicillin MIC 8 μg/ml, cefotaxime MIC 2 μg/ml).

In community-acquired *S. aureus* meningitis, all were caused by methicillin-sensitive *S. aureus* (MSSA). In contrast, methicillin-resistant *S. aureus* (MRSA) was the cause of all episodes of nosocomial *S. aureus* meningitis. All cases of MRSA meningitis had neurosurgery or neurointervention performed before.

Table 5
Multivariate analysis of risk factor of mortality.

Factors	Odds ratio	95% CI	p-value
Age older than 60 year	4	1.4-11.7	0.014
Impaired mental status	5.3	1.1-26.4	0.017
HIV infection	15.9	2.6-26.2	0.003
Shock	13.7	2.1-91.1	0.006

Overall, one third of acute bacterial meningitis of presumed bacterial etiology were culture negative. There were no differences between community-acquired and nosocomial bacterial meningitis.

Mortality

Twenty-five patients died from bacterial meningitis, causing an overall mortality rate of 15.5%. The mortality rate was not significantly different between patients with community-acquired and nosocomial meningitis (14.9% *vs* 13.2%, p=0.752).

According to the univariate analysis, nine factors were associated with a significantly higher overall mortality rate among patients with acute bacterial meningitis: an age older than 60 years (p=0.015), impaired mental status (p=0.012), seizure (p=0.004), CSF leakage (p=0.005), shock (p<0.0005), papilledema (p=0.011), HIV infection (p=0.001), bacteremia (p=0.038), and *S. aureus* meningitis (p=0.044). After multivariated analysis by logistic regression model, only an age older than 60 years, HIV infection, impaird mental status, and shock still significantly increased the mortality rate (Table 5).

DISCUSSION

Acute bacterial meningitis remain a major cause of death and long term neurological sequelae. In our study, the mean annual incidence of the cases was 9 episodes per year. This incidence had increased significantly throughout the time of the study. It is difficult to compare this incidence with

the results of other studies because of the variation in hospitals and inclusion criteria in the studies. In previous studies, such as reported by Massachusetts General Hospital, the incidence of acute bacterial meningitis was 19 episodes per year (Durand *et al*, 1993). In contrast, the incidence reported from Iceland in community acquired meningitis was 6 cases per year (Sigurdardottir *et al*, 1997). The majority of episodes of acute bacterial meningitis in our study were nosocomial meningitis (58.9%), while a previous study reported a nosocomial infection rate of about 13% (Hussein and Shafran, 2000). This significant discrepancy is likely attributable to the inclusion of neurological patients in this study.

The vast majority of our patients presented with fever and neck stiffness, but only 54% had the classic clinical triad. This finding was compatible with previous studies where classic symptoms were reported to range from 33-66% (Durand *et al*, 1993; Sigurdardottir *et al*, 1997). Seizure, in our series, was documented in only 8.9%, which was lower than the rate reported in other studies (10-23%) (Durand *et al*, 1993; Sigurdardottir *et al*, 1997; Tang *et al*, 1999; Chotmongkol and Techoruangwiwat, 2000; Hussein and Shafran, 2000) due to the definition of seizure. Similarly, focal neurological deficit and cranial nerve palsy were found less in our study because these were classified as meningitis related, rather than due to a preexisting illness.

S. pneumoniae was the most common organism to cause bacterial meningitis in our study, as in previous reports (Durand *et al*, 1993; Sigurdardottir *et al*, 1997; Aroni *et al* 1998; Tang *et al*, 1999; Chotmongkol and Techoruangwiwat, 2000; Hussein and Shafran, 2000). The prevalence of PRSP and highly PRSP in our study (19% and 9.5%, respectively) were lower than the rates, of 36% and 14% of bacterial meningitis in the United States (Schuchat *et al*, 1997). However, the incidence of PRSP increased during the last 5 years of our study. We should be concerned about PRSP being an increasing cases of miningitis. In this study, there was no cases of *N. meningitidis* or *L. monocytogenes* infections, which were common etiologic organisms in other reports (Durand *et al*, 1993; Hussein and Shafran, 2000).

Not all cases of suspected bacterial meningitis yielded an identifiable pathogen from the CSF or blood culture. In our study, 30.6% were culture negative. This value was higher than the rate observed in both the Massachusetts (Durand *et al*, 1993) and Scandinavian (Sigurdardottir *et al*, 1997) reviews (15% and 11%, respectively).

The mortality rate from our study was 15.5%, which is lower than the rates in previous reports (18-34%) (Durand *et al*, 1993; Sigurdardottir *et al*, 1997; Tang *et al*, 1999; Chotmongkol and Techoruangwiwat, 2000; Hussein and Shafran, 2000). It is possible that mortality in our study was classified as meningitis related, but not due to total in-hospital mortality. In previous studies, as in ours, older age, impaired mental status, and shock on the first day correlate with a poor outcome in patients with meningitis. Other risk factors for death were observed in some studies, notably, diabetes mellitus, seizures, bacteremia, gram-negative bacilli meningitis, CSF WBC more than 5,000 cells/mm^3 (Durand *et al*, 1993; Aronin *et al*, 1998; Tang *et al*,1999), but were not significant correlated with morality in our study.

A limitation of our study was that we were unable to collect all the important clinical data, because it was a retrospective study. There are many different risk factors for death for community-acquried and nosocomial meningitis which differ between the two groups. Further study is needed to evaluate this.

Over the two decades of the study, the mortality rate decreased; but not significantly. This may be due to the use of new antibiotics, such as third generation cephalosporins, beta lactam-beta lactamase inhibitors, carbapenem, and vancomycin to replace penicillin/ampicillin and chloramphenicol. The introduction of new antimicrobial agents has not markedly decreased the mortality rate among adults with acute bacterial meningitis. Further progress in improving the outcome of meningitis may result from newer developments in the management of meningeal infection, such as the reduction of the inflammatory process, and cytokines in the cerebrospinal fluid by corticosteroids, cytokine antagonists and/or monoclonal antibodies to adhesion glycoprotein, which may decrease mortality and morbidity in acute bacterial meningitis (Toumanen *et al*, 1989; Quagliarello and Scheld, 1992; Gans and van de Beek, 2002). The

role of adjunctive corticosteroids in acute bacterial meningitis in adults remains conterversial (Spach and Jackson, 1995; Quagliarello and Scheld, 1997; Phillips and Simor, 1998; Rose, 2000; Chowdhury and Tunkel, 2000), although a new prospective randomized control trial of dexamethasone in adults with bacterial meningitis shows that early, short course treatments improve the outcome and decrease mortality, especially in pneumococcal meningitis, and does not increase the risk of gastrointestinal bleeding (Gans and van de Beek, 2002).

At present, early diagnosis, early appropriate empirical antibiotics, early recognition and treatment of complications of bacterial meningitis are still the main recommendations for the treatment of acute bacterial meningitis.

In conclusion, this is the first study of community-acquried and nosocomial bacterial meningitis in adults in Thailand. It shows an increasing incidence of bacterial meningitis, especially nosocomial infection and an increasing incidence of PRSP meningitis.

REFERENCES

Aronin SI, Peduzzi P, Quagliarello VJ. Community acquired bacterial meningitis : risk stratification for adverse clinical outcome and effect of antibiotic timing. *Ann Intern Med* 1998; 129: 862-9.

Choi C. Bacterial meningitis in aging adults. *Clin Infect Dis* 2001; 33: 1380-5.

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

Chotpitayasunondh T. Bacterial meningitis in children: etiology and clinical features, an 11 year review of 618 cases. *Southeast Asian J Trop Med Public Health* 1994; 25: 107-15.

Chowdhury MH, Tunkel AR. Antibacterial agent in infections of the central nervous system. *Infect Dis Clin North Am* 2000; 14: 391-407.

Durand ML, Calderwood SB, Weber DJ, *et al*. Acute bacterial meningitis in adults: a review of 493 episodes. *N Engl J Med* 1993; 328: 21-8.

Gans JD, van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002; 347: 1549-56.

Garner JS, Jarvis WR, Emori TG, Hughes JM. CDC definitions for nosocomial infections,1988. *Am J Infect Control* 1988; 16: 128-40.

Gorse GJ, Thrupp LD, Nudleman KL, Wyle FA, Havkins B, Cesario TC. Bacterial meningitis in the elderly. *Arch Intern Med* 1984; 144: 1603-7.

Hussein AS, Shafran SD. Acute bacterial meningitis: a 12 year review. *Medicine* 2000; 79: 360-8.

Phillips EJ, Simor AE. Bacterial meningitis in children and adults. *Postgrad Med* 1998; 109: 102-17.

Quagliarello VJ, Scheld WM. Bacterial meningitis: pathogenesis, pathophysiology and prognosis. *N Engl J Med* 1992; 327: 864-72.

Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. *N Engl J Med* 1997; 336: 708-15.

Rose KL. Acute bacterial meningitis. *Semi Neurol* 2000; 20: 293-306.

Schuchat A, Robinson K, Wenger JD, *et al*. Bacterial meningitis in the United States in 1995. *N Engl J Med* 1997; 337: 970-6.

Sigurdardottir B, Bjornsson OM, Jonsdttir KE, Erlendsdottir H, Gudmundsson. Acute bacterial meningitis in adults: a 20 year overview. *Arch Intern Med* 1997; 157: 425-30.

Song JH, Lee NY, Ichiyama S, *et al*. Spread of drug-resistant *Streptococcus pneumoniae* in Asian countries: Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. *Clin Infect Dis* 1999; 28: 1206-11.

Spach DH, Jackson LA. Bacterial meningitis. *Neurol Clinics* 1995; 17: 711-35.

Tang LM, Chen ST, Hsu WC, Lyu RK. Acute bacterial meningitis in adults: a hospital base epidemiological study. *Q J Med* 1999; 92: 719-25.

Tuomanen EI, Saukkonen K, Sande S, Cioffe C, Wright SD. Reduction of inflammation, tissue damage and mortality in bacterial meningitis in rabbits treated with monoclonal antibody against adhesion promoting receptor of leukocytes. *J Exp Med* 1989; 170: 959-69.