The Etiological Role of Parameningeal Infections in Adult Patients with Community-Acquired Acute Bacterial Meningitis in Eastern Turkey

Türkiye'nin Doğusunda Erişkinlerdeki Toplumdan Edinilmiş Akut Bakteriyel Menenjitlerde Parameningiyal Enfeksiyonların Etiyolojideki Rolü

Serpil EROL, MD,[a]
Zülal ÖZKURT, MD,[a]
Ayten KADANALI, MD,[a]
Kemalettin ÖZDEN, MD[a]

[a]Department of Clinical Bacteriology and Infectious Diseases, Atatürk University Faculty of Medicine, Erzurum

Geliş Tarihi/*Received:* 04.06.2008
Kabul Tarihi/*Accepted:* 31.10.2008

This manuscript was presented at the XIII[th] Türk Clinical Microbiology and Infectious Diseases Congress, 14-18 March 2007, Antalya, Turkey.

Yazışma Adresi/*Correspondence:*
Serpil EROL, MD
Atatürk University Faculty of Medicine, Aziziye Hospital, Department of Clinical Bacteriology and Infectious Diseases, Erzurum, TÜRKİYE/TURKEY
sererol@gmail.com

ABSTRACT Objective: To determine the etiological role of parameningeal infections in community-acquired acute bacterial meningitis in adults. **Material and Methods:** This prospective study included 69 (45 males, 24 females; mean age 39.2±20.4 years, range: 14-76 years) patients with community acquired acute bacterial meningitis hospitalized in the Department of Infectious Diseases and Clinical Microbiology, Atatürk University Medical School Hospital between December 2002 and December 2006. The diagnosis was based on the clinical pictures and physical examination, laboratory, and radiological findings. **Results:** Fifty-five patients (79.7%) had at least one underlying medical condition; 55.1% had one or more parameningeal infections and 24.6% had another underlying disease. Among the underlying medical conditions, paranasal sinusitis and otitis media were the most common; 23.2% and 18.8%, respectively. The maxillary sinuses were the most common focus for sinusitis. Of the patients, 15.9% died during hospitalization. Five of the survivors (8.6%) had several complications and 3 (5.1%) had permanent neurological sequelae. The mean age of the fatal group (51.4±21.6 years) was higher than that of the non-fatal group (36.9.±19.4 years, p=0.03). In univariate analysis, significant risk factors for mortality were older age, female gender, and deteriorated consciousness level. Underlying medical conditions had no effect on mortality. In stepwise logistic regression analysis, only the initial consciousness level and female gender were independently associated with mortality. **Conclusion:** Parameningeal infections are the major predisposing factor for community-acquired bacterial meningitis in adults. In all cases of adult bacterial meningitis, parameningeal infections or other underlying conditions should be investigated carefully and should be managed properly.

Key Words: Meningitis, bacterial

ÖZET Amaç: Erişkinlerdeki toplum kaynaklı akut bakteriyel menenjitlerde parameningiyal enfeksiyonların etiyolojideki rolünü irdelemek. **Gereç ve Yöntemler:** Bu prospektif çalışmaya Aralık 2002 ve Aralık 2006 tarihleri arasında Atatürk Üniversitesi Tıp Fakültesi Hastanesi Enfeksiyon Hastalıkları Kliniği'nde yatarak tedavi gören 69 hasta (45 erkek, 24 kadın, ortalama yaş 39.2 ± 20.4 yıl, yaş aralığı: 14-76 yıl) dahil edilmiştir. Menenjit ve parameningiyal enfeksiyonların tanısı klinik bulgular, fiziksel muayene bulguları, laboratuvar sonuçları ve radyolojik bulgulara göre konulmuştur. **Bulgular:** Elli beş hastada (%79.7) menenjit için altta yatan en az bir hazırlayıcı faktör saptandı. Bu hastaların %55.1'inde bir veya daha fazla parameningiyal enfeksiyon saptanırken, %24,6'sında altta yatan başka bir hazırlayıcı faktör bulundu. En sık saptanan hazırlayıcı faktör paranazal sinüzit (%23.2) ve otitis media (%18,8) idi. Sinüzit tanısı almış hastalarda en sık tutulan sinüsler maksiller sinüslerdi. Yatış süresi içinde hastaların %15.9'u kaybedildi. Sağ kalan hastalardan 5'inde (%8.6) çeşitli komplikasyonlar ortaya çıkarken, 3 hastada (%5.1) kalıcı nörolojik sekeller gelişti. Ölen hastaların yaş ortalaması (51.4 ± 21.6 yıl) sağ kalan hastalarınkinden (36.9. ± 19.4 yıl) daha yüksekti (p= 0.03). Tek değişkenli analizde ileri yaş, kadın cinsiyet ve bozulmuş bilinç düzeyi mortalite için anlamlı risk faktörleri olarak saptandı. Altta yatan hazırlayıcı faktörlerin mortalite üzerinde etkisi saptanmadı. Lojistik regresyon analizinde yalnızca başlangıçtaki bilinç düzeyi ve kadın cinsiyet mortalite için bağımsız risk faktörü olarak belirlendi. **Sonuç:** Parameningiyal enfeksiyonlar erişkinlerdeki toplumdan kazanılmış bakteriyel menenjitler için en önemli hazırlayıcı faktördür. Bütün erişkin bakteriyel menenjit olgularında parameningiyal enfeksiyonlar ve altta yatan diğer hazırlayıcı faktörler dikkatlice araştırılmalı ve ortadan kaldırılmalıdır.

Anahtar Kelimeler: Bakteriyel menenjit

Turkiye Klinikleri J Med Sci 2009;29(6):1483-90

Apart from epidemics, at least 1.2 million cases of bacterial meningitis are estimated to occur each year; 135 000 of them are fatal. These numbers have made bacterial meningitis a top-ten infectious cause of death worldwide. About half the survivors have neurological and other consequences of the disease.[1-3] Because of the vaccine-related decline in meningitis due to *H. influenzae* type b, the median age of patients with meningitis has remarkably shifted to adulthood in developed countries.[4,5] However, in developing countries, bacterial meningitis in adult age remains to be a problem.[5-8]

Pathogens causing bacterial meningitis reach the subarachnoid space via three different routes: 1. Bloodstream, 2. Spread from infections of surrounding tissues (sinusitis, otitis media, mastoiditis), 3. Directly from dural defect after trauma or surgical procedures.[9,10]

Although bacterial spread via bloodstream has been considered a major route, other routes also have a considerable role in the emergence of bacterial meningitis.[2] In this study, we aimed to determine the frequency of parameningeal infections in acute bacterial meningitis in adults.

MATERIAL AND METHODS

This prospective study was run at the Department of Infectious Disease and Clinical Microbiology Atatürk University Medical School, Erzurum, Turkey between December 2002 and December 2006. The Atatürk University Medical School has a 1200-bed teaching hospital, which is a referral center in the eastern part of Turkey. All community-acquired acute bacterial meningitis patients at 14 years of age or older were enrolled in the study. Patients who were initially treated at other hospitals but were transferred to this hospital for further therapy were also included; patients with nosocomial meningitis were excluded.

The diagnosis of bacterial meningitis was based on clinical signs and/or symptoms consistent with this infection and identification of a specific bacterial pathogen in the cerebrospinal fluid (CSF) culture. In culture negative cases, the diagnosis was based on the history of acute disease, presence of clinical findings such as headache, fever and nuchal rigidity, and typical CSF features including decreased glucose level (<40 percent of simultaneously measured serum glucose), increased protein concentration (>50 mg/dl), and pleocytosis with predominant polymorphonuclear cells.[6] All patients were investigated for the presence of parameningeal infections by medical history and physical, laboratory and radiological examinations.

The data on gender, age, duration of illness, clinical manifestations, associated diseases, head injury or neurosurgical procedures, laboratory findings, use of antibiotics, and outcome were recorded and non-fatal and fatal cases were compared.

The diagnosis of parameningeal infections was based on the clinical pictures and physical examination, laboratory, and radiological findings. The initial consciousness level was classified into three stages according to Glasgow Coma Scale (GCS) score/: Stage I. Normal consciousness, GCS 15; Stage II. Inattention, confusion, and clouding of consciousness, GCS score 10-14; Stage III. Comatose, GCS score 3-9.

STATISTICAL ANALYSIS

Statistical analyses were performed on SPSS 13.0 for Windows, SPSS Inc, Chicago IL, USA. Comparisons between groups were made using the unpaired Student's t test for continuous variables and the Pearson[2] or Fisher's Exact Test for nominal variables. The level of significance was 0.05. To assess risk factors for mortality, multivariate analysis using logistic regression was performed. Candidate variables were entered using a backwards, stepwise approach. Predictor variables were kept in the final model if $P<0.05$.

RESULTS

Sixty-nine patients with community-acquired acute bacterial meningitis were hospitalized during the study period. There were 45 (62.5%) male and 24 female (34.8%) patients. The mean age of the patients was 39.2 ± 20.4 years (45.8 ± 20.6 years in the female, 35.7 ± 19.6 years in the male, range, 14-79

years). Six patients (8.7%) had a history of recurrent meningitis.

Fifty-five (79.7%) of the 69 patients had at least one underlying medical condition or predisposing factors for acute bacterial meningitis, and 11 (15.9%) had two or more underlying medical conditions (Table 1). The distribution of the underlying conditions among the patients were as follows; 55.1% (38/69) had one or more (total: 44) parameningeal infections, and 24.6% (17/69) had another (total: 24) underlying disease. The remaining 14 patients (20.3%) had no underlying conditions. The distribution of underlying conditions was shown in Table 2. Table 3 shows the localizations of the inflammation in 16 patients with paranasal sinusitis.

In 15 (21.7%) patients, pathogen bacteria were isolated from CSF cultures. Gram's staining of CSF revealed the microorganism in 8 (11.6%) patients. In the remaining patients (66.6%), no pathogens were identified. *Streptococcus pneumoniae* was the most frequently isolated bacteria. Distribution of the etiological agents was shown in Table 4. Thirty-nine patients (56.5%) received some antibiotic therapy before admission. Only 2 (5.1%) had positive CSF culture results. Blood cultures were done for all 69 patients, and only 3 patients had positive blood culture findings (1 *S. pneumoniae*, 1 *Enterobacter aerogenes*, 1 *Escherichia coli*). The organisms grown in the blood cultures were identical to those grown in the CSF cultures.

Of the 6 patients with a recurrent meningitis history, 2 had paranasal sinusitis, 2 otitis media, 1 CSF leakage and 1 a remote history of head trauma as predisposing factors.

Eleven patients (15.9%) died during the hospitalization period. Five of the survivors (8.6%) had

TABLE 1: Predisposing factors in patients with acute bacterial meningitis.

	n	%
Patients with any predisposing factor	55	79.7
Patients with no predisposing factor	14	20.3
Patients with 2 or more predisposing factors	11	15.9

TABLE 2: The distribution of underlying conditions.

Parameningeal infection	n %	Other underlying medical condition	n %
Paranasal sinusitis	16 (23.2)	Head trauma	9 (13.0)
Otitis media	13 (18.8)	Diabetes mellitus	4 (5.8)
Mastoiditis	7 (10.1)	Ventriculo-peritoneal shunt	3 (4.3)
Pneumonia	4 (5.8)	Malignancy**	3 (4.3)
Periodontal infection	2 (2.9)	CSF fistulae	2 (2.9)
Endocarditis	1 (1.4)	Chronic subdural hematoma	1 (1.4)
Tonsillopharyngitis	1 (1.4)	Chronic renal failure	1 (1.4)
-	-	Vertebral surgery*	1 (1.4)
Total	44	Total	24

§ Metastasis of cranial bones in two cases, and maxillary osteosarcoma in one case,
*Occured more than two months before the onset of meningitis,
CSF: Cerebrospinal fluid.

TABLE 3: Localization of paranasal sinusitis in patients with acute bacterial meningitis.

Localization	n	%
Maxillary	7	43.7
Maxillary + frontal	1	6.2
Maxillary + ethmoid	1	6.2
Maxillary + sphenoid	1	6.2
Maxillary + ethmoid + sphenoid	1	6.2
Ethmoid	2	12.5
Frontal	1	6.2
Sphenoid	1	6.2
Pansinusitis (maxillary + ethmoid + frontal + sphenoid)	1	6.2
Maxillary sinusitis total	12	75
Ethmoid sinusitis total	5	31.2
Sphenoid sinusitis total	3	18.7
Frontal sinusitis total	3	18.7
Total patients with sinusitis	16	100

TABLE 4: Distribution of etiological agents.

	n	%
Cerebrospinal fluid cultures	15	21.7
Streptococcus pneumoniae	8	
Escherichia coli	1	
Enterobacter aerogenes	1	
Enterococcus spp.	1	
Haemophilus influenzae	1	
Neisseria meningitidis	1	
Staphylococcus epidermidis	1	
Pseudomonas aeruginosa	1	
Cerebrospinal fluid Gram staining	8	11.6
Gram positive cocci	7	
Gram negative cocci	1	
No etiological agent	46	66.6

several complications (3 brain abscesses, 1 subdural empyema, and 1 third nerve paralysis), and 3 (5.1%) had permanent neurological sequelae (2 had hearing loss and 1 had strabismus). The mean age of the fatal group (51.4 ± 21.6 years) was higher than that of the non-fatal group (36.9. ± 19.4 years) (p= 0.03). In univariate analysis, the significant risk factors for mortality were older age, female gender and deteriorated consciousness level.

Parameningeal infections and other underlying medical conditions had no effect on mortality in univariate analysis**.** Risk factors related to mortality in patients with acute bacterial meningitis were shown in Table 5. Variables used in the stepwise logistic regression included age, gender, initial consciousness level, presence of parameningeal infection, and presence of other underlying medical conditions. The results showed that after considering all the above variables, female gender and deteriorated consciousness level were independently associated with mortality (Table 6).

DISCUSSION

Acute bacterial meningitis is an important cause of morbidity and mortality among adults in developing countries. Most of the cases have underlying medical conditions such as otitis media, sinusitis, pneumonia, endocarditis, head injury, neurosurgical procedures, immunodeficiency, diabetes mellitus (DM), alcoholism, and CSF leakage.[11-13] Although age is the most important determinant of pneumococcal meningitis, these patients often have a pre-existing medical condition. Recognized medical conditions include splenectomy, thalassemia, sickle-cell disease, alcoholism, myeloma, hypogammaglobulinemia, complement deficiency, ear or sinus infections, and DM.[10,14]

In previous series, the rates of underlying medical conditions or predisposing conditions were between 48% and 75% in community-acquired bacterial meningitis in adults.[11-13,15] The rate was much higher (92%) in pneumococcal meningitis.[14] Although our series included meningitis due to various bacterial pathogens, 79.7% of our patients had at least one underlying medical condition, which is a striking finding. This higher rate was probably due to the prospective nature of this study. Many studies cited in this article were retrospective.

Meningitis sometimes emerges as a complication of paranasal sinusitis. However, most cases of sinusitis are uncomplicated and occur in the outpatient setting. In view of the common occurrence of sinusitis and the rarity of complications, the incidence is presumed to be low although precise estimates are unavailable since many cases of sinusitis do not present for medical treatment. In hos-

TABLE 5: Risk factors related to mortality in patients with acute bacterial meningitis.

	Survivors (%) n= 58	Deaths (%) n= 11	p
Age (years)	36.9 ± 19.4	51.4 ± 21.6	0.03
Sex (Male)	42/45 (93.3)	3/45 (6.7)	0.01
(Female)	16/24 (66.7)	8/24 (33.3)	
White Bolood Cell	18 565 ± 10 506	15 418 ± 6951	0.34
C-reactive protein	10.7 ± 7.6	11.6 ± 9.4	0.71
Cerebrospinal fluid glucose(mg/dL)	38.3 ± 27.7	27.9 ± 23.0	0.24
Cerebrospinal fluid glucose protein (mg/dL)	263.6 ± 209.4	219.4 ± 156.9	0.5
Initial level of consciousness			
Stage I	24/58 (41.4)	0/11 (0)	
Stage II	26/58 (44.8)	7/11 (63.6)	0.02
Stage III	8/58 (13.8)	4/11 (36.4)	
Parameningeal infection	32/58 (55.1)	6/11 (54.5)	1.0
Other underlying medical condition	20/58 (34.5)	4/11 (36.4)	1.0

TABLE 6: Multivariate analysis of potential predictors in patients with acute bacterial meningitis.

	Coefficient	Standard error	Wald statistic	Degree of freedom	Odds ratio	p
Age	1.054	0.791	1.776	1	2.870	0.18
Gender (female)	2.040	0.801	6.489	1	7.68	0.01
Parameningeal infection	0.639	0.870	0.539	1	1.09	0.46
Predisposing factor	-101	1.099	0.008	1	0.92	0.92
Initial consciousness level	1.487	0.605	6.036	1	4.42	0.01

pitalized patients with sinusitis, the reported rate of intracranial complications varies from 3.7% to 47.6%. By selecting for severe sinus disease, these series clearly overestimate the incidence of intracranial complications. Overall, sinus disease is the presumed underlying cause of about 10% of intracranial suppuration. Most case series of complicated sinusitis are in the surgical literature. Since meningitis from sinusitis rarely requires surgery, this complication might be under-represented in these case series.[15] Durand et al. reported paranasal sinusitis rate as 12% in community acquired bacterial meningitis. In contrast to previous studies, interestingly, the most frequent underlying condition (23.2%) was paranasal sinusitis in our study.[6,11,12] To our knowledge, this is the highest reported rate.

Previous reports indicated that meningitis following sinusitis arose most often from ethmoid or sphenoid sinusitis.[16-18] Our study does not confirm previous reports. In this study, the most common type of sinusitis was maxillary, in 75% of the patients, followed by ethmoid (31.2%), sphenoid (18.7%), and frontal (18.7%) sinusitis. The maxillary sinuses were the only site of involvement in 43.8%, and concurrently involved with other sinuses in 28.8% of meningitis cases with paranasal sinusitis. To our knowledge, this is the first clinical study that demonstrates the high frequency of maxillary sinusitis in cases with acute bacterial meningitis.

Meningitis also emerges as a complication of otitis media. In many studies, the major underlying condition in bacterial meningitis was otitis media, and reported rates were 21-26%.[7,12,19] The rate was 18.8% in our study. Both acute and chronic otitis media remain among the most common childhood infectious diseases worldwide, affecting diverse racial and cultural groups in both developing and industrialized countries and most often occurring in the first 5 years of life. Otitis media is associated with considerable morbidity and can cause several extra- and intra-cranial complications. The incidence of intracranial complications of otitis media has fallen from 2.3% in the pre-antibiotic era to a considerably lower level between 0.04 and 0.15%.[20] The most common intracranial complication of otitis media is meningitis with a reported incidence of 21-72% among all intracranial complications.[21]

The rate of total ear or sinus infections has been reported as 52.7% in pneumococcal meningitis, and 25% to 38% in all types of community acquired bacterial meningitis.[12,14,15] The corresponding rate was 42% in our series. These two infections are the leading predisposing conditions of community-acquired bacterial meningitis in many series as in ours.[7,12,14,15] On the other hand, in two studies from Taiwan, DM was the most common underlying medical condition, occurring in 44% and 12.2% of cases.[11,13] However, the low prevalence of DM in our study (5.8%) is in agreement with the results of studies from western countries.[12,14,15]

Another striking finding of this study was the low identification rate of causative pathogen. The CSF Gram's stain is usually positive in 60-90% of cases with acute bacterial meningitis.[13] However, the likelihood of detecting the microorganism by Gram's stain may decrease to 40-60% in patients who have already received an antibiotic, and the yield of CSF cultures similarly falls to below 50% from 70-85 %.[22,23] Two studies from Turkey have also demonstrated low bacteriologic identification

rates.[7,19] Preadmission parenteral antibiotic treatment has been widely recommended as a significant strategy to improve patient prognosis whenever the diagnosis of bacterial meningitis is suspected, particularly if lumbar puncture is not considered safe. The reduction in bacterial concentration following preliminary antibiotic treatment decreases the diagnostic effectiveness of the Gram's stain and CSF culture.[24,25] In this study, 56.5% of the patients received some antibiotic therapy before hospital admission, and only 5.1% had positive culture results. However, in patients with no previous antibiotic therapy, positive culture results were also lower (43.3%) compared to the results of previous studies. The low bacteriological identification rate may be attributed to delayed transport of CSF samples to the laboratory, as well as administration of antibiotics prior to admission. As in our study, the leading cause of acute bacterial meningitis in adults is *S. pneumoniae.*[14] Because of low identification rates, we could not compare etiological agents between patients with parameningeal infections and those with no exracranial infections.

CSF leakage is significantly more common among patients with recurrent meningitis than among patients with single episodes of meningitis.[12] Only two of our cases had CSF leakage and one of them had a history of recurrent bacterial meningitis. Of the remaining patients with recurrent meningitis history, four had paranasal infections and one had a remote history of head trauma as predisposing factors. This result suggests that parameningeal infections may be a predisposing factor for recurrent bacterial meningitis, especially if they are not treated properly.

In acute bacterial meningitis, up to 30% of survivors have long-term neurological sequelae, including hearing loss and other focal neurological deficits. The frequency of brain abscess is less than 1%.[6] Brain abscess is also a complication of otitis media, and frontal and etmoid sinusitis.[16,21] Geyik el al. reported a high incidence (16.0%) of brain abscess in otogenic meningitis.[18] Our study revealed relatively high incidence of brain abscess, parallel to the rates in patients with otitis media and sinusitis. However, the frequency of long-term neurological sequelae was low (5.1%) among our surviving patients.

The reported mortality rates of adult community-acquired bacterial meningitis in large group studies were 19-37%.[6,11,12] Despite our low identification rate of pathogen bacteria, mortality rate (15.9 %) in this study was not high compared with the rates reported in previous studies. This may be attributed to the relatively younger age (mean 39.2 ± 20.4 years) and low rate of severely impaired consciousness level on admission (of the patients, 17.4% were stage III). Age and initial consciousness level are the well-known prognostic factors in bacterial meningitis.[7,12-15] The results of our univariate analysis confirm the findings of previous reports. In addition, although the majority (62.5%) of our patients was male, interestingly, the ratio of female gender was significantly higher in the fatal cases (Table 5).

In some studies, comorbidity has been reported as a poor prognostic factor for acute bacterial meningitis in adults.[15, 26] van de Beek et al. reported the presence of sinusitis or otitis as a risk factor for an adverse outcome.[16] Some studies have combined conditions such as pneumonia, head trauma, ear or sinus infections with malignant diseases or immune disorders as underlying or predisposing conditions and have not found an association with adverse outcome in pneumococcal meningitis.[27,28] Kastenbauer analyzed all underlying medical conditions separately and found that chronic debilitating conditions and pneumonia were associated with poor outcome.[14] In contrast to van de Beek, Kastenbauer did not find ear or sinus infections, head trauma or CSF fistulae as adverse outcome factors. Parameningeal infections and other underlying conditions were not associated with mortality in our study. Different parameters were also reported as prognostic factors in previous studies such as CSF glucose and protein levels, erythrocyte sedimentation rate, thrombocytopenia, and CSF white blood cell count.[7,13,14] We compared peripheral blood white-cell count, C-Reactive Protein, CSF glucose and protein levels of the fatal and non fatal groups and no differences were detected. In our

study, multiple logistic regression analysis revealed that only female gender and deteriorated initial consciousness level were independently associated with mortality. Higher mortality rate among female cases has not been reported previously.

S. pneumoniae and *H. influenzae* are major pathogens in community-acquired bacterial meningitis, otitis media, pneumonia, and sinusitis. Since the introduction and widespread use of *H. influenzae* type b vaccine in infancy and childhood in some countries, the epidemiology of community-acquired bacterial meningitis has changed. *S. pneumoniae* is now the most common cause in children and adults overall although *Neisseria meningitidis* is the etiological agent usually in patients between 2-18 years.[29,30] As in *H. influenzae* model, the development of effective vaccines for *S. pneumoniae* and other etiological agents raises the hope of making bacterial meningitis largely a problem of the past.

CONCLUSION

The majority of community-acquired acute bacterial meningitis in adults is secondary to extra-cranial infections such as sinusitis or otitis media. In order to reduce the incidence of the disease, the incidence of parameningeal infections, especially otitis media, must be reduced in childhood. In all cases of adult bacterial meningitis, parameningeal infections or other predisposing conditions should be investigated carefully and should be managed properly for a favorable outcome. In addition, early diagnosis and effective treatment of these infections will prevent emergence of bacterial meningitis.

Acknowledgement

The authors are thankful to Şafak Uğur from the Department of Modern Languages Middle East Technical University Ankara-Turkey for English editing.

REFERENCES

1. Scheld WM, Koedel U, Nathan B, Pfister HW. Pathophysiology of bacterial meningitis: mechanism(s) of neuronal injury. J Infect Dis 2002;186 Suppl 2:S225-33.
2. Koedel U, Scheld WM, Pfister HW. Pathogenesis and pathophysiology of pneumococcal meningitis. Lancet Infect Dis 2002;2(12): 721-36.
3. Uysal G, Güven A, Köse G, Yüksel G, Yüksel S, Oskovi H. [Etiologic agents, clinical features andprognosis in childhood acute bacterial meningitis]. Turkiye Klinikleri J Pediatr 2001; 10(2):93-8.
4. Neuman HB, Wald ER. Bacterial meningitis in childhood at the Children's Hospital of Pittsburgh: 1988-1998. Clin Pediatr (Phila) 2001; 40(11):595-600.
5. Schuchat A, Robinson K, Wenger JD, Harrison LH, Farley M, Reingold AL, et al. Bacterial meningitis in the United States in 1995. Active Surveillance Team. N Engl J Med 1997;337(14):970-6.
6. van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. Community-acquired bacterial meningitis in adults. N Engl J Med 2006; 354(1):44-53.
7. Ayaz C, Geyik MF, Hosoglu S, Celen MK, Akalın S, Kokoglu OF. Characteristics of acute bacterial meningitis in Southeast Turkey. Indian J Med Sci 2004;58(8):327-33.
8. Ulutan F. [Acute bacterial meningitis]. Turkiye Klinikleri J Int Med Sci 2006;2(28):69-74.
9. Tunkel AR, Scheld WM. Pathogenesis and pathophysiology of bacterial meningitis. Clin Microbiol Rev 1993;6(2):118-36.
10. Cartwright KAV. Bacterial meningitis. In: Boriello SP, Murray PR, Funke G, eds. Topley and Wilson's Microbiology and Microbial Infections, Bacteriology. 10th ed. Philadelphia: Hodder Arnold; 2005. p. 555-80.
11. Lu CH, Huang CR, Chang WN, Chang CJ, Cheng BC, Lee PY, et al. Community-acquired bacterial meningitis in adults: the epidemiology, timing of appropriate antimicrobial therapy, and prognostic factors. Clin Neurol Neurosurg 2002;104(4):352-8.
12. Durand ML, Calderwood SB, Weber DJ, Miller SI, Southwick FS, Caviness VS Jr, et al. Acute bacterial meningitis in adults. A review of 493 episodes. N Engl J Med 1993;328(1): 21-8.
13. Tang LM, Chen ST, Hsu WC, Lyu RK. Acute bacterial meningitis in adults: a hospital-based epidemiological study. QJM 1999;92(12):719-25.
14. Kastenbauer S, Pfister HW. Pneumococcal meningitis in adults: spectrum of complications and prognostic factors in a series of 87 cases. Brain 2003;126(Pt 5):1015-25.
15. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med 2004; 351(18):1849-59.
16. Osborn MK, Steinberg JP. Subdural empyema and other suppurative complications of paranasal sinusitis. Lancet Infect Dis 2007; 7(1):62-7.
17. Younis RT, Anand VK, Davidson B. The role of computed tomography and magnetic resonance imaging in patients with sinusitis with complications. Laryngoscope 2002;112(2): 224-9.
18. Giannoni CM, Stewart MG, Alford EL. Intracranial complications of sinusitis. Laryngoscope 1997;107(7):863-7.
19. Geyik MF, Kokoglu OF, Hosoglu S, Ayaz C. Acute bacterial meningitis as a complication of otitis media and related mortality factors. Yonsei Med J 2002;43(5):573-8.
20. Kuczkowski J, Mikaszewski B. Intracranial complications of acute and chronic mastoiditis: report of two cases in children. Int J Pediatr Otorhinolaryngol 2001;60(3):227-37.

21. Verhoeff M, van der Veen EL, Rovers MM, Sanders EA, Schilder AG. Chronic suppurative otitis media: a review. Int J Pediatr Otorhinolaryngol 2006;70(1):1-12.

22. Tunkel AR, Scheld WM. Acute bacterial meningitis. Lancet 1995;346(8991-8992): 1675-80.

23. Aktas F. [Cerebrospinal fluid (CSF) in central nervous system infections]. Turkiye Klinikleri J Int Med Sci 2006;2(28):6-10.

24. Matos Jde A, Madureira DJ, Rebelo MC, Hofer CB, Barroso DE. Diagnosis of Streptococcus pneumoniae meningitis by polymerase chain reaction amplification of the gene for pneumolysin. Mem Inst Oswaldo Cruz 2006;101(5):559-63.

25. Kanegaye JT, Soliemanzadeh P, Bradley JS. Lumbar puncture in pediatric bacterial meningitis: defining the time interval for recovery of cerebrospinal fluid pathogens after parenteral antibiotic pretreatment. Pediatrics 2001; 108(5):1169-74.

26. McMillan DA, Lin CY, Aronin SI, Quagliarello VJ. Community-acquired bacterial meningitis in adults: categorization of causes and timing of death. Clin Infect Dis 2001;33(7):969-75.

27. Hoen B, Viel JF, Gérard A, Dureux JB, Canton P. Mortality in pneumococcal meningitis: a multivariate analysis of prognostic factors. Eur J Med 1993;2(1):28-32.

28. Stanek RJ, Mufson MA. A 20-year epidemiological study of pneumococcal meningitis. Clin Infect Dis 1999;28(6):1265-72.

29. Phillips EJ, Simor AE. Bacterial meningitis in children and adults. Changes in community-acquired disease may affect patient care. Postgrad Med 1998;103(3):102-117.

30. Segal S, Pollard AJ. Vaccines against bacterial meningitis. Br Med Bull 2005;72:65-81.