



Factors associated with early complications in inpatients who were treated in our clinic between 1992 and 2011 with a diagnosis of acute bacterial meningitis

Kliniğimizde 1992–2011 yılları arasında akut bakteriyel menenjit tanısıyla yatarak tedavi gören hastalarda erken komplikasyonlarla ilişkili etmenler

Meltem Bor¹, Haluk Çokuğraş²

¹Department of Pediatrics, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

²Division of Pediatric Allergy and Immunology, Department of Pediatrics, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

The known about this topic

Acute bacterial meningitis is often seen in children, under one year. The average age for pediatric patients is generally under five years of age. The frequency of early complications was found to be between 13–36.6% in the studies. Most studies have shown that the younger age group (especially under two years of age) is a poor risk factor for prognosis.

Contribution of the study

Acute bacterial meningitis was often under five years of age, as we have shown in our study, as in the world. The incidence of early complications in our study was 27.8% and it was found in the range of studies (13–36.6%). The frequency of complications was between the ages of three months and five years, under two years of age. In many studies, the younger age group (especially under two years of age) has been shown to be a poor risk factor.

Abstract

Aim: To evaluate factors associated with the development of early complications in acute bacterial meningitis.

Material and Methods: In our study, 389 patients diagnosed with acute bacterial meningitis between January 1992 and January 2011 at Cerrahpaşa Medical Faculty were retrospectively analyzed to determine the risk factors for the development of early complications.

Results: The causative agent was *N. meningitidis* in 17% of cases, *S. pneumoniae* in 13.6%, and *H. influenzae type b* in 6.4%. In 55.5% of cases, the causative agent could not be identified. The mortality rate was found as 1% and the early complication rate was 27.8%. The complications observed included septic shock and disseminated intravascular coagulation (33.3%), hydrocephalus (23.1%), subdural effusion (19.4%), and epilepsy (12%). Risk factors for early complications included being aged below two years ($p<0.010$), restlessness ($p<0.010$), rash ($p<0.010$), leukocytosis in complete blood count ($p<0.010$), and a cerebrospinal fluid glucose level of <45 mg/dL ($p<0.010$). Three of the four patients who died were male. The incidence of

Öz

Amaç: Akut bakteriyel menenjitte erken komplikasyon gelişimi ile ilişkili etmenleri değerlendirmek.

Gereç ve Yöntemler: Çalışmamızda Cerrahpaşa Tıp Fakültesi'nde Ocak 1992–Ocak 2011 tarihleri arasında akut bakteriyel menenjit tanısı konulan 389 olgu erken komplikasyon gelişimi için risk etmenlerin belirlenmesi amacıyla geriye dönük olarak incelendi.

Bulgular: Değerlendirilen olguların %17'si *N. meningitidis*, %13,6'sı *S. pneumoniae*, %6,4'ü *H. influenzae tip b* menenjitisi idi, %55,5'inde etken saptanamadı. Ölüm oranı %1, erken komplikasyon %27,8 oranındaydı. Komplikasyonlar sıklık sırasıyla septik şok ve dissemine intravasküler koagülasyon (%33,3), hidrosefali (%23,1), subdural efüzyon (%19,4) ve epilepsi (%12) idi. Erken komplikasyonlar için risk etmenleri iki yaş altında olma ($p<0,010$), huzursuzluk ($p<0,010$), döküntü ($p<0,010$), serumda lökositöz ($p<0,010$), beyin omurilik sıvısı glukozunun <45 mg/dl olması ($p<0,010$) olarak saptandı. Ölen dört olgudan üçü erkekti. Ampisilin-se-

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Corresponding Author/Sorumlu Yazar: Meltem Bor E-mail/E-posta: meltembor@yahoo.com

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hydrocephalus was higher in patients who used ampicillin-ceftaxime and who did not receive steroid therapy before treatment ($p < 0.050$).

Conclusion: When acute bacterial meningitis is treated properly and adequately, recovery without sequela is possible. Knowing the risk factors for early complications will guide in the monitoring of patients and decrease morbidity and mortality rates.

Keywords: Bacterial, complication, meningitis, prognosis

fotaksim kullanılanlarda ve tedavi öncesi steroid verilmeyen olgularda hidrosefali gelişme oranı yüksekti ($p < 0,050$).

Çıkarımlar: Akut bakteriyel menenjit doğru ve yeterli tedavi edildiğinde sekelsiz iyileşme mümkündür. Erken komplikasyonlar için risk etmenlerinin bilinmesi hastanın izlenmesinde yol gösterici olup, hastalık ve ölüm oranını azaltacaktır.

Anahtar sözcükler: Bakteriyel, komplikasyon, menenjit, prognoz

Introduction

Acute bacterial meningitis (ABM) is one of the common infectious diseases that have high morbidity and mortality rates in childhood despite advances in vaccination, chemoprophylaxis, diagnosis, and treatment, and efforts to improve accessibility to healthcare services. Acute bacterial meningitis occurs in children with a rate of 80% and frequently below the age of one year; its prevalence decreases between the ages of 10 and 50 years, and increases again above the age of 70 years (1–3). Although the mean age in pediatric patients is generally below five years, it shows variance (1, 2, 4–13). Early diagnosis and the selection of the correct antibiotic, and administration of steroid treatment and supportive treatment, if necessary, influence morbidity and mortality rates. Currently, the mortality rate is 2% in children, and it increases up to 30% in the neonatal period (14).

Patients diagnosed as having meningitis should be closely monitored in terms of early and late complications, which may occur during hospitalization and later on. These include circulatory failure, disseminated intravascular coagulation (DIC), mortality, involvement of the cranial nerves (blindness, deafness), hydrocephalus, focal neurological deficits, convulsion and abscess formation in the early phase, and disorders that could influence quality of life including mental retardation, permanent hearing loss, and epilepsy in the long term (14, 15).

In our study, 389 patients who were diagnosed as having ABM and hospitalized for treatment in our Pediatric Infectious Diseases Unit, were retrospectively evaluated to elucidate factors related to early complications.

Material and Methods

Three hundred eighty-nine patients who were diagnosed as having ABM and treated in Istanbul University Cerrahpaşa Medical Faculty in a 19-year period between January 1992 and January 2011, were included in this study. These patients' ages, sexes, symptoms, antibiotic use before presentation, time until hospitalization, serum and cerebrospinal fluid (CSF) findings, agents grown in culture, antibiotics used, steroid treatment, on which day the CSF findings improved, treatment duration, healing status and early complications (hydrocephalus, subdural effusion,

epilepsy, septic shock, DIC, dural venous sinus thrombosis, cerebral ischemia, infarction, atrophy, ventriculitis, subdural abscess, empyema, cranial nerve involvement, reactive arthritis, inappropriate antidiuretic hormone release syndrome, hearing loss, increased intracranial pressure syndrome, papiledema) were recorded.

The diagnosis of ABM was made with symptoms, physical examination findings, CSF findings (pressure, appearance, cell count and type, glucose, protein levels, Gram, Giemsa stains) and culture according to the World Health Organization (WHO) definition of meningitis (16).

The protocols that we use as empirical antibiotic treatment in our clinic (17);

- Neonatal period (0–3 months): Ampicillin and cefotaxim,
- The age group above three months with normal immune system: combination of crystalline penicillin and chloramphenicol or ceftriaxone; ampicillin, if *H. influenzae type b* (Hib) is considered,
- In patients who are considered to have immune failure: Cefazidime and amikacin,
- In the presence of penicillin-resistant pneumococcus: Cefalosporin and glycopeptide combinations (vancomycin, teikoplanin).

Dexamethasone was administered by the intravenous route (0.15 mg/kg/6 hours) in purulent meningitis in patients who were aged above six weeks starting 20 minutes before antibiotic treatment and not exceeding four days, because it decreased the mortality and neurologic sequelae, especially hearing loss.

The study was conducted in accordance with the Declaration of Helsinki 2008 principles and with approval obtained from the Medical Faculty Ethics Committee (Date: 20/07/2009, No.: 22487). Patient consent was not obtained because the study was conducted retrospectively.

Statistical Analysis

When evaluating the findings obtained in the study, the NCSS (Number Cruncher Statistical System) 2007&PASS 2008 Statistical Software (Utah, USA) was used for statistical analyses. Descriptive statistical methods (mean, standard deviation) were used when evaluating the study

Table 1. The patients’ diagnosis distribution

Diagnosis	n=389	%
Umknown causative agent	216	55.52
<i>Meningococccemia+</i>		
<i>Meningococcal meningitis</i>	40	10.28
<i>Meningococcal meningitis</i>	26	6.68
<i>Pneumococcal meningitis</i>	53	13.62
<i>Haemophilus influenzae type-b meningitis</i>	25	6.42
<i>Klebsiella meningitis</i>	4	1.02
Group B streptococcal meningitis	3	0.77
<i>Proteus meningitis</i>	1	0.26
<i>Staphylococcal meningitis</i>	13	3.34
<i>Salmonella meningitis</i>	2	0.51
<i>Pseudomonas meningitis</i>	3	0.77
<i>Leptospira meningitis</i>	2	0.51
<i>Brucella meningitis</i>	1	0.26

data. In addition, the Mann-Whitney U test was used in inter-group comparison of criteria that did not show normal distribution in comparisons of quantitative data. The Chi-square test and Fisher’s exact Chi-square test were used in comparisons of qualitative data. A p value below 0.05 was considered significant.

Results

The total number of patients who were treated with a diagnosis of meningitis in a 19-year period in our Pediatric Infectious Diseases Ward was 639. Four hundred sixty-five (72.8%) patients were diagnosed as having ABM, 109 (17.1%) had viral meningitis, 60 (9.4%) had tuberculosis meningitis, three (0.5%) had candida meningitis, and two (0.3%) patients had leptospira meningitis. Among the patients who were diagnosed as having ABM, *Neisseria meningitidis* was found in 106 (22.8%) patients, *S. pneumoniae* was found in 61 (13.1%) patients, Hib was found in 35 (7.5%) patients, and no causative agent could be found in 260 (56.3%) patients. Among a total of 465 patients, 389 patients whose data could be reached, were included in

the study (Table 1). Acute bacterial meningitis with an unknown etiologic agent constituted 55.5% of these cases, and was found with the highest rate in all years and age groups (Table 2). *Neisseria meningitidis* was found with a frequency of 17%, *S. pneumoniae* was found with a frequency of 13.6%, and Hib was found with a frequency of 6.4% (Table 1, Fig. 1).

Male sex (60.9%) predominated in our patients. Although no correlation was found between sex and complications, three of our four patients who died were male. Most of the patients were aged between three months and five years (56%). Complications generally occurred below the age of two years (62%), and concentrated between three months and five years (Table 3). The time between onset of symptoms and presentation was found as 0–45 (4.15±4.72) days. Fifty-six point five percent of the patients presented in the first 48 hours after the onset of symptoms. The presentation time was not found to be significantly associated with mortality and complications. Previous antibiotic use (frequently with the diagnoses of upper respiratory tract infection, otitis media and sinusitis) was found with a rate of 48.6%. In these patients, hospitalization occurred late because clinical findings were masked (mean time: 5.56±5.71 days) and the time to hospitalization was significantly longer (2.82±3.01 days) compared with the patients who did not use antibiotics (p=0.001). However, this was not found to have significant effect in terms of development of complications.

The most common sign and symptom was fever (85.1%), which was found with a higher rate in patients aged above three months (p<0.010). Poor appetite-absence of suckling, restlessness, and seizure were more prominent in children aged between 0 and 3 months (p<0.010, p<0.010, p<0.010); fever, nausea-vomiting, change in consciousness, and rash were found with a higher rate in children aged between three and five months (p<0.010, p<0.050, p<0.010, p<0.010); and fever, nausea-vomiting, and diplopia and headache (as they could state their symp-

Table 2. Distribution of the agents by age groups

Age	Agent grown in acute meningitis								p
	<i>Neisseria meningitidis</i>		<i>Streptococcus pneumoniae</i>		<i>Haemophilus influenzae</i>		Unknown agent		
	n=66	%	n=53	%	n=25	%	n=216	%	
0–3 months	1	1.5	7	13.2	1	4	24	11.1	0.002^a
3 months-5 years	41	62.1	29	54.7	23	92	105	48.6	
5 years	24	36.4	17	32.1	1	4	87	40.3	

Chi-square test was used; a: p<0.01

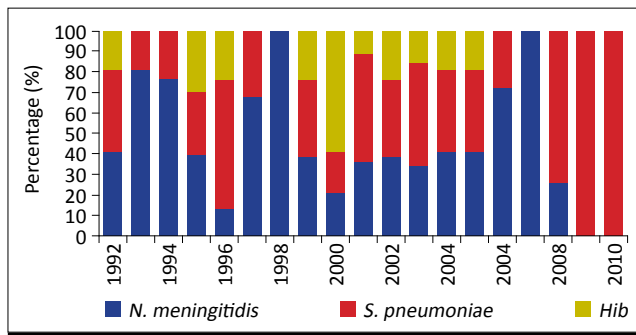


Figure 1. Distribution of the causative agents by years (n=389)

toms verbally) were found with a higher rate in children aged above 5 years ($p<0.010$, $p<0.010$, $p<0.010$, $p<0.010$). The association of fever, vomiting, and headache, which is known as the classic triad, was found with a rate of 11.31%. The rates of nausea-vomiting and headache were found to be high in patients who did not develop complications ($p<0.010$), whereas obscure signs and symptoms including restlessness and rash with low intrafamilial alarmism were found to be significantly high in patients who developed complications ($p<0.010$).

In 58.6% of our patients, leukocytosis was present, and the frequency of complications was found to be significantly high ($p=0.002$). The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were found to be increased in most patients (73.3–85.6%), but a significant increase in ESR and CRP was not found in patients who developed complications. The CSF cell count was found to be above 500/mm³ in most of our patients (65.6%), and PNL predominated (77.4%). No significant correlation was found between the development of complications and CSF cell count and protein level, whereas the frequency of complications was found to be significantly increased in patients who had a CSF glucose level of 45 mg/dL and below ($p<0.010$) (Table 4).

Table 4. Evaluation of leukocytes, CSF glucose and protein by development of complication

	Complications				p
	Present		Absent		
	n=108	%	n=281	%	
Leukocytes					
<4000	2	1.8	8	2.8	0.733
4000–10,000	29	26	122	43.4	0.003
>10,000	77	71.3	151	53.7	0.002
CSF glucose					
≤45 mg/dL	63	58.9	116	42.5	0.004^a
>45 mg/dL	44	41.1	157	57.5	
CSF protein					
≤50 mg/dL	34	32.7	108	40.3	0.175
>50 mg/dL	70	67.3	160	59.7	
CRP					
>0.3 mg/dL	66	90	141	86.5	0.212
<0.3 mg/dL	7	0.9	22	13.5	
ESH					
>20 mm/h	64	83	146	79	0.345
<20 mm/h	13	16.8	38	20.6	

CSF: Cerebrospinal fluid; CRP: C-reactive protein; ESH: erythrocyte sedimentation rate. Chi-square test was used. a: $p<0.01$

The causative agent was grown in CSF culture with a rate of 31.8%. *Streptococcus pneumoniae* was grown with a rate of 10.9%, *N. meningitidis* with a rate of 7%, and Hib with a rate of 4.7%. Serotype-B was found in five patients in whom *N. meningitidis* was grown.

The success rate for growing a causative agent in hemoculture was found as 21.5%. Mostly, *N. meningitidis* (5.4%) and coagulase (-) *staphylococcus* (5.4%) were grown, followed by *S. pneumoniae* (4.5%), Hib (1.8%), and *Klebsiella* (1.8%).

Table 3. Complication distribution by age groups

Complication	Age					
	0–3 months		3 months–5 years		>5 years	
	n	%	n	%	n	%
Hydrocephalus	12	52.17	12	20.00	1	4.00
Subdural effusion	4	17.39	16	26.66	1	4.00
Epilepsy	1	4.34	11	18.33	1	4.00
Septic shock	6	26.08	20	33.33	10	40.00
Presence of complications	Age groups					
	Below 2 years		Above 2 years			
	n	%	n	%		
Present	67	36.41	41	20.00		
Absent	117	63.8	164	80.00		

Table 5. Evaluation of complications by use of steroid

Complications	Steroid				p
	Present		Absent		
	n	%	n	%	
Hydrocephalus	13	16.66	12	40.00	0.010^a
Subdural effusion	18	23.07	3	10.00	0.124
Epilepsy	10	12.82	3	10.00	0.687
Septic shock, DIC	32	41.02	4	13.33	0.006^b

a: p<0.05; b: p<0.01; DIC: Disseminated intravascular coagulation. Chi-square test was used

The patients in whom empirical antibiotic treatment was used were mostly aged between 0 and 3 months (75.0%), and the frequency of the development of hydrocephaly was found to be higher in this group compared with the groups in which other empirical antibiotic treatment protocols were used (p<0.050).

Dexamethasone was administered as supportive treatment before antibiotic treatment for purulent meningitis in more than half of our patients who were aged above six months because it reduced the mortality rate and hearing loss. The frequency of hydrocephalus was found to be increased in patients who were not given dexamethasone (p<0.050) (Table 5).

The mean time for improvement of lumbar puncture findings was found as 8.92±7.42 days, and the mean hospitalization time was found as 14.77±10.01 days.

Early complications were found in 27.8% of our patients. In order of frequency, the complications included septic shock, DIC, hydrocephalus, subdural effusion, and epilepsy (Table 6). The risk for the development of hydrocephalus was found to be increased in patients aged between 0 and 3 months. The rate of complications was found to be significantly lower in patients in whom *N. meningitidis* was found, com-

Table 6. Distribution of early complications

Complications	n	%
Absent	281	72.2
Present	108	27.8
Hydrocephalus	25	23.14
Subdural effusion	21	19.44
Epilepsy	13	12.03
Septic shock, DIC	36	33.33
Dural venous sinus thrombosis	3	2.77
Cerebral ischemia, infarction, atrophy	4	3.70
Ventriculitis	2	1.85
Subdural empiyema, abscess	2	1.85
Cranial nerve involvement	3	2.77
Reactive arthritis	1	0.92
SIADH	3	2.77
Hearing loss	5	4.62
IIPS, Papiledema	4	3.70

DIC: Disseminated intravascular coagulation; IIPS: Increased intracranial pressure syndrome; SIADH: Syndrome of inappropriate antidiuretic hormone secretion

pared with patients in whom Hib and *S. pneumoniae* were found (Table 7).

Among our patients, 98.7% were discharged with improvement and full recovery, and 1% died. One patient was referred because of a need for intensive care. Three of the patients who died were male and one was female; *S. pneumoniae* was grown in three and *Klebsiella* was grown in one.

Being aged between three months and five years, restlessness at presentation, presence of rash, leukocytosis and a CSF glucose level below 45 mg/dL were found to be risk factors in terms of early complications. Use of ampicillin-cefotaxim and the lack of use of steroids before treatment were found to be risk factors in terms of the development of hydrocephalus.

Table 7. Distribution of complications by the agent grown in acute meningitis

Complications	Acute meningitis agent grown						p
	<i>Neisseria meningitidis</i>		<i>Streptococcus pneumoniae</i>		<i>Haemophilus influenzae</i>		
	n	%	n	%	n	%	
Hydrocephalus	0	0	2	15.38	4	33.33	0.015^a
Subdural effusion	2	8.33	4	30.76	8	66.66	0.001^b
Epilepsy	0	0	3	23.07	3	25.00	0.037^a
Septic shock, DIC	3	12.50	10	76.92	11	91.66	0.001^b

a: p<0.05; b: p<0.01; DIC: Disseminated intravascular coagulation. Chi-square test was used

Discussion

Male sex predominated in the patients in our study in accordance with the literature (1, 2, 4–8, 10, 12, 13, 18). Three of the four patients who died were male. There was no difference between sexes in terms of complications. In a meta-analysis including 31 studies, it was found that male sex was a significant risk factor in determining prognosis (mortality and neurological sequela) in ABM (19). In some studies, however, it was shown that sex had no influence on prognosis (5, 7–9, 11, 20).

Most of our patients (67.4%) were aged below five years, similar to worldwide data (1, 2, 4, 6–13). The frequency of complications was increased below the age of two years, and intensified between the ages of three months and five years. In most studies, young age was shown to be a poor prognostic risk factor (especially below the age of two years) (8–10, 19, 21).

Although some studies specified a time period longer than 48 hours up to presentation to be a poor prognostic criterion (9, 10, 19), other studies found no significant difference, similar to our study (2, 7, 8).

In our study, it was found that use of antibiotic before presentation delayed the diagnosis, but did not increase the frequency of complications (5, 10, 13).

Although there is no pathognomonic clinical sign for the diagnosis of ABM, our study showed that the most common symptom at presentation was fever (86%), as in many other studies (22). This was followed by rash with a rate of 15.4%, restlessness (11.8%), seizure (11%), malaise (9.3%), loss of appetite-absence of suckling (8%), diarrhea (4.1%), symptoms of upper respiratory tract infection (URTI) (4.6%), neck pain (2.3%), and diplopia (1%). Generally, studies have reported the following rates for the signs and symptoms: fever, 90.9–97.8%; vomiting, 59.8–82.6%; headache, 38.6–6.9%; seizure 20–64.9%; diarrhea, 4.5%; rash, 2.3–41.2%, restlessness, 2.3–92.9%, and change in consciousness, 10.2–40.9% (4, 5, 7, 8, 10, 20). Although studies have found change in consciousness, coma, seizure, anisochoria, positive Babinski reflex, disrupted peripheral circulation, severe respiratory distress, petechia, and fever lasting longer than seven days to be poor prognostic factors, we found that restlessness and rash to be significant poor prognostic factors in our study (5, 8–10, 15, 19, 20, 23–25).

In some studies, leukopenia or reduced hemoglobin levels (<9 g/dL) were among poor prognostic factors. In our study, however, the presence of leukocytosis was associated with the development of complications (10, 19, 20, 25). The development of complications was found with

a higher frequency in patients with a CSF glucose levels below 45 mg/dL, as in our study, and this level was shown to be associated with hearing loss (8, 10, 19, 20, 25). Some studies reported that increased CSF protein levels were among poor prognostic factors (10, 19, 20, 25), we found no significant difference.

The causative agent of ABM could be specified in 44.2% of our patients. The frequencies of the causative agents were as follows: *N. meningitidis*, 17%; *S. Pneumoniae*, 13.6%; and Hib, 6.4%. Serogroup-B was found in five of the patients in whom *N. meningitidis* was grown. In our study, the most common causative agent was *N. meningitidis* (17%) in all age groups. *Streptococcus pneumoniae* was found more frequently in patients aged between 0 and 3 months, Hib was found more frequently in the patients aged between three months and five years, and *N. meningitidis* and *S. pneumoniae* were found more frequently in patients aged above five years. When the causative agents found in our country were examined, Ceyhan et al. (1) found the causative agent in 60% of subjects in a study conducted in seven geographic regions in 12 centers; *N. meningitidis* was reported with a rate of 56%, *S. pneumoniae* at a rate of 22%, and Hib at a rate of 20%.

Although we found that the development of hydrocephalus occurred with a significantly higher rate in our patients who did not receive steroids, no significant difference was found in some other studies (5, 10). In a meta-analysis including 20 studies in six centers in five countries in Europe including Turkey, van de Beek et al. (26) concluded that steroid use was not effective in terms of preventing mortality, hearing loss, and neurologic sequelae. Steroid treatment is not administered in babies aged below six weeks (14, 15, 17, 27). The American Infectious Diseases Committee, European Neurological Sciences Association, and United Kingdom Infection Committee recommend that dexamethasone should be used, if pneumococcus meningitis is suspected (22, 28).

Studies have found the frequency of early complications to range between 13% and 36.6%, it was found as 27.8% in our study (2, 4–6, 10) (Table 6). The mortality rate in our study was found as 1%, whereas studies have reported mortality rates ranging between 2% and 33% (1, 2, 4, 5, 8, 19–21, 29–31). The highest mortality rates have been observed with *P. meningitis*, as found in our study (4, 32).

When the association between vaccination and meningitis was investigated, it was found that Hib meningitis had not been detected in any patient since November 2006 when the Hib vaccine was included in the routine vaccination schedule in our country, and the frequency

of cases of *P. meningitis* reduced by 66.6% after the date when the pneumococcus vaccine was included in the routine vaccination schedule compared with previous years (the frequency fell from 17% to 5.4%). Although the meningococcus vaccine is not included in the vaccination schedule, no hospitalization because of meningococcus meningitis occurred in 2009 and thereafter, probably due to the gradually increasing use of unprescribed antibiotics and high sensitivity of meningococcus to penicillin group antibiotics.

Acute bacterial meningitis is generally observed below the age of five years, as we showed in our study. Interpretation of laboratory results and careful evaluation of signs and symptoms enable early diagnosis and treatment. Knowing the risk factors for early complications will guide in monitoring patients and decreasing morbidity and mortality rates.

Ethics Committee Approval: Ethics committee approval was received for this study from ethics committee of the Istanbul University, Cerrahpaşa Medical Faculty, (20.07.2009, 22487).

Informed Consent: Informed consent was not obtained because the study was conducted retrospectively.

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Hasta Onamı: Çalışmanın geriye dönük olarak yapılması nedeni ile hasta onamı alınmadı.

Hakem Değerlendirmesi: Dış bağımsız.

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