Community-acquired acute bacterial meningitis in the elderly in Turkey

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Abstract

This investigation aimed both to delineate the current status of community-acquired acute bacterial meningitis and to produce data on the interrelationships between clinical, laboratory and therapeutic parameters in the elderly. This retrospective cohort study was conducted in 28 Turkish institutions in 159 culture-positive patients over the age of 50 years. *Streptococcus pneumoniae* was the most common pathogen (69.2%), followed by *Listeria monocytogenes* (8.8%). For this reason, antilisterial antibiotics such as ampicillin or benzylpenicillin should be added to the therapeutic regimen. Pathogen-specific mortality did not vary between *S. pneumoniae* and *L. monocytogenes*. The overall mortality was 2.5% at the third day, 12.6% at the seventh day, 20.1% at the 14th day and 21.4% at the 21st day. The risk factors for fatality were increasing age, the presence of stupor, sepsis and inappropriate antibiotic administration. Cerebrospinal fluid (CSF) leukocyte counts and CSF/blood glucose ratios were lower in patients who died. Fever did not differ between survivors and fatal cases. The mean duration of antibiotic therapy in survivors was 16.3 ± 6.4 days. One-fifth of the patients had complications, and in 5.7% of the patients sequelae persisted at follow-up.

Keywords: Acute, community-acquired, elderly, meningitis, Turkey
Original Submission: 12 February 2009; **Revised Submission:** 28 July 2009; **Accepted:** 28 July 2009
Editor: G. Pappas
Article published online: 2 September 2009
Clin Microbiol Infect 2010; **16**: 1223–1229
10.1111/j.1469-0691.2009.03039.x

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Introduction

In the literature, few studies of bacterial meningitis have focused on the characteristics of the illness in the elderly, and these publications are relatively old [1–4]. One current investigation did evaluate the epidemiology of bacterial meningitis in the elderly in The Netherlands, but the demographic and microbiological characteristics of Turkey, located at the southeast border of Europe, appear to be very different [5,6]. The rate of antibiotic resistance in pneumococci and in community-acquired Gram-negative pathogens, in particular, is quite high in Turkey, and this could obviously affect therapeutic outcomes [7,8]. Bacterial meningitis in elderly patients is associated with greater diagnostic difficulty as well as with higher mortality [9]. This study aimed both to delineate the current status of community-acquired acute bacterial meningitis (CA-ABM) among the elderly in Turkey and to produce data on the interrelationships among clinical, laboratory and therapeutic parameters in this group of patients.

Materials and Methods

This retrospective cohort study was conducted in 28 Turkish medical institutions. Overall, 159 patients (69 females and 90 males), hospitalized after the year 2000, were included in the study. The mean age of the cases was 63 years (SD = 9.0, min: 50, max: 80). Medical records of all patients with CA-ABM were retrieved from a computer database generated for statistical evaluation. In Turkey, the life-expectancy is 71 years for males and 75 years for females [10]. As 50 years of age is a critical threshold for a shift in the causative agents of CA-ABM [11], we enrolled patients over the age of 50 years.

Patients with hospital-acquired meningitis, defined as meningitis that occurred during hospitalization or within 1 week after discharge, were excluded. Patients with neurosurgical devices were also excluded from the study. [12]. All patients suspected to be suffering from CA-ABM after initial clinical evaluation were subjected to lumbar puncture. The presence of leukocytes and protein and glucose levels in the cerebrospinal fluid (CSF) and blood biochemical markers were evaluated. Positive CSF culture was the primary criterion for inclusion of a patient in the study. In addition, patients whose CSF cultures yielded no growth, but in whom there was evidence of inflammatory response in the CSF and whose blood cultures yielded a pathogen consistent with meningitis, were also included in the study. CSF opening pressure was recorded as an observation, but numerical values were generally not recorded. For this reason, these data were excluded from the study.

As no Turkish consensus guidelines exist for the management of CA-ABM, Turkish clinicians generally utilize foreign guidelines [11]. Inappropriate antibiotic therapy was defined as the use of an antimicrobial agent that subsequent antibiotic susceptibility testing showed to be ineffective. CLSI guidelines are used to detect antibiotic resistance in Turkey. Clinical sepsis was recorded according to the definitions of a consensus committee of US experts in 1992 [13]. Coma was defined as unarousable unresponsiveness. The terms 'confusion' and 'stupor', which are described more extensively elsewhere, referred to states between alertness and coma [14]. Glasgow coma scales of the patients could not be provided. Steroids were used in all cases with mental status changes (dexamethasone or prednisolone; for 2–11 days, median 4 days).

The statistical analyses were performed with the SPSS 12.0 (SPSS Inc., Chicago, IL, USA) program. Results were given as mean ± standard deviation, median (minimum–maximum) for continuous variables and frequencies, and percentages for categorical variables. The comparisons between the two groups were analysed with independent-samples *t*-tests or Mann–Whitney *U*-tests, as appropriate. The comparisons in more than two groups were performed with one-weay ANOVA or Kruskal–Wallis variance analysis, as appropriate. Spearman or Pearson correlation analyses were

used to determine the linear association. Chi-square tests or Fisher's exact tests were used for the comparisons of categorical variables. Survival analysis was performed with log-rank tests and Cox proportional regression analysis. All of the variables that appeared to be related to mortality were included in univariate analysis. Although some of the variables did not have a significant p-value, we included clinically important variables in a multivariate analysis. A p-value of <0.05 was accepted as statistically significant.

For statistical comparisons, the bacterial isolates were grouped as follows: *Streptococcus pneumoniae*, *Listeria monocytogenes*, enteric Gram-negative bacteria, coagulase-negative staphylococci, other *Streptococcus* species, *Neisseria meningitidis* and *Staphylococcus aureus*.

Results

Laboratory data

Laboratory data on the patients are shown in Table 1. CSF culture positivity was 92.5%. The rate of positive blood culture in the case of negative CSF culture was 7.5%. In 23.9% of the cases, the same pathogen was detected in both CSF and blood cultures. In nine patients (5.7%), the CSF white blood cell (WBC) count was found to be lower than 100/mm^3. In one case, CSF pleocytosis was not detected, but *S. pneumoniae* was isolated from the CSF culture, and the patient died on the day of hospital admission.

CSF glucose levels were significantly higher among diabetic patients than among non-diabetic patients (p = 0.008). Accordingly, CSF/blood glucose ratios were significantly lower in diabetic patients than in non-diabetic patients (p = 0.032). CSF WBC counts and CSF/blood glucose ratios were significantly lower for fatal cases than for survivors (p = 0.005 and p = 0.013, respectively). The CSF WBC counts of the patients with immunosuppressive disorders were significantly lower than those of immunocompetent patients (1561.6, standard deviation (SD) 1905.8; 4529.6, SD 6963.6; p 0.008). Similarly, CSF/blood glucose ratios in the immunosuppressed group were significantly lower than those in the immunocompetent group (0.249, SD 0.171; 0.165, SD 0.156; p = 0.004). When the CSF/blood glucose ratios were compared between the patients with immunosuppressive disorders other than diabetes and those without immunosuppressive disorders, there was no significant difference (p = 0.151). The blood WBC count, erythrocyte sedimentation rate and C-reactive protein level were similar in the immunocompetent and immunosuppressed groups. There was no statistical association among the biochemical markers CSF WBC, blood WBC, erythrocyte sedimentation rate, C-reactive protein, CSF/blood glucose ratios, CSF protein levels and increase in age (p-values of 0.296, 0.114, 0.260, 0.791, 0.450 and 0.182, respectively).

TABLE 1. Demographic and laboratory data of the 159 patients

	n	%
Causative agents		
Streptococcus pneumoniae	110	69.2
Listeria monocytogenes	14	8.8
Staphylococcus epidermidis	7	4.4
Other streptococci	5	3.1
Staphylococcus aureus	4	2.5
Escherichia coli	4	2.5
Neisseria meningitidis	4	2.5
Enterococci	3	1.9
Haemophilus influenzae	2	1.3
Other[a]	6	3.8
CSF appearance		
Turbid	138	86.4
Clear	10	6.4
Purulent	9	5.7
Haemorrhagic	2	1.4
Laboratory parameters	**Median**	**Minimum–maximum**
CSF		
WBC count (cells/mm^3)	1445	0–44 000
Glucose (mg/dL)	21	0–285
Protein (mg/dL)	300	2–3670
Blood		1000–57 800
WBC count (cells/mm^3)	16 950	63–558
Glucose (mg/dL)	138.5	1–453
CRP (mg/L)	48	2–140
ESR (mm/h)	60	
CSF/blood glucose level	0.191	0.0–0.604

CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; SD, standard deviation; WBC, white blood cell.
[a]Other: *Alcaligenes faecalis*, *Corynebacterium genitalium*, *Enterobacter cloacae*, *Klebsiella pneumoniae* and *Proteus vulgaris* as single cases. In one patient, dual aetiology was detected with *Staphylococcus epidermidis* and *P. vulgaris*.

Clinical data

Demographic data on the patients are shown in Table 1, and clinical findings are presented in Table 2. There were 64 coexisting immunosuppressive disorders, which are shown in Table 3, in 46 patients. Altered mental status was seen in 81.8% of the patients. In all patients, there was at least one of the three clinical features of headache, fever and altered mental status; in 70% of the patients, at least two of these three features were detected; and this classic triad of findings was complete in 39% of the patients. Although 88% of the patients complained of fever, significant fever levels (more than 38°C) were not detected in 30% of the patients on admission. The mean body temperature was 38.3°C (SD 1.0°C, minimum 36°C, maximum 40°C). There was no significant association between body temperature and increasing age (p 0.826).

In our cohort, the initial empirical antibiotic choices were as follows. The majority of patients, 135 (85%), were treated with ceftriaxone-based or cefotaxime-based regimens. Eight patients (5%) were treated with meropenem, ten (6.3%)

TABLE 2. Clinical findings

Complaints	Number of patients	%
Fever	139	87.6
Headache	87	54.7
Vomiting	72	45.3
Nausea	61	38.4
Ear pain	22	13.8
Dizziness	7	4.4
Rhinorrhoea	7	4.4
Incontinence	4	2.5
Diplopia	3	1.9
Visual loss	1	0.6
Physical findings		
Nuchal rigidity	126	79.2
Confusion	102	64.2
Disorientation	22	13.8
Stupor	16	10.1
Agitation	12	7.5
Labial herpes	9	5.7
Rales	14	9.0
Convulsions	4	2.5
Coma	3	1.9
Hepatomegaly	3	1.9
Oral candidiasis	2	1.2
Coexisting infections		
Respiratory infections		
Otitis and sinusitis	20	12.6
Community-acquired pneumonia	14	8.8
Presence of sepsis	50	31
Complications	31	19.5
Infectious		
Subdural empyema	1	0.6
Septic arthritis	1	0.6
Extraventricular shunt infection	1	0.6
Hospital-acquired pneumonia	2	1.3
Aspiration	1	0.6
Peripheral venous catheter infection	1	0.6
Non-infectious		
Hydrocephalus	6	3.8
Hearing loss	5	3.1
Acute renal failure	4	2.5
Convulsions	3	1.9
Hemiparesis	2	1.3
Hemiplegia	1	0.6
Subarachnoid haemorrhage	1	0.6
Polyneuropathy	1	0.6
Depression	1	0.6
Dysarthria	1	0.6
Acute lung oedema	1	0.6
Atelectasis	1	0.6
Sequela	9	5.7
Hearing loss	5	3.1
Hemiparesis	1	0.6
Hemiplegia	1	0.6
Polyneuropathy	1	0.6
Depression	1	0.6
Dysarthria	1	0.6

TABLE 3. Coexisting immunosuppressive conditions

	Overall (n = 159)	*Listeria* cases (n = 14)
Type 1 diabetes mellitus	20 (12.6%)	1
Type 2 Diabetes mellitus	5%	
Malignancy	5%	1
Steroid use	3.8%	1
Multiple myeloma	3.1%	1
Chronic renal insufficiency	2.5%	
Chemotherapy	1.9%	1
Splenectomy	1.9%	1
Pemphigus	1.3%	
Oral candidiasis	0.6%	
Neutropenia	0.6%	
Still's disease	0.6%	
Anti-TNF use	0.6%	
Alcoholism	0.6%	1
Total	64 disorders in 46 patients	7 disorders in 7 patients

TNF, tumour necrosis factor.

were treated with crystallized penicillin, and six (3.8%) were treated with ampicillin. The mean duration of antibiotic treatment of survivors was 16.3 ± 6.4 days (median 14 days, minimum 8 days, maximum 42 days). In 87.4% of the cases, empirical therapy that was subsequently confirmed to be suitable by antibiotic susceptibility tests was employed. Inappropriate initial antibiotic therapy, which was afterwards modified because of antibiotic resistance in the infecting microorganism, resulted in a 46.2% overall survival rate, whereas appropriate initial therapy led to 80.6% survival. The resistance patterns of *S. pneumoniae* and *L. monocytogenes*, the two major causative agents, are presented in Table 4, and a comparison of *S. pneumonaie* and *L. monocytogenes* meningitis is shown in Table 5. There was no association between the causative agents and neurological complications or fatality (p 0.756 and p 0.725, respectively).

There were 125 patients (78.6%) who recovered from the disease, and 34 patients (21.4%) died despite antibiotic treatment. The mean age of the patients who died was 67.0 years (SD 9.1 years), and the mean age of the patients who recovered was 61.9 years (SD 8.6 years). Sixteen of 50 patients (32%) with clinical sepsis died, and 18 of 109 (16.5%) patients whose condition on admission did not meet the criteria for sepsis died. The cause of death was reported in the medical records for only seven of the 34 patients. Six patients died because of multiple organ dysfunction following septic shock, and one because of intercurrent hospital-acquired pneumonia. The overall fatality rate was 2.5% at the third day, 12.6% at the seventh day, 20.1% at the 14th day, and 21.4% at the 21st day. The Kaplan–Meir survival curve of the patients is shown in Fig. 1. The effects of different variables on fatality in univariate and multivariate analyses are shown in Table 6.

Discussion

The two most important epidemiological changes in CA-ABM have been the reduction in the incidence of *Haemophilus influenzae* meningitis and the emergence of antibiotic-resistant pneumoccocci [15]. Today, pneumococci are known as the major pathogens in CA-ABM [16,17], and this was also the case in our elderly patients. Fortunately, the incidence of the formerly more prevalent *H. influenzae* was as low as 1.3%, and the agent of epidemic meningitis, *N. meningitidis*, was detected in 2.5% of the patients in our study. Pneumococci were responsible for more than two-thirds of all cases, and one-fifth of the patients infected with

TABLE 4. **Antibiotic resistance profiles (no. (%)) of *Streptococcus pneumoniae* and *Listeria monocytogenes***

	PEN	AMP	CXN	E	CLN	CLA	RIF	LEV	SXT
S. pneumoniae	14/110 (13)		1/110 (1%)	5/55 (9)	0/38 (0)	2/34 (6)	2/101 (2)	0/29 (0)	9/39 (23)
L. monocytogenes	0/14 (0)	0/14 (0)	14/14 (100)						

PEN, penicilllin; AMP, ampicillin; CXN, ceftriaxone; E, erythromycin; CLN, clindamycin; CLA, chloramphenicol; RIF, rifampicin; LEV, levofloxacin; SXT, trimethoprim–sulphamethoxazole.

TABLE 5. **Comparison of *Streptococcus pneumonaie* and *Listeria monocytogenes* meningitis**

	S. pneumonaie	*L. monocytogenes*	p-value
Coma (%)	2.7	0.0	1.00
Stupor (%)	10.9	14.3	0.66
Confusion (%)	65.5	57.1	0.56
Neck stiffness (%)	77.3	78.6	1.00
Immunosuppression (%)	26.4	42.9	0.22
Fatality (%)	22.7	28.6	0.74
Neurological complication (%)	8.2	0	0.60
Age, years	61 (50–86)	61 (50–80)	0.92
Fever (°C)	38.5 (36–40)	38.5 (36.8–39.8)	0.90
CSF WBC count (/mm^3)	1600 (10–44 000)	660 (20–1983)	0.03
CSF/blood glucose	0.12 (0.0–0.60)	0.23 (0.06–0.46)	0.019
CSF protein (mg/dL)	317 (2–3670)	168.5 (47–1400)	0.06
Blood WBC count (/mm^3)	16 500 (1000–45 500)	22 000 (8300–31 300)	0.60
ESR	60 (11–140)	57 (30–88)	0.99
CRP	48 (1–453)	64 (14–248)	0.34

CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; WBC, white blood cell. Unless otherwise stated, the results are given as median (minimum–maximum).

pneumococci died. Antibiotic resistance in invasive pneumococci has been increasing steadily in Turkey [8,18,19]. In our study, penicillin resistance was found in 13% of pneumococci. Thus, penicillin is not a reliable empirical treatment option in pneumococcal meningitis (PM). Resistance to ceftriaxone was reported in 1% of pneumococci. Ceftriaxone or cefotaxime seem to be effective in the management of PM, and the 23-valent pneumococcal vaccine appears to be effective in preventing pneumococcal disease in Turkey [20].

L. monocytogenes is an infectious agent in newborns, pregnant women, immunosuppressed people and the elderly [21–23]. Our investigation shows that it is a significant pathogen for this age group in Turkey, and immunosuppresive conditions were present in half of the patients. In our study, all *L. monocytogenes* strains were susceptible to benzylpenicillin or ampicillin, but all were resistant to cephalosporins. Given the fact that benzylpenicillin and ampicillin are not suitable choices in PM (which accounts for the majority of cases) in Turkey, combined therapy would be the rational approach [24]. In our study, the features of *L. monocytogenes* meningitis were very similar to those of PM. The CSF/blood glucose ratio was higher in listerial meningitis than in PM, whereas the CSF WBC count was higher in the latter.

The classic triad of acute bacterial meningitis consists of fever, headache, and changes in mental status. All of our patients exhibited at least one of these. Approximately two-thirds of the patients presented two of the classic triad, whereas only 39% had all three. Similarly, most adult patients with CA-ABM are known to have high fevers, often greater than 38°C [25]. However, in this older population, 30% of the patients did not. Hypothermia, which is defined as a core temperature below 35°C [26], was not detected in any of the patients. Mental status was altered in three-quarters of the patients, most of whom were confused. We could not evaluate the effect of coma, as there were only three comatose cases, but the presence of stupor was a poor prognostic factor.

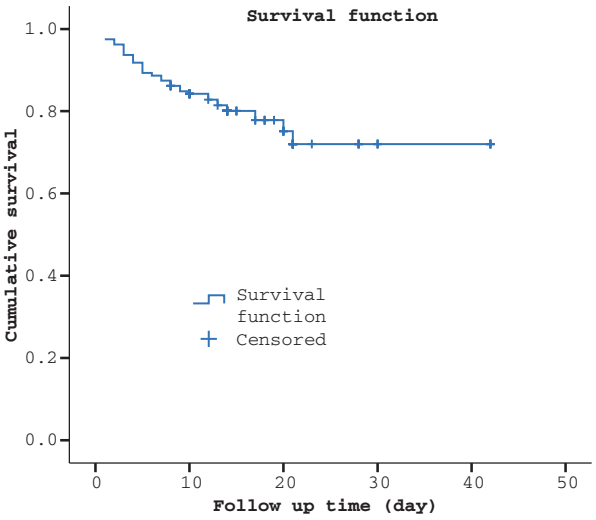

FIG. 1. Overall survival of the patients over time.

TABLE 6. Effects of different variables on fatality, in univariate and multivariate Cox proportional regression analysis

	Unadjusted HR	95% CI	p-value	Adjusted HR[a]	95% CI	p-value
Age	1.05	1.01–1.09	0.007	1.04	1.01–1.08	0.019
Timing of antimicrobials in relation to onset of symptoms[b]	1.30	0.58–2.93	0.53			
Immunosuppression	1.42	0.70–2.86	0.33	1.29	0.62–2.66	0.49
Sepsis	2.38	1.09–5.19	0.027	2.16	1.05–5.82	0.041
Inappropriate antimicrobial treatment	3.90	1.68–9.08	0.002	3.70	1.57–8.70	0.003
Male sex	1.88	0.90–3.94	0.09	1.94	0.92–4.09	0.08
Neurological complication	2.64	0.36–19.39	0.34	9.54	0.58–156.83	0.11
Confusion	1.49	0.69–3.19	0.31	3.13	0.73–13.51	0.13
Stupor	2.93	1.27–6.75	0.011	7.91	1.64–38.24	0.01

CI, confidence interval; HR, hazard ratio.
[a]Adjusted for age, gender, immunosupression, sepsis, neurological complication, confusion, stupor, and inappropriate antimicrobial treatment.
[b]Reference group includes patients receiving antibiotics within 48 h from onset of symptoms. These data are included for 126 of 159 cases, and as the result of univariate analysis is not significant, this parameter is excluded from the multivariate analysis.

Fatality rates of CA-ABM are believed to be related to the various infecting microorganisms [27], but in our elderly patients we could not establish significant correlations between fatality or the presence of complications and the causative agents. Reasons for this difference may be the lower numbers infected by pathogens other than pneumococci, or the confounding factors related to altered immunity in this age group. Moreover, we could not establish a correlation between the delay from onset of symptoms to antibiotic administration and fatality: there was no significant difference between patients given antibiotics within 2 days following the onset of symptoms and those treated later. This finding may have resulted from the initial symptoms in these patients being unrelated to meningitis itself, but rather to coexisting infections. However, the rational approach would be to administer antimicrobial therapy as soon as possible after the diagnosis of bacterial meningitis is suspected or proven [11]. On the other hand, inappropriate antibiotic use was significantly associated with higher fatality rates, even though the treatment was later modified in response to the results of antibiotic susceptibility tests. As CA-ABM is a fatal infection, rational antibiotic use is very important, particularly in the presence of sepsis, which was found to be a poor prognostic factor for mortality in our study. Thus, surveillance of meningeal pathogens in a given community is essential for optimizing empirical therapies.

Pneumococcal infections are associated with immunosuppressive conditions. In addition, it is known that immunosuppressive conditions mediate worse outcomes in systemic infections [28–35]. In our patients with immunosuppressive disorders, CSF/blood glucose ratios were significantly lower than in the immunocompetent patients. When the diabetic patients were excluded, however, there was no significant difference between the CSF/blood glucose ratios in the two groups. In contrast, although CSF glucose levels were higher, the CSF/blood glucose ratios were lower in diabetic patients. This is probably due to the rapid utilization of excessive CSF glucose by the infecting agent in the course of CA-ABM in diabetic patients. Lower CSF/blood glucose ratios in fatal cases may be indicative of higher bacterial loads. Furthermore, lower CSF WBC counts were detected in patients in our study who died. In the subset of immunocompromised elderly people, however, this was not a poor prognostic factor. The clinical disease observed when bacteria enter the CSF is a result of complex interactions between the components of bacteria and the host inflammatory response. These interactions influence both the blood–brain barrier and neuronal integrity. In this context, the immunosuppression may not have marked negative effects on outcome in CA-ABM.

The ageing process is characterized by structural and functional changes affecting all organ systems [36]. Although significant associations could not be established among fever levels, numerical values of biochemical or inflammatory markers or increasing age, the fatality rate was higher in this elderly population.

Acknowledgements

We thank D. Robert for his contribution to the presentation of this material.

Transparency Declaration

No funding of any kind has been received. The authors have no conflicts of interest to declare.

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