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# Pooled Analysis of 2,408 Cases of Acute Adult Purulent Meningitis from Turkey

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**Key Words**
Bacterial meningitis, Turkey · Epidemiology · Systematic review · Pooled analysis · *Staphylococcus aureus* · Mortality

**Abstract**
***Objectives:*** The aim of this study was to systematically review the Turkish literature of acute adult purulent meningitis. ***Materials and Methods:*** The published series of three national databases and two international databases were searched to perform the review. In addition to the databases, abstracts of congresses held between 1994 and 2003 by the Turkish Clinical Microbiology and Infectious Diseases Association, Turkish Microbiology Association, and the Antibiotic and Chemotherapy Association were searched for reports about acute purulent meningitis. ***Results:*** Data for 2,408 patients with a diagnosis of acute purulent meningitis were obtained from 30 reports. In terms of clinical findings, 1,254 of 1,570 (79.8%) had fever (>38°C), 1,408 of 1,595 (88.2%) headache, 1,403 of 1,562 (89.8%) stiffness of the neck, and 649 of 784 (82.7%) leukocytosis (>10,000/mm$^3$). Cerebrospinal fluid culture yielded a pathogen in 873 of 2,260 (38.6%) patients. The most common pathogen was *Streptococcus pneumoniae*, followed by *Neisseria meningitidis* and *Staphylococcus aureus*. Overall mortality was 425 of 2,408 (17.6%). Pathogen-specific mortality was 60 of 202 (29.7%) for *S. pneumoniae* and 6 of 100 (6%) for *N. meningitidis*. ***Conclusion:*** Meningitis is a serious, life-threatening disease. More preventive measures should be sought to further decrease the mortality and morbidity related to acute purulent meningitis.



## Introduction

Despite developments in antimicrobial agents and intensive care units, meningitis is still associated with significant mortality and morbidity [1–30]. Vaccination has changed the epidemiology of acute purulent meningitis in developed countries [31]. Several studies of epidemiological or clinical features and prognostic factors in adults with bacterial meningitis have been performed; however, nearly all are retrospective and relatively small in size and many are from developed countries. Studies from Turkey are also retrospective and carry the disadvantage of low patient numbers 1–30]. The aim of this study was to systematically review the literature from Turkey for acute adult purulent meningitis between 1990 and 2004 and compare several parameters for series related to 1995 or earlier and 1996 or later.

## Methods

Three national databases (Ulakbim Turkish Medical Literature database, http://www.turkishmedline.com, http://medline.pleksus.com.tr) and two international databases (Index Medicus and Science Citation Index-Expanded) were searched. The Ulakbim Turkish Medical Literature Database was founded by Tubitak (The Scientific and Technologic Council of Turkey) in 1996. The other two national databases (http://www.turkishmedline.com, http://medline.pleksus.com.tr) are private sector databases. Thus, three different databases were consulted in an endeavor to perform a comprehensive search. Key words for national databases were 'menenjit' or 'meninjit' or 'meningitis'. Key words used for Index Medicus and Science Citation Index were 'meningitis and

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Turkey' and 'central nervous system infection and Turkey'. In addition to the published articles extracted by the above-mentioned methods, abstracts of congresses held by the Turkish Clinical Microbiology and Infectious Diseases Association (KLIMIK), Turkish Microbiology Association and Turkish Antibiotic and Chemotherapy Association (ANKEM) between 1994 and 2003 were searched for studies regarding acute purulent meningitis. The congress proceedings from 1990 to 1993 were not available, therefore, abstracts from this period have not been included. For a more comprehensive review, articles cited in references extracted from sources have also been included. All abstracts found either in databases or in congress abstract books were analyzed by two separate investigators. For studies that were both published and presented at congresses, only the form of the article was taken into consideration. In case of presentations from a single study with overlapping periods, the study covering a longer duration was chosen.

The following categories were excluded: (1) articles published before 1990; (2) pediatric series; (3) *Brucella* spp., fungus or *Mycobacterium tuberculosis*-associated case reports/series; (4) aseptic meningitis series; (5) chronic meningitis series, and (6) case reports or series with less than 5 patients.

In mixed series, only cases with acute purulent meningitis were included. Statistical comparisons were made by $\chi^2$ test; a p value less than 0.05 was considered as significant.

## Results

Data for 2,408 patients with a diagnosis of acute purulent meningitis were obtained from 30 reports (20 published articles and 10 congress abstracts). Of the 20 published articles, 18 were in peer-reviewed medical journals indexed in national databases and two were published in peer-reviewed journals indexed in international databases.

Of 1,633 patients, 1,032 (63.1%) were male. In terms of clinical findings, 1,254 out of 1,570 (79.8%) presented with fever (>38°C), 1,408 out of 1,595 (88.2%) headache, 1,403 out of 1,562 (89.8%) stiffness of the neck, 649 out of 784 (82.7%) leukocytosis (>10,000/mm$^3$), 882 out of 1,265 (69.7%) vomiting or nausea, 796 out of 1,380 (57.6%) disturbances in consciousness, 126 out of 535 (23.5%) epileptic attacks, 34 out of 237 (14.3%) herpes labialis and 71 out of 758 (9.3%) rash.

Cerebrospinal fluid (CSF) culture yielded a pathogen in 873 out of 2,260 (38.6%) of the patients (table 1). Gram stain was reported to be positive in 462 out of 1,256 (36.7%) cases. The most common pathogen was *Streptococcus pneumoniae*, followed by *Neisseria meningitidis*. Interestingly *Staphylococcus aureus* was the third most common pathogen and *Haemophilus influenzae* was reported to be isolated in only 2 cases.

Overall mortality was 425 out of 2,408 (17.6%). Mortality data for CSF culture-positive and -negative patients were available for only 561 patients. Mortality rates were similar, 42 out of 245 (17.1%) in those with a negative CSF culture and 53 out of 316 (16.7%) in those with a positive CSF culture ($p > 0.05$). Pathogen-specific mortality was 60 out of 202 (29.7%) for *S. pneumoniae* and 6 out of 100 (6%) for *N. meningitidis*. Frequency of complications and sequelae are summarized in table 2.

When series related to 1995 or earlier and after 1995 were compared, *N. meningitidis*-related meningitis decreased significantly whereas CSF culture positivity and *S. pneumoniae*-related meningitis increased significantly (table 3).

**Table 1.** Distribution of pathogens isolated in the CSF cultures

| Pathogen | Number |
|---|---|
| *Streptococcus pneumoniae* | 457 |
| *Neisseria meningitidis* | 251 |
| *Staphylococcus aureus* | 29 |
| Enterobacteriacea (species not mentioned) | 8 |
| Coagulase-negative staphylococci | 6 |
| *Listeria monocytogenes* | 6 |
| *Acinetobacter baumannii* | 5 |
| *Escherichia coli* | 4 |
| Gram-negative bacilli (species not mentioned) | 4 |
| *Klebsiella pneumoniae* | 3 |
| *Streptococcus pyogenes* | 3 |
| *Pseudomonas aeruginosa* | 3 |
| *Haemophilus influenzae* | 2 |
| *Branhamella catarrhalis* | 1 |
| *Proteus mirabilis* | 1 |
| *Enterococcus* spp. | 1 |
| Total | 784 |

In three reports, the specific bacterial yield of the CSF culture is not shown.

**Table 2.** Frequency of complications and sequelae

| Parameter | Number | Percent |
|---|---|---|
| Brain edema | 33/285 | 11.5 |
| Brain abscess | 15/279 | 5.4 |
| Arthritis | 4/77 | 5.2 |
| Paralysis | 15/558 | 2.6 |
| Deafness | 10/507 | 1.9 |
| Aphasia | 4/234 | 1.7 |
| Diplopia | 2/93 | 2.1 |
| Cranial nerve involvement | 50/649 | 7.7 |
| Hydrocephalus | 28/434 | 6.4 |

**Table 3.** Comparison of several parameters for series related to 1995 or earlier [1, 2, 4, 6, 9, 10, 11, 13, 14, 16, 17, 24, 28] and related to 1996 or later [3, 5, 15, 20, 23, 26, 27, 30]

| Parameter | Rate | | |
|---|---|---|---|
| | 1995 or earlier | 1996 or later | p |
| Mortality | 137/980 (13.9) | 117/746 (15.7) | >0.05 |
| CSF culture positivity | 263/832 (31.6) | 302/746 (40.4) | <0.05 |
| *S. pneumoniae* | 112/832 (13.4) | 156/618 (25.2) | <0.05 |
| *N. meningitidis* | 115/798 (14.4) | 59/618 (9.5) | <0.05 |

Comparisons were made by $\chi^2$ test.
Figures in parentheses are percentages.

## Discussion

The mortality rate in community-acquired meningitis in published series from developed countries differs by a wide range, depending on the specific organism. Durand et al. [31] reported a mortality rate of 25% in 296 community-acquired meningitis episodes, whereas Schuchat et al. [32] reported an overall mortality of 13.3 in 248 patients. The overall mortality of 17.6% accords with data of Durand et al. [31] and Schuchat et al. [32]. Interestingly, the overall mortality of series related to 1995 or earlier and related to 1996 or later was similar. *N. meningitidis* and *S. pneumoniae* meningitis-related mortality is also in accordance with the literature [32, 33]. Ceftriaxone entered the Turkish market in 1988. The possible contribution of this molecule to therapy might have been lessened by relatively low prevalence of high-level penicillin-resistant *S. pneumoniae* in Turkey [33].

In this systematic review *H. influenzae* was encountered in only two of 783 (0.25%) CSF culture-positive cases. Although exclusion of pediatric cases might also have affected the situation, 0.25% is very low when compared with data of Durand et al. [31], who reported an *H. influenzae* rate of 4% in 296 adult community-acquired meningitis episodes. This may be due to the high natural immunity of Turkish people to *H. influenzae* [34], despite the absence of *H. influenzae* type B vaccine in the National Immunization Program. The decrease in *N. meningitidis*-related meningitis before and after 1995 is probably due to the routine vaccination program conducted by the military 17]. In an earlier report from Turkey [35] in which 295 acute purulent meningitis cases between 1974 and 1986 were reviewed retrospectively, the most common pathogen was *N. meningitidis* (76.4% of all cases) and most cases were soldiers on military duty. According to the registry of the Turkish Ministry of Health, there were 9,167 cases of *N. meningitidis*-related meningitis between 1993 and 2002. *S. pneumoniae* and other acute purulent meningitis cases are not routinely registered in Turkey.

The overall CSF culture positivity level ranges between 60 and 80% in the literature [31, 36], and it was 38.6% in this study. CSF culture positivity and *S. pneumoniae*-related meningitis was higher in the series related to 1996 or later than in the series related to 1995 or earlier (31.6 vs. 40.4%, $p < 0.05$, table 1). This comparison may be criticized due to heterogeneity in the microbiologic methods, but the only aim of this comparison was to give the sum of the yield of existing methods in pathogen isolation. In four studies, only classical microbiological techniques were used. The percentage of patients diagnosed with automatic and/or classical methods were not detailed in other studies. The relatively low yield of CSF cultures and the increase in CSF culture positivity in the series related to 1996 or later may be attributed to the recently widespread use of more developed culture systems (automatic culture systems etc.) [37].

There is a tendency not to publish bad results in medicine. For this reason, we included unpublished series as well. The mortality rate of published results and results only presented in congresses were similar (data not shown).

In the present study, data from articles published before 1990 were not included since it was not possible to search those articles in the mentioned databases; series of fewer than 5 patients were excluded since patients in these small series would overlap with the articles or congress abstracts. The three most comprehensive national congresses in the field of infectious diseases and clinical microbiology were searched for data of congress abstracts that had not been converted to published articles. We accessed all of the articles that our searches yielded.

An important disadvantage of our study is the heterogeneity of the data. Because of this heterogeneity, the ratios in different variables have different denominators, therefore, we did not analyze the results of different treatment regimens. Although all centers are tertiary care educational hospitals, possible double report of a single patient from two different centers cannot be excluded. In spite of these disadvantages, this is the first pooled analysis on this topic and may provide major clues about the epidemiology of meningitis in Turkey.

## Conclusion

Despite developments in the quality of care in hospitals and critical care units as well as those in antibiotic therapy, meningitis is still a life-threatening disease. The vectors that make *S. aureus* the third most common pathogen need to be analyzed. In order to identify the epidemiologic changes, it is necessary to create an appropriate national registration system with fewer bureaucratic entities. It is questionable whether or not the existing sanctions may increase the reporting rate. Increased preventive measures should be sought by the medical community to further decrease the mortality and morbidity related to acute purulent meningitis.

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