



## Mortality indicators in pneumococcal meningitis: therapeutic implications



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## SUMMARY

**Background:** The aim of this study was to delineate mortality indicators in pneumococcal meningitis with special emphasis on therapeutic implications.

**Methods:** This retrospective, multicenter cohort study involved a 15-year period (1998–2012). Culture-positive cases ( $n = 306$ ) were included solely from 38 centers.

**Results:** Fifty-eight patients received ceftriaxone plus vancomycin empirically. The rest were given a third-generation cephalosporin alone. Overall, 246 (79.1%) isolates were found to be penicillin-susceptible, 38 (12.2%) strains were penicillin-resistant, and 22 (7.1%) were oxacillin-resistant (without further minimum inhibitory concentration testing for penicillin). Being a critical case (odds ratio (OR) 7.089, 95% confidence interval (CI) 3.230–15.557) and age over 50 years (OR 3.908, 95% CI 1.820–8.390) were independent predictors of mortality, while infection with a penicillin-susceptible isolate (OR 0.441, 95% CI 0.195–0.996) was found to be protective. Empirical vancomycin use did not provide significant benefit (OR 2.159, 95% CI 0.949–4.912).

**Conclusions:** Ceftriaxone alone is not adequate in the management of pneumococcal meningitis due to penicillin-resistant pneumococci, which is a major concern worldwide. Although vancomycin showed a trend towards improving the prognosis of pneumococcal meningitis, significant correlation in statistical terms could not be established in this study. Thus, further studies are needed for the optimization of pneumococcal meningitis treatment.

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## 1. Introduction

Pneumococci are the most common agents of acute purulent meningitis. The disease has a case fatality rate of 17–30%, which is largely attributed to the complicated pharmacokinetics of the leptomeninges.<sup>1–6</sup> In addition, the worldwide emergence of penicillin-resistant pneumococcus (PenRP) has complicated the management of pneumococcal meningitis, eliminating penicillin from empirical treatment protocols. Ceftriaxone or cefotaxime with or without vancomycin are currently recommended as the first-line antibiotics.<sup>7–9</sup> However, data on the outcome performance of current regimens in this PenRP era are few, and critical questions regarding whether a vancomycin supplement is adequate or whether other options such as linezolid or daptomycin should be considered, remain unanswered.

To expand our understanding of the management problems in pneumococcal meningitis, we undertook a nationwide retrospective study. This study aimed to investigate independent predictors of the outcome in pneumococcal meningitis, with special emphasis on therapeutic implications.

## 2. Patients and methods

### 2.1. Study design

This retrospective, multicenter cohort study involved the 15-year period from January 1998 to December 2012. Patients with acute bacterial meningitis caused by *Streptococcus pneumoniae* were included in the study. A Microsoft Windows-based computer database was sent out and data were collected from 38 participating centers in Turkey. The Institutional Review Board of Istanbul Haydarpasa Numune Training and Research Hospital approved the study protocol.

### 2.2. Inclusion criteria

Patients with symptoms and signs compatible with meningitis and with positive cerebrospinal fluid (CSF) cultures for *S.*

*pneumoniae*, were included in this study. Patients with CSF pleocytosis and a clinical picture consistent with meningitis were also included when blood cultures were positive for *S. pneumoniae* in the absence of any other probable focus of infection for pneumococcal disease, in those who were CSF culture-negative.

### 2.3. Microbiological investigations

All *S. pneumoniae* isolates were identified by standard laboratory methods in the clinical microbiology laboratory of the participating center. Antimicrobial susceptibilities of the pneumococcal isolates were determined by disk diffusion test, automated systems, Etests, or microdilution tests, in accordance with the criteria of the Clinical and Laboratory Standards Institute (CLSI), or former National Committee for Clinical Laboratory Standards. The penicillin and ceftriaxone minimum inhibitory concentration (MIC) values of the isolates were reinterpreted in accordance with the current guidelines, in which thresholds were as follows:<sup>10,11</sup> penicillin MIC  $\leq 0.06$  mg/l as susceptible and MIC  $\geq 0.12$  mg/l as resistant; ceftriaxone MIC  $\leq 0.5$  mg/l as susceptible, MIC of 1 mg/l as intermediately resistant, and MIC  $\geq 2.0$  mg/l as resistant.

In most of our centers, *S. pneumoniae* was screened by oxacillin disk test as recommended, and oxacillin-resistant strains were confirmed by penicillin MIC tests. However, in some of the centers, oxacillin-resistant isolates were not further tested for MICs. Therefore, the susceptibility status of isolates was subgrouped as penicillin susceptible pneumococcus (PenSP), PenRP, or oxacillin-resistant pneumococcus (OxaRP). Since there is a potential overlap between penicillin- and oxacillin-resistant strains, these variables were assessed separately in multivariate models.

### 2.4. Definitions

Glasgow coma scale (GCS) scores of  $\geq 13$  were recorded as mild, 9–12 as moderate, and  $\leq 8$  as poor.<sup>12</sup> GCS scores were recorded separately because patients with severe coma scores might not have been admitted to the intensive care unit (ICU) unless they

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