International Journal of Infectious Diseases 19 (2014) 13–19

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Mortality indicators in pneumococcal meningitis: therapeutic implications

Hakan Erdem [a,*], Nazif Elaldi [b], Nefise Öztoprak [c], Gonul Sengoz [d], Oznur Ak [e], Selcuk Kaya [f], Asuman Inan [g], Saygın Nayman-Alpat [h], Ayşegül Ulu-Kilic [i], Abdullah Umut Pekok [j], Alper Gunduz [k], Mustafa G. Gozel [b], Filiz Pehlivanoglu [d], Kadriye Yasar [l], Hava Yılmaz [m], Mustafa Hatipoglu [a], Gonul Cicek-Senturk [n], Fusun Z. Akcam [o], Ahmet C. Inkaya [p], Esra Kazak [q], Ayşe Sagmak-Tartar [r], Recep Tekin [s], Derya Ozturk-Engin [g], Yasemin Ersoy [t], Oguz Resat Sipahi [u], Tumer Guven [v], Gunay Tuncer-Ertem [w], Selma Alabay [i], Ayhan Akbulut [r], Ilker I. Balkan [x], Oral Oncul [a], Birsen Cetin [y], Saim Dayan [s], Gulden Ersoz [z], Ahmet Karakas [aa], Nail Ozgunes [bb], Alper Sener [cc], Aysegul Yesilkaya [dd], Ayse Erturk [ee], Sibel Gundes [ff], Oguz Karabay [gg], Fatma Sirmatel [hh], Selma Tosun [ii], Vedat Turhan [a], Aysun Yalci [jj], Yasemin Akkoyunlu [kk], Emsal Aydın [ll], Husrev Diktas [mm], Sukran Kose [nn], Asim Ulcay [a], Derya Seyman [c], Umit Savasci [oo], Hakan Leblebicioglu [m], Haluk Vahaboglu [bb]

[a] *GATA Haydarpasa Training Hospital, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey*
[b] *Cumhuriyet University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Sivas, Turkey*
[c] *Antalya Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Antalya, Turkey*
[d] *Haseki Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey*
[e] *Lutfi Kirdar Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey*
[f] *Karadeniz Technical University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Trabzon, Turkey*
[g] *Haydarpasa Numune Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey*
[h] *Osmangazi University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Eskisehir, Turkey*
[i] *Erciyes University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Kayseri, Turkey*
[j] *Private Erzurum Sifa Hospital, Department of Infectious Diseases and Clinical Microbiology, Erzurum, Turkey*
[k] *Sisli Etfal Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey*
[l] *Bakırkoy Dr. Sadi Konuk Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey*
[m] *Ondokuz Mayis University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Samsun, Turkey*
[n] *Diskapi Yildirim Beyazit Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey*
[o] *Suleyman Demirel University, School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Isparta, Turkey*
[p] *Hacettepe University, School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey*
[q] *Uludag University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Bursa, Turkey*
[r] *Firat University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Elazig, Turkey*
[s] *Dicle University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Diyarbakir, Turkey*
[t] *Inonu University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Malatya, Turkey*
[u] *Ege University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Izmir, Turkey*
[v] *Ankara Atatürk Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey*
[w] *Ankara Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey*
[x] *Istanbul University Cerrahpasa School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey*
[y] *Koc University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey*
[z] *Mersin University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Mersin, Turkey*
[aa] *Gulhane Medical Academy, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey*
[bb] *Medeniyet University, Goztepe Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey*
[cc] *Onsekiz Mart University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Canakkale, Turkey*
[dd] *Baskent University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey*
[ee] *Recep Tayyip Erdoğan University, School of Medicine, Department of Department of Infectious Diseases and Clinical Microbiology, Rize, Turkey*
[ff] *Kocaeli University School of Medicine, Department of Department of Infectious Diseases and Clinical Microbiology, Izmit, Turkey*
[gg] *Sakarya University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Sakarya, Turkey*
[hh] *Izzet Baysal University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Bolu, Turkey*
[ii] *Izmir Bozyaka Training and Research Hospital, Department of Infectious diseases and Clinical Microbiology, Izmir, Turkey*
[jj] *Ankara University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey*

* Corresponding author. Tel.: +90 216 5422020/3655.
E-mail address: hakanerdem1969@yahoo.com (H. Erdem).

http://dx.doi.org/10.1016/j.ijid.2013.09.012

[kk] Bezmi Alem Vakif University, School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey
[ll] Kafkas University School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Kars, Turkey
[mm] Military Hospital, Department of Infectious Diseases and Clinical Microbiology, Tatvan, Turkey
[nn] Tepecik Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Izmir, Turkey
[oo] Department of Infectious Diseases and Clinical Microbiology, Sarikamis Military Hospital, Kars, Turkey

ARTICLE INFO

Article history:
Received 21 July 2013
Received in revised form 16 September 2013
Accepted 20 September 2013

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Streptococcus pneumoniae
Meningitis
Mortality
Penicillin
Resistance
Vancomycin

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.

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.[1–6] 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.[7–9] 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:[10,11] 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.[12] GCS scores were recorded separately because patients with severe coma scores might not have been admitted to the intensive care unit (ICU) unless they

required mechanical ventilation. Eventually, ICU patients plus non-ICU patients with poor GCS scores were classified as 'critical cases'.

Underlying diseases were classified according to the McCabe and Jackson classification scheme.[13] Empirical vancomycin treatment was recorded if vancomycin was initiated during the hospital admission, whereas escalation therapy was defined when vancomycin was added during the course of treatment. De-escalation therapy was defined as either a switch to a narrower spectrum agent or the reduction in the number of initial antibiotics,[14] which were penicillin or mostly ceftriaxone alone.

The primary endpoint of this study was 30-day all-cause mortality.

2.5. Data collection and statistical methods

Data related to demographic characteristics, hospital admission dates, antibiotic initiation time, and duration of hospital stay were collected for all patients. For patients followed in the ICUs, the duration of the ICU stay was also recorded. In univariate analysis, categorical variables were compared by Pearson's Chi-square test, or when necessary by Fisher's exact test; continuous variables were compared by Student's *t*-test, or by unequal variances *t*-test with Welch's approximation. Significance was inferred at the 0.05 level and was always two-sided.

Variables with a significance value of $\leq$0.2 and those recognized as significant in previous studies were included in the initial multivariate model. A stepwise backward selection approach was used in the logistic regression analysis. Variables such as age were entered and removed from models in categorical or continuous forms until the best fit was achieved. Confounding, collinearity, and interaction between terms were tested, and models were modified accordingly. Model fit was estimated by post-estimation diagnostic routines such as Hosmer–Lemeshow goodness-of-fit statistics and classification performances. Adjusted odds ratios (aOR) were obtained from the final model. Statistical comparisons were performed using Stata 12 (StataCorp LP, College Station, TX, USA).

3. Results

A total of 306 patients fulfilling the inclusion criteria were admitted to the participating centers between 1998 and 2012; 213 were male (69.6%) and 93 were female (30.4%). Pneumococcus was recovered from the CSF of 301 (98.4%) and from the blood of 71 (22.8%) patients. Blood was the only culture-positive specimen in five (1.6%) of our patients. Characteristics of the cohort are shown in Table 1. Briefly, the mean age was 45.3 years (standard deviation (SD) 18.4, range 14–86 years), and the mean leukocyte and thrombocyte counts $\times 10^9$/l of blood on admission were 18.4635 $\pm$ 8.8142 and 238.0114 $\pm$ 101.8171, respectively. On admission, 259 (84.6%) patients presented with leukocytosis and 10 (3.27%) with leukopenia. The GCS score was poor in 72 (23.5%), moderate in 143 (46.7%), and mild in 91 (29.7%) patients. Interestingly, 98 (32%) of the patients gave a prior history of head trauma. Two patients (0.6%) had experienced recurrent pneumococcal meningitis.

Table 1
Descriptive characteristics of patients with pneumococcal meningitis (n = 306)

Variable	n (%)
Male gender	213 (69.61)
Leukopenia or leukocytosis	269 (87.91)
Head trauma	98 (32.03)
Diabetes mellitus	40 (13.07)
Cerebrovascular event	14 (4.58)
Chronic obstructive lung disease	13 (4.25)
Splenectomy operation	11 (3.59)
Malignancy	8 (2.61)
HIV infection	3 (0.98)
Pregnancy	2 (0.65)
Collagen tissue disorder	1 (0.33)

3.1. Antibiotic treatment

Following the diagnoses of bacterial meningitis on admission, 243 patients received ceftriaxone, five patients received cefotaxime, and 58 patients received ceftriaxone plus vancomycin empirically. The mean time elapsed between hospitalization and the institution of antibiotics was 3 h (SD 7, range 0.5–72 h) and did not differ significantly between antibiotic regimens.

Therapy was de-escalated in 28 patients; of these patients, two (7.1%) died. Therapy was escalated in 28 patients. In 13 of these patients, vancomycin was added to the therapy following the isolation of PenRP. Three of these 13 (23.7%) patients died, and six out of the 10 remaining patients had one of the therapeutic failure parameters other than penicillin resistance. Neither escalating nor de-escalating treatment was found to have a significant effect in terms of the outcome.

3.2. Susceptibility to beta-lactams

All 306 isolates had been screened with oxacillin. A total of 241 (78.7%) isolates were susceptible to oxacillin, while 65 (21.2%) isolates were found to be resistant. Among oxacillin-resistant isolates, 43 (14%) were further tested for penicillin MICs and 38 were found to be penicillin-resistant. The remaining 22 oxacillin-resistant isolates were not tested for the penicillin MIC, hence they were not confirmed as penicillin-resistant. Eventually, 246 (79.1%) isolates were assigned as PenSP and 60 isolates were assigned as OxaRP, of which 38 (12.2%) were PenRP; 22 (7.1%) remained undetermined in terms of penicillin susceptibility.

3.3. Outcome

A total of 42 out of the 306 patients died of pneumococcal meningitis within the 30-day follow-up period. The crude mortality rate (CFR) was 13.7%. Comparison of demographics and other variables between those who died and those who survived are shown in Tables 2 and 3. Briefly, age over 50 years, admission to the ICU, empirical institution of vancomycin, a severe GCS score, underlying disease, and penicillin resistance of the isolates were significantly more common among fatal cases.

All these significant variables plus gender, corticosteroid treatment, and escalation of the treatment, were entered into the initial model and tested in various forms. We kept gender in the final model despite this being insignificant. The results of the final model are presented in Table 4. Accordingly, being a critical case and age over 50 years were independent predictors of mortality, while infection with a PenSP isolate was found to be protective. In this model, PenSP versus the rest (PenRP plus OxaRP) was entered into the multivariate analysis. In the next step, we dropped patients infected with OxaRP and analyzed a subgroup of patients consisting only of patients infected with PenSP and PenRP. In this subgroup of patients (n = 284) the aORs and corresponding 95% confidence intervals (CIs) were comparable with the main cohort: being a critical case (OR 8.34, 95% CI 3.533–19.669) and age over 50 years (OR 4.09, 95% CI 1.813–9.209) were associated with an adverse outcome, while infection with a PenSP was protective (OR 0.37, 95% CI 0.140–0.960). Controlling corticosteroid treatment did not change this picture.

Interestingly, in this study the early institution of vancomycin did not significantly protect patients against an adverse outcome. In order to further interpret this finding, we performed a subgroup

Table 2
Comparison of risk factors for patients with pneumococcal meningitis who died and those who survived (univariate analysis)[a]

	Died (n = 42)	Survived (n = 264)	OR	95% CI	p-Value
Male gender	25 (59.52)	188 (71.21)	0.59	0.29–1.25	0.126
Age >50 years	28 (66.67)	95 (35.98)	3.56	1.71–7.66	<0.001
Age >65 years	14 (33.33)	34 (12.88)	3.38	1.48–7.41	<0.001
ICU admission	20 (47.62)	45 (17.05)	4.42	2.09–9.26	0.001
COPD	4 (9.52)	9 (3.41)	2.98	0.64–11.31	0.0001
Diabetes mellitus	9 (21.43)	31 (11.74)	2.05	0.79–4.91	0.068
Prior hospitalization[b]	6 (14.29)	21 (7.95)	1.93	0.59–5.37	0.084
Head trauma	7 (16.67)	66 (25)	0.6	0.21–1.46	0.179
Treatment options					
Empirical vancomycin	14 (33.33)	44 (16.67)	2.5	1.12–5.37	0.010
Mannitol use	10 (23.81)	80 (30.3)	0.72	0.30–1.59	0.391
Corticosteroid use	22 (52.38)	148 (56.06)	0.86	0.43–1.75	0.656
Prior antibiotic use[b]	6 (14.29)	44 (16.67)	0.83	0.27–2.16	0.698
Neurosurgery operation	4 (9.52)	30 (11.36)	0.82	0.20–2.53	0.725
Head trauma	9 (21.43)	89 (33.71)	0.54	0.22–1.21	0.113
Glasgow coma scale (GCS) score					
13–15 (mild)	5 (11.9)	86 (32.58)			<0.0001
9–12 (moderate)	14 (33.33)	129 (48.86)			
0–8 (poor)	23 (54.76)	49 (18.56)			
McCabe and Jackson (MCJ)					
No underlying disease	19 (45.24)	194 (73.48)			0.001
Non-fatal disease	15 (35.71)	49 (18.56)			
Ultimately fatal disease	8 (19.05)	21 (7.95)			
Susceptibility of pneumococcus					
Penicillin-resistant	10 (23.81)	28 (10.61)			0.016
Penicillin-susceptible	27 (64.29)	219 (82.95)			
Oxacillin-resistant	5 (11.9)	17 (6.44)			
Antibiotic modification					
De-escalated	2 (4.76)	26 (9.85)			0.531
Escalated	5 (11.9)	23(8.71)			
Unchanged	35 (83.33)	215 (81.44)			
Leukopenia	2 (4.76)	8 (3.03)	1.60	0.16–8.41	0.633
Leukocytosis	34 (80.95)	225 (85.23)	0.74	0.31–1.98	0.491
Thrombocytopenia	15 (35.71)	32 (12.12)	4.03	1.78–8.80	<0.001
Thrombocytosis	2 (4.76)	18 (6.82)	0.68	0.07–3.04	1.000

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease.
[a] Data presented as n (%).
[b] In the last 3 months.

analysis. The outcome among patients stratified according to vancomycin institution among penicillin-resistant versus penicillin-susceptible isolates is shown in Table 5. In this analysis, among patients infected with PenRP, two out of nine (22%) died when vancomycin was instituted, while eight out of 29 (27.6) died among those who did not receive early vancomycin. On the other hand, the prognosis of PenSP meningitis was worse when empirical treatment included vancomycin (n = 17 (23.8%) vs. n = 17 (8.3%); p = 0.007).

The risk analysis for the development of penicillin resistance is presented in Table 6. Briefly, the absence of a comorbid disease was found to be protective against being infected by a PenRP, whereas having an ultimately fatal comorbid disease significantly increased the risk.

4. Discussion

This was a nationwide study, and the power of this study lies in its multicenter nature and high volume of data collection. The weaknesses of this study include its retrospective design and the fact that the infecting oxacillin-resistant strains were not further tested for MIC values in 7% of the patients. However, due to its fatal nature, data were recorded precisely for pneumococcal meningitis patients in these Turkish hospitals. Basically, we found several parameters to be directly related to mortality in patients with pneumococcal meningitis. Patients of advanced age (over 50 years) and those with a critical status, including ICU admission or a poor GCS score, were more likely to die. On the other hand, patients with meningitis due to susceptible pneumococci more significantly

Table 3
Comparison of biochemical parameters for patients with pneumococcal meningitis who died and those who survived (continuous variables)

	Died		Survived		p-Value
	Mean	(SD)	Mean	(SD)	
WBC, $\times 10^9$/l	18.1814	(8.4599)	18.5084	(8.884)	0.824
Platelet count, $\times 10^9$/l	200.2286	(11.3273)	244.0223	(98.7814)	0.009
CSF leukocyte count, $\times 10^6$/l	4.1825	(5.215)	4.014	(4.911)	0.849
CSF protein (mg/dl)	433.7	(250.30)	322.3	(253.5)	0.013
CSF glucose (mg/dl)	14.68	(36.15)	25.23	(26.91)	0.029
Blood glucose (mg/dl)	164.7	(81.93)	148.6	(66.07)	0.168
CSF/serum glucose	0.08	(0.11)	0.18	(0.17)	<0.001

SD, standard deviation; WBC, white blood cell count; CSF, cerebrospinal fluid.

Table 4
Independent risk factors for death in pneumococcal meningitis (multivariate logistic regression analysis)

	Adjusted OR	95% CI
Male gender	0.480	0.221–1.041
Empirical vancomycin use	2.159	0.949–4.912
Meningitis due to penicillin-susceptible pneumococcus	0.441	0.195–0.996
Age >50 years	3.908	1.820–8.390
Critical case[a]	7.089	3.230–15.557
Constant	0.0711	0.024–0.206

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; GCS, Glasgow coma scale.
[a] Defined as a case admitted to the ICU or a non-ICU case with a poor GCS score (≤8).

survived. Finally, the use of empirical vancomycin did not contribute statistically to improving mortality rates. In fact, patients with a critical status[3,15] and of an advanced age[3,16] have been known to die more frequently. However, the antibiotic resistance issues and empirical antibiotic regimens are known to impose real challenges on the treating clinician due to their dynamic natures, and the therapeutic implications may change rapidly.

There are various risk factors for penicillin nonsusceptibility in *S. pneumoniae* isolates, previous antibiotic use being the most frequent one.[17] According to our data, the existence of ultimately fatal comorbid conditions was linked to the presence of penicillin resistance. The probable reasons for this association are either frequent use of antibiotics or repeated attendance in health care settings for these coexisting disorders. Pneumococcus maintains penicillin resistance through alterations in penicillin-binding proteins (PBPs) 1A, 2B, and 2X.[18–20] Also, beta-lactam MICs, including carbapenems, were found to rise with increases in the number of PBP 1A, 2B, and 2X alterations.[21,22] Thus, penicillin resistance appears to be an indicator of the probability of higher MICs for other beta-lactam antibiotics among *S. pneumoniae* isolates, and accordingly resistance issues appear to be the reason for the higher mortality in our study. In the study of Gouveia et al., various antibiotics were used in the treatment of pneumococcal meningitis and penicillin resistance seemed to increase mortality.[23] According to the current Infectious Diseases Society of America (IDSA) guidelines, it is recommended that vancomycin is given with ceftriaxone or cefotaxime in the empirical treatment of pneumococcal meningitis until susceptibility results are available. Subsequently, if the infecting isolate is PenSP, the use of vancomycin is unnecessary. On the other hand, if the infecting strain is penicillin- or cephalosporin-resistant, the guidelines recommend that the patient should continue with the initial antibiotic combination including vancomycin.[7] However, the use of extended-spectrum cephalosporins alone has been advocated previously in the literature due to the low resistance profiles in various parts of the world.[9] Accordingly, in a Turkish acute bacterial meningitis study, the authors commented that vancomycin should be reserved for patients with significant risk factors for the development of penicillin resistance, and not used on an empirical basis.[8] Many Turkish academics have backed the use of ceftriaxone alone over the years, due to the less than 1% ceftriaxone resistance in invasive pneumococci in the country.[24,25] Apparently, this point of view is shared by most Turkish clinicians, and 80% of the patients in our study received empirical third-generation cephalosporin alone. In our study, ceftriaxone seemed to fail more frequently in patients infected with PenRP and OxaRP. More interestingly, the use of empirical vancomycin seemed not to compensate significantly for therapeutic failure among pneumococcal meningitis patients, although vancomycin showed a trend towards improving the prognosis, since the 95% CI was very close to the statistical threshold (OR 2.159, 95% CI 0.949–4.912). Conflicting data exist in relatively small studies in the literature.

Table 5
The distribution of empirical vancomycin use with respect to penicillin susceptibility patterns of *Streptococcus pneumoniae*

Vancomycin	Penicillin-resistant[a]					Penicillin-susceptible[b]				
	Died		Survived		Total	Died		Survived		Total
Yes	2	(22.2%)	7	(77.8%)	9	10	(23.8%)	32	(76.2%)	42
No	8	(27.6%)	21	(72.4%)	29	17	(8.3%)	187	(91.7%)	204
Total	10	(26.3%)	28	(73.7%)	38	27	(11.0%)	219	(89.0%)	246

[a] Fisher's exact test $p = 1.000$.
[b] Pearson Chi-square test = 8.5376, $p = 0.003$.

Table 6
Risk factors for the development of penicillin resistance among pneumococci

Exposure	PenR ($n = 38$)		PenS ($n = 246$)		OR	95% CI	p-Value
	n	%	n	%			
Gender	26	(68.42)	174	(70.73)	0.90	0.41–2.06	0.771
Age >50 years	15	(39.47)	97	(39.43)	1.00	0.46–2.12	0.996
Underlying disease[a]							
No underlying disease	20	(52.63)	182	(73.98)	0.39	0.18–0.84	0.007
Non-fatal disease	11	(28.95)	46	(18.70)	1.77	0.74–4.01	0.142
Ultimately fatal disease	7	(18.42)	18	(7.32)	2.86	0.93–7.88	0.025
Diabetes	5	(13.16)	29	(11.79)	1.13	0.32–3.26	0.809
Head trauma	10	(26.32)	83	(33.74)	0.70	0.29–1.58	0.364
Trauma	7	(18.42)	62	(25.20)	0.67	0.24–1.66	0.364
Neurosurgery	5	(13.16)	28	(11.38)	1.18	0.33–3.40	0.751
Splenectomy	2	(5.26)	7	(2.85)	1.90	0.18–10.47	0.428
COPD	2	(5.26)	10	(4.07)	1.31	0.13–6.52	0.733
Antibiotic exposure[b]	4	(10.53)	41	(16.67)	0.59	0.14–1.79	0.335
Hospitalization[b]	2	(5.26)	23	(9.35)	0.54	0.06–2.34	0.408

PenR, penicillin-resistant pneumococcus; PenS, penicillin-susceptible pneumococcus; OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.
[a] According to the McCabe and Jackson classification.
[b] During the 3 months prior to the onset of meningitis.

For example, in a Korean study, in-hospital mortality did not differ significantly in pneumococcal meningitis when the infecting agents were either resistant or susceptible to cefotaxime/ceftriaxone.[26] The probable reasons for the inadequacy of vancomycin as part of the combination regimen may be due to its low CSF penetration and pneumococcal vancomycin tolerance. The use of steroids is known to further contribute to reduced vancomycin penetration into the CSF.[27,28] In addition, although vancomycin-resistant *S. pneumoniae* has not been identified in the world, the emergence of vancomycin-tolerant pneumococci is a matter of great concern and is a relatively new issue that needs to be clarified on an epidemiological basis.[29,30] Consequently, the hampered efficacy of vancomycin will probably have a potential impact on the therapeutic strategies in the management of pneumococcal meningitis. On the other hand, the higher mortality in the vancomycin arm in PenSP meningitis patients in this study may highlight the possibility that a third-generation cephalosporin may not be synergistic or additive with vancomycin; this issue needs further clarification.

What are the potential strategies to overcome therapeutic failures in these particular patients? When surveillance data disclose a higher susceptibility to meropenem, this drug can be considered as a substitute for ceftriaxone. On the other hand, since linezolid penetrates the CSF satisfactorily,[31] regardless of the use of steroids, adding this antibiotic to ceftriaxone could be a good alternative to the vancomycin and ceftriaxone combination. Nonetheless, linezolid is known to have a bacteriostatic effect,[32] which may lead to unsatisfactory outcomes. Initial data for the efficacy of linezolid and ceftriaxone combination in pneumococcal meningitis have been published in the literature.[33] Several case series on the use of linezolid in Gram-positive bacterial meningitis other than pneumococci have also been reported,[34–37] as well as the superiority of linezolid to vancomycin in methicillin-resistant *Staphylococcus aureus* meningitis.[38] Moreover, resistance to linezolid in pneumococci has not been observed in Turkey[25,39,40] and is not a real problem in most parts of the world.[41] Thus, linezolid could be a potential option either alone or in combination, although this point of view must be supported by well-designed randomized clinical trials.

Adding rifampin to other antibiotics in the management of pneumococcal meningitis is another option in cases where vancomycin has the potential to fail.[7] Further studies are also needed on daptomycin and newer glycopeptides to determine their place in the management of pneumococcal meningitis.[6] There are promising animal pneumococcal meningitis studies favoring daptomycin over ceftriaxone.[42,43] However, the daptomycin penetration rate in the CSF in humans was found to be around 5–6% through an inflamed blood–brain barrier[44] and the compound was found to be rapidly bactericidal.[45] On the other hand, although daptomycin has been approved at doses of 4 and 6 mg/kg for skin infections and bacteremia, respectively, the drug has been found to be well tolerated intravenously when dosed up to 12 mg/kg for 2 weeks.[46] There are several case reports in the literature that show high-dose daptomycin to be promising as part of a combination regimen in the management of meningitis.[44,47] However, comprehensive data are still lacking on the use of this drug in central nervous system infections. Another alternative drug is moxifloxacin, which is recommended as a substitute to the vancomycin and ceftriaxone combination. In that context, moxifloxacin can be considered either alone or as part of the combination regimen, since this antibiotic has been known to be unaffected by pneumococcal penicillin resistance.[48]

In conclusion, our data show that ceftriaxone alone is not adequate in the management of PenRP meningitis compared to meningeal infections with susceptible strains. Penicillin resistance is around 20% according to our data obtained through enrolling patients treated in the last 15 years. However, penicillin nonsusceptibility is quite frequent across the world[49] and comprises more than a third of meningeal strains in Turkey today.[50,51] Thus, penicillin resistance is of serious concern to the treating clinician and this study encourages the decision to institute a combination regimen on an empirical basis rather than using third-generation cephalosporins alone in the management of pneumococcal meningitis. In addition, although a significant correlation in statistical terms could not be established in this study, vancomycin tended to improve the prognosis of pneumococcal meningitis. Hence, the data from this study do not strictly discourage the supplementation of vancomycin when the data available in the literature are considered. However, new studies investigating the efficacy of different antibiotic combinations are needed for the optimization of treatment strategies in the management of pneumococcal meningitis.

Conflict of interest: We have no competing interests to declare.

References

1. Durand ML, Calderwood SB, Weber DJ, Miller SI, Southwick FS, Caviness Jr VS, et al. Acute bacterial meningitis in adults. A review of 493 episodes. *N Engl J Med* 1993;**328**:21–8.
2. 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**:970–6.
3. 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**:1849–59.
4. Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, et al. Bacterial meningitis in the United States, 1998–2007. *N Engl J Med* 2011;**364**:2016–25.
5. Lutsar I, Ahmed A, Friedland IR, Trujillo M, Wubbel L, Olsen K, et al. Pharmacodynamics and bactericidal activity of ceftriaxone therapy in experimental cephalosporin-resistant pneumococcal meningitis. *Antimicrob Agents Chemother* 1997;**41**:2414–7.
6. Hameed N, Tunkel AR. Treatment of drug-resistant pneumococcal meningitis. *Curr Infect Dis Rep* 2010;**12**:274–81.
7. Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 2004;**39**:1267–84.
8. Celal A, Faruk GM, Salih H, Kemal CM, Serife A, Faruk KO. Characteristics of acute bacterial meningitis in Southeast Turkey. *Indian J Med Sci* 2004;**58**:327–33.
9. Rossoni AM, Dalla Costa LM, Berto DB, Farah SS, Gelain M, Brandileone MC, et al. Acute bacterial meningitis caused by *Streptococcus pneumoniae* resistant to the antimicrobian agents and their serotypes. *Arq Neuropsiquiatr* 2008;**66**:509–15.
10. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. M100-S22. Wayne, PA: CLSI; 2012.
11. European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. Version 3.1. Basel, Switzerland: EUCAST; 2013.
12. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974;**2**:81–4.
13. McCabe WR, Jackson GG. Gram-negative bacteremia, I: etiology and ecology. *Arch Intern Med* 1962;**110**:847–53.
14. Morel J, Casoetto J, Jospe R, Aubert G, Terrana R, Dumont A, et al. De-escalation as part of a global strategy of empiric antibiotherapy management. A retrospective study in a medico-surgical intensive care unit. *Crit Care* 2010;**14**:R225.
15. des Portes V. [Long-term follow-up of bacterial meningitis—sequels in children and adults: incidence, type, and assessment issues]. *Med Mal Infect* 2009;**39**:572–80.
16. Erdem H, Kilic S, Coskun O, Ersoy Y, Cagatay A, Onguru P, et al. Community-acquired acute bacterial meningitis in the elderly in Turkey. *Clin Microbiol Infect* 2010;**16**:1223–9.
17. Tsai HY, Lauderdale TL, Wang JT, Chen YS, Liu JW, Huang JH, et al. Updated antibiotic resistance and clinical spectrum of infections caused by *Streptococcus pneumoniae* in Taiwan: emphasis on risk factors for penicillin nonsusceptibilities. *J Microbiol Immunol Infect* 2013;**46**(5):345–51.
18. Barcus VA, Ghanekar K, Yeo M, Coffey TJ, Dowson CG. Genetics of high level penicillin resistance in clinical isolates of *Streptococcus pneumoniae*. *FEMS Microbiol Lett* 1995;**126**:299–303.
19. du Plessis M, Bingen E, Klugman KP. Analysis of penicillin-binding protein genes of clinical isolates of *Streptococcus pneumoniae* with reduced susceptibility to amoxicillin. *Antimicrob Agents Chemother* 2002;**46**:2349–57.
20. Karlowsky JA, Jones ME, Draghi DC, Sahm DF. Clinical isolates of *Streptococcus pneumoniae* with different susceptibilities to ceftriaxone and cefotaxime. *Antimicrob Agents Chemother* 2003;**47**:3155–60.
21. Davies TA, Shang W, Bush K, Flamm RK. Activity of doripenem and comparator beta-lactams against US clinical isolates *of Streptococcus pneumoniae* with

defined mutations in the penicillin-binding domains of pbp1a, pbp2b and pbp2x. *J Antimicrob Chemother* 2008;**61**:751–3.
22. Aslan G, Tezcan S, Delialioglu N, Aydin FE, Kuyucu N, Emekdas G. Evaluation of penicillin-binding protein genotypes in penicillin susceptible and resistant *Streptococcus pneumoniae* isolates. *Mikrobiyol Bul* 2012;**46**:190–201.
23. Gouveia EL, Reis JN, Flannery B, Cordeiro SM, Lima JB, Pinheiro RM, et al. Clinical outcome of pneumococcal meningitis during the emergence of penicillin-resistant *Streptococcus pneumoniae*: an observational study. *BMC Infect Dis* 2011;**11**:323.
24. Erdem H. An update on invasive pneumococcal antibiotic resistance in Turkey, 2008. *J Chemother* 2008;**20**:697–701.
25. Erdem H, Pahsa A. Antibiotic resistance in pathogenic *Streptococcus pneumoniae* isolates in Turkey. *J Chemother* 2005;**17**:25–30.
26. Choi SH, Chung JW, Kim BN, Kwak YG, Kim TH, Lee EJ, et al. Clinical implication of extended-spectrum cephalosporin nonsusceptibility in *Streptococcus pneumoniae* meningitis. *Eur J Clin Microbiol Infect Dis* 2012;**31**:3029–34.
27. Viladrich PF, Gudiol F, Linares J, Pallares R, Sabate I, Rufi G, et al. Evaluation of vancomycin for therapy of adult pneumococcal meningitis. *Antimicrob Agents Chemother* 1991;**35**:2467–72.
28. Ahmed A, Jafri H, Lutsar I, McCoig CC, Trujillo M, Wubbel L, et al. Pharmacodynamics of vancomycin for the treatment of experimental penicillin- and cephalosporin-resistant pneumococcal meningitis. *Antimicrob Agents Chemother* 1999;**43**:876–81.
29. Moscoso M, Domenech M, Garcia E. Vancomycin tolerance in clinical and laboratory *Streptococcus pneumoniae* isolates depends on reduced enzyme activity of the major LytA autolysin or cooperation between CiaH histidine kinase and capsular polysaccharide. *Mol Microbiol* 2010 [Epub ahead of print].
30. Hidalgo M, Castaneda E, Arias CA. Tolerance to vancomycin in a multiresistant, Colombian isolate of Streptococcus pneumoniae. *J Antimicrob Chemother* 2003;**52**:300–2.
31. Tsuji Y, Hiraki Y, Matsumoto K, Mizoguchi A, Sadoh S, Kobayashi T, et al. Pharmacokinetics and protein binding of linezolid in cerebrospinal fluid and serum in a case of post-neurosurgical bacterial meningitis. *Scand J Infect Dis* 2011;**43**:982–5.
32. MacGowan AP. Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections. *J Antimicrob Chemother* 2003;**51**(Suppl 2):ii17–25.
33. Faella F, Pagliano P, Fusco U, Attanasio V, Conte M. Combined treatment with ceftriaxone and linezolid of pneumococcal meningitis: a case series including penicillin-resistant strains. *Clin Microbiol Infect* 2006;**12**:391–4.
34. Sipahi OR, Bardak S, Turhan T, Arda B, Pullukcu H, Ruksen M, et al. Linezolid in the treatment of methicillin-resistant staphylococcal post-neurosurgical meningitis: a series of 17 cases. *Scand J Infect Dis* 2011;**43**:757–64.
35. Sabbatani S, Manfredi R, Frank G, Chiodo F. Linezolid in the treatment of severe central nervous system infections resistant to recommended antimicrobial compounds. *Infez Med* 2005;**13**:112–9.
36. Steinmetz MP, Vogelbaum MA, De Georgia MA, Andrefsky JC, Isada C. Successful treatment of vancomycin-resistant Enterococcus meningitis with linezolid: case report and review of the literature. *Crit Care Med* 2001;**29**:2383–5.
37. Zeana C, Kubin CJ, Della-Latta P, Hammer SM. Vancomycin-resistant *Enterococcus faecium* meningitis successfully managed with linezolid: case report and review of the literature. *Clin Infect Dis* 2001;**33**:477–82.
38. Sipahi OR, Bardak-Ozcem S, Turhan T, Arda B, Ruksen M, Pullukcu H, et al. Vancomycin versus linezolid in the treatment of methicillin-resistant Staphylococcus aureus meningitis. *Surg Infect (Larchmt)* 2013;**14**(4):357–62.
39. Telli M, Eyigor M, Gultekin B, Aydin N. Evaluation of resistance mechanisms and serotype and genotype distributions of macrolide-resistant strains in clinical isolates of *Streptococcus pneumoniae* [corrected] in Aydin, Turkey. *J Infect Chemother* 2011;**17**:658–64.
40. Gonullu N, Catal F, Kucukbasmaci O, Ozdemir S, Torun MM, Berkiten R. Comparison of in vitro activities of tigecycline with other antimicrobial agents against *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* in two university hospitals in Istanbul, Turkey. *Chemotherapy* 2009;**55**:161–7.
41. Brandon M, Dowzicky MJ. Antimicrobial susceptibility among Gram-positive organisms collected from pediatric patients globally between 2004 and 2011: results from the Tigecycline Evaluation and Surveillance Trial. *J Clin Microbiol* 2013;**51**(7):2371–8.
42. Barichello T, Goncalves JC, Generoso JS, Milioli GL, Silvestre C, Costa CS, et al. Attenuation of cognitive impairment by the nonbacteriolytic antibiotic daptomycin in Wistar rats submitted to pneumococcal meningitis. *BMC Neurosci* 2013;**14**:42.
43. Grandgirard D, Burri M, Agyeman P, Leib SL. Adjunctive daptomycin attenuates brain damage and hearing loss more efficiently than rifampin in infant rat pneumococcal meningitis. *Antimicrob Agents Chemother* 2012;**56**:4289–95.
44. Vena A, Falcone M, Comandini E, Meledandri M, Novelli A, Campanile F, et al. Daptomycin plus trimethoprim/sulfamethoxazole combination therapy in post-neurosurgical meningitis caused by linezolid-resistant *Staphylococcus epidermidis*. *Diagn Microbiol Infect Dis* 2013;**76**:99–102.
45. Cottagnoud P, Pfister M, Acosta F, Cottagnoud M, Flatz L, Kuhn F, et al. Daptomycin is highly efficacious against penicillin-resistant and penicillin- and quinolone-resistant pneumococci in experimental meningitis. *Antimicrob Agents Chemother* 2004;**48**:3928–33.
46. Benvenuto M, Benziger DP, Yankelev S, Vigliani G. Pharmacokinetics and tolerability of daptomycin at doses up to 12 milligrams per kilogram of body weight once daily in healthy volunteers. *Antimicrob Agents Chemother* 2006;**50**:3245–9.
47. Taglietti F, Campanile F, Capone A, Di Caro A, Grilli E, Stazi G, et al. Daptomycin efficacy in the central nervous system of a patient with disseminated methicillin-resistant *Staphylococcus aureus* infection: a case report. *J Med Case Rep* 2012;**6**:264.
48. Soriano F, Cafini F, Aguilar L, Tarrago D, Alou L, Gimenez MJ, et al. Breakthrough in penicillin resistance? *Streptococcus pneumoniae* isolates with penicillin/cefotaxime MICs of 16 mg/l and their genotypic and geographical relatedness. *J Antimicrob Chemother* 2008;**62**:1234–40.
49. Imohl M, Reinert RR, van der Linden M. Serotype-specific penicillin resistance of Streptococcus pneumoniae in Germany from 1992 to 2008. *Int J Med Microbiol* 2010;**300**:324–30.
50. Erdem H, Akova M. Leading infectious diseases problems in Turkey. *Clin Microbiol Infect* 2012;**18**:1056–67.
51. Dogan O, Gulmez D, Hascelik G. Effect of new breakpoints proposed by Clinical and Laboratory Standards Institute in 2008 for evaluating penicillin resistance of *Streptococcus pneumoniae* in a Turkish University Hospital. *Microb Drug Resist* 2010;**16**:39–41.