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BRIEF REPORT

Managing penicillin resistant pneumococcal meningitis: an international id-iri study

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Abstract

Penicillin-resistant pneumococcal meningitis (PRPM) is a challenging and fatal infection. We conducted a multicentre international retrospective study to evaluate the clinical features, outcomes, predictors of outcomes antimicrobial efficacy and drug susceptibility in patients with PRPM. The study, conducted through the "Infectious Diseases–International Research Initiative" across 33 centers in 11 countries, analyzed PRPM patients treated between 2019 and 2024 using univariate and multivariate analyses. A total of 138 patients were included. Of these, 83 (60.1%) were fully cured, 27 (19.6%) died, and 28 (20.3%) survived with sequelae. Mortality was associated with ICU admission (OR 14.886; $p=0.021$), mechanical ventilation (OR 7.205; $p=0.049$), and vasopressor use (OR 8.983; $p=0.025$). Higher CSF leukocyte count (OR 0.854; $p=0.060$) and blood leukocyte count (OR 0.283; $p=0.021$) were linked to lower mortality risk. Patients who developed sequelae were more likely to require mechanical ventilation (OR 9.354; $p=0.001$), experience recurrent meningitis (OR 5.562; $p=0.081$), and have lower platelet counts (OR 0.001; $p=0.050$), compared to those who fully recovered. Sequelae patients had higher GCS scores (OR 1.365; $p=0.014$), more corticosteroid use (OR 5.301; $p=0.061$), and less vasopressor use (OR 0.205; $p=0.019$) compared to those who died. The antibiotic susceptibility profiles of the isolates in our PRSP cohort were: Ceftriaxone (75/134, 55.9%), meropenem (26/44, 59%), moxifloxacin (47/48, 97.9%). PRPM is a fatal disease in which mortality and sequelae occurring in two-fifths of cases. Severe illness markers such as ICU admission, mechanical ventilation, and vasopressor use, along with recurrent meningitis are linked to worse outcomes. Thrombocytopenia, low leukocyte counts, and lower GCS scores are indicators of poor prognosis, while corticosteroid therapy appears protective in PRPM. Therapeutic optimization is challenged by rising resistance and pharmacokinetic limitations, though moxifloxacin shows the highest susceptibility; further research is warranted.

Keywords Streptococcus pneumoniae · Pneumococci · Penicillin · Resistant · Meningitis

Introduction

Pneumococcal meningitis is a life-threatening medical emergency requiring prompt action to identify the cause and initiate appropriate treatment [1, 2]. The infection is the most common form of bacterial central nervous system infections [3]. If left untreated, the disease is fatal, and even with culture guided therapy, it remains linked to substantial morbidity, neurological complications in particular, and mortality [1, 2, 4]. In addition, penicillin resistance is known to compromise the effectiveness of

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third-generation cephalosporins, which serve as the cornerstone of treatment for pneumococcal meningitis [4] and is associated with prolonged hospital stays and increased healthcare costs.

Given the rarity of the disease, the literature on penicillin-resistant pneumococcal meningitis (PRPM) is scarce. We conducted a multi-center, international retrospective study to identify the clinical features, outcomes such as mortality, neurological sequelae, the microbiological characteristics and the predictors of clinical outcomes in patients with PRPM.

Methods

Setting The study was performed through "Infectious Diseases – International Research Initiative" platform and involved 33 centers, which provided data across 11 countries (Türkiye, Romania, Poland, Slovak Republic, Serbia, North Macedonia, Nigeria, Kazakhstan, Egypt, Bulgaria, Afghanistan).

Design This is a multicenter retrospective observational study, which included patients hospitalized with PRPM between January 1, 2019 and October 15, 2024.

Data collection The data were retrospectively collected online between October 16 and December 1, 2024, using a web-based case report form. This form recorded demographic, clinical, and laboratory information, comorbid conditions, antimicrobial susceptibility profiles, treatment details, and in-hospital mortality outcomes.

Inclusion criteria This study included patients aged 15 years or older diagnosed with pneumococcal meningitis [1], provided that the infecting pneumococcus had a penicillin minimum inhibitory concentration (MIC) of at least 0.12 mcg/mL. Additionally, only cases with available MIC data for third-generation cephalosporins, such as ceftriaxone or cefotaxime, were eligible. Patients with a history of recurrent meningitis were included only once in our study.

Outcome Death, sequelae formation, and survival were the outcome parameters.

Therapeutic efficacy Empirical treatments were classified as appropriate or inappropriate based on the final AST results.

MIC testing Broth microdilution, automated systems, gradient testing (E-test) were used for the detection of MIC values.

Definitions Recurrent meningitis: Recurrent meningitis is defined by at least two episodes of meningitis associated with CSF pleocytosis with the absence of symptoms between the episodes [5].

Dutch meningitis score It is a clinical prediction model based on six parameters, developed to assess the likelihood of poor outcomes in adults with community-acquired bacterial meningitis [6].

HAMSI score It is a clinical scoring system developed to predict unfavorable outcomes in adults with tuberculous meningitis [7].

Paresis Partial or incomplete loss of voluntary muscle movement or strength [8].

Statistical analysis

Descriptive statistics of numerical and categorical variables were given in tables as mean, standard deviation (SD), quartiles (25th, median, 75th), number and percent frequencies. The normality assumption of the numerical variables was checked with Shapiro-Wilk test and it was determined that they haven't normal distribution. Simple relationships between clinical outcome and risk factors were examined with univariate tests (Pearson chi-square and Mann-Whitney U test). After this step, Stepwise Binary Multinomial Logistic Regression model was used to examine the adjusted effects of risk factors on mortality. In univariate tests, $P<0.05$ was accepted as the statistical significance level. In the multiple model, the statistical significance level was set at $P<0.20$ to account for both clinical and statistical significance together [9]. The success of the model in mortality prediction was compared with ROC curve and goodness of fit measures (AIC, R-square). Statistical analysis was done by SPSS (ver. 29).

RESULTS

Data from 153 patients were submitted by the participating centers. However, 15 cases were excluded from the study due to ineligibility or missing data, leaving a total of 138 patients included in the analysis. The mean age of the patients was 55.2±17.1 years (median 58) and 56 (40.6%) patients were females. Of these, 83 (60.1%) were cured, 27 died (19.6%), and 28 (20.3%) were cured with sequelae. The average hospital stay for cured patients was 19.2±8.6 days, for those who died it was 13.5±13.4 days, and for those cured with sequelae it was 27.1±17.3 days.

Clinical findings: The distribution of findings at presentation was as follows: Headache ($n=120$, %86), altered mental status ($n=119$, %86), neck stiffness ($n=106$, %76),

Kerning's sign ($n=74$, %53), Brudzinski sign positivity ($n=74$, %53), convulsions ($n=44$, %31), paresis ($n=28$, 20%) skin rashes ($n=13$, %9), cranial nerve palsy ($n=9$, %6).

Inflammatory markers: The median values of inflammatory markers were as follows: CRP at 27.6 mg/dL (IQR 13.85-116.75), procalcitonin at 4 mg/dL (IQR 1.05–11.9), and erythrocyte sedimentation rate at 55 mm/h (IQR 37–76).

Microbiological data: The infecting pneumococcus was identified in the CSF in 107 cases (91.3%) and in the blood in 31 cases (22.5%), with concordant positivity in 19 cases (13%). The distribution of antibiotic susceptibility profiles is as follows: Benzylpenicillin [0/121 (susceptible/tested), 0%; MIC_{50} 1 µg/ml, MIC_{90} 6 µg/ml], ceftriaxone (75/134, 55.9%; MIC_{50} 0.5 µg/ml, MIC_{90} 2 µg/ml), cefotaxime (18/28, 64.2%; MIC_{50} 0.5 µg/ml, MIC_{90} 1 µg/ml), meropenem (26/44, 59%; MIC_{50} 0.19 µg/ml, MIC_{90} 6 µg/ml), levofloxacin (49/51, 96%; MIC_{50} 0.5 µg/ml, MIC_{90} 1 µg/ml), moxifloxacin (47/48, 97.9%; MIC_{50} 0.12 µg/ml, MIC_{90} 0.25 µg/ml), vancomycin (68/68, 100%; MIC_{50} 0.5 µg/ml, MIC_{90} 1 µg/ml), erythromycin (16/50, 32%; MIC_{50} 4 µg/ml, MIC_{90} 8 µg/ml), doxycycline (10/23, 43.4%; MIC_{50} 8 µg/ml, MIC_{90} 32 µg/ml), linezolid (16/16, 100%; MIC_{50} 1 µg/ml, MIC_{90} 2 µg/ml), and rifampicin (3/5, 60%; MIC_{50} 0,125 µg/ml, MIC_{90} 0.25 µg/ml).

Comorbid conditions Comorbidities were identified in 89 patients (64.5%). The most common conditions included coronary artery disease ($n=29$, 21%), diabetes mellitus ($n=26$, 18.8%), and trauma ($n=23$, 16.7%). Other comorbidities observed were chronic obstructive pulmonary disease ($n=19$, 13.8%), malignancy ($n=18$, 13%), cerebrovascular disease ($n=14$, 10.1%), immunosuppression ($n=13$, 9.4%), congestive heart failure ($n=12$, 8.7%), chronic renal failure ($n=12$, 8.7%), collagen tissue disorders ($n=8$, 5.8%), chronic liver disease ($n=7$, 5.1%), splenectomy ($n=6$, 4.3%), neurological disease ($n=5$, 3.6%), burns ($n=4$, 2.9%), and HIV infection ($n=3$, 2.2%).

Coexisting infections 140 coexisting infections were identified in 100 patients (72.5%). Among these cases, pneumonia was observed in 29 (21%), acute otitis media in 29 (21%), acute sinusitis in 27 (19.6%), chronic sinusitis in 23 (16.6%), mastoiditis in 19 (13.7%), and chronic otitis media in 13 (9.4%).

Therapeutic Modalities

a) **Empirical treatment**: Ceftriaxone was administered to 93 patients (67.4%), meropenem to 36 patients (26.1%), and cefotaxime to 5 patients (3.6%). Moxifloxacin and penicillin were each given to 1 patient (0.8%). Vancomycin was included in the therapy of 115 patients (83.3%), ampicillin in 25 patients (18.1%), and linezolid in 3 patients (2.2%). Additionally, rifampicin, trimethoprim-sulfamethoxazole, and chloramphenicol were each administered to 1 patient (0.8%) as part of combination regimens.

b) **Therapeutic adjustment**: Empirical treatment was deemed appropriate in 132 patients (95.7%) and irrational in 6 patients (4.3%). Among the 6 patients who received irrational treatment, no adjustments were made for 2 patients due to delayed AST data and clinical improvement. For the remaining 4 patients, vancomycin was added to their therapy following the availability of microbiological data. Evaluating the efficacy of beta-lactams, 65 (47.1%) patients received appropriate empirical beta-lactam therapy, while 55 (39.8%) received inappropriate beta-lactams, with 51 of these cases receiving vancomycin as part of combination therapy. Additionally, 17 (12.3%) patients were treated with meropenem-based combinations despite the absence of meropenem MIC data, with vancomycin supplementation. One patient did not receive a beta-lactam but was treated with a combination of moxifloxacin and vancomycin. Overall, the antimicrobial regimen was deescalated in 25 (18.1%) and escalated in 15 (10.9%) patients.

Sequelae formation: Sequelae were identified in 28 (16.7%) patients upon discharge from the hospital. The distribution of these sequelae is as follows: Paresis ($n=8$, 5.8%), hearing loss ($n=5$, 3.6%), cognitive impairment ($n=3$, 2.2%), palliative care dependent ($n=2$, 1.4%), facial nerve palsy ($n=2$, 1.4%), dysarthria ($n=2$, 1.4%), hydrocephalus ($n=2$, 1.4%).

Results of Univariate Analyses

Descriptive statistics for the numerical characteristics of the patients according to their clinical outcomes are presented in Table 1. The differences found to be significant at the $P<0.05$ level in the univariate analyses revealed that means of Glasgow Coma Score (GCS) ($p=0.004$), CSF leukocyte count ($p=0.050$), and blood leukocyte count ($p=0.049$) were significantly lower in patients who died compared to the other two groups. In contrast, the average platelet count was significantly higher in cured patients compared to the other two groups ($p=0.008$). Besides, the Dutch Meningitis Score ($p=0.67$) was higher among fatal cases, while the duration of antimicrobial treatment in days ($p=0.160$) and the dosage of corticosteroid treatment ($p=0.081$) were significantly lower in the same group when the p value below 0.20 considered for multiple model.

The distribution of patients' categorical characteristics according to clinical outcomes is presented in Table 1. Significant associations ($P<0.05$) were found between poor clinical outcomes and ICU admission ($p=0.001$), mechanical ventilation ($p=0.001$), vasopressor use ($p=0.001$), chronic liver disease ($p=0.036$), and meropenem use ($p=0.037$). Additionally, pregnancy ($p=0.107$), HIV infection ($p=0.107$), empirical beta-lactam use where AST data is not available ($p=0.100$), and recurrent meningitis ($p=0.185$) were considered noteworthy for poor outcomes while use of ceftriaxone/cefotaxime ($p=0.174$), corticosteroid treatment ($p=0.060$), antibiotic deescalation ($p=0.076$) prevented poor outcome when a p-value threshold of 0.20 was used for inclusion in the multiple-model.

Results of Binary Multinomial Logistic Regression

Risk factor candidates with a P-value < 0.20 in Table2 and Table 1 were re-evaluated in a multiple model to assess their adjusted effects together.

a) **Died versus fully cured**: The risk factors that significantly distinguished the "died" and "cured" outcomes—meaning those that provided a meaningful difference between the two groups—are presented in the upper section of Table 3. When the patients who died due to PRPM were compared with those who survived, the following factors were identified as predictors of poor outcomes: ICU admission (OR 14.886; 90% CI 2.167-102.256, $p=0.021$), Recurrent meningitis (OR 11.840; 90% CI 1.008-139.128, $p=0.099$), mechanical ventilation (OR 7.205; 90% CI 1.382–37.554, $p=0.049$), and vasopressor use (OR 8.983; 90% CI 1.804–44.743, $p=0.025$) were all associated with higher odds of mortality. Additionally, an increase of 1,000 in CSF leukocyte count was linked to lower odds of death (OR 0.854; 90% CI 0.744–0.980, $p=0.060$), as was an increase of 10,000 in blood leukocyte count (OR 0.283; 90% CI 0.115–0.695, $p=0.021$).
b) **Cured patients with sequelae vs. fully cured patients**: Risk factors that significantly distinguished the "Cured with Sequelae" and "Cured" groups are presented in the middle section of Table 3. The factors that were significantly associated with the development of neurological sequelae include mechanical ventilation (OR 9.354; 90% CI 3.566–24.539, $p=0.001$), recurrent meningitis (OR 5.562; 90% CI 1.103–28.015, $p=0.081$), and platelet count (/mm^3) (OR 0.001; 90% CI 0.000-0.345, $p=0.050$ for each 1,000,000 increase).
c) **Patients cured with sequelae vs. died patients**: Risk factors that significantly distinguished the "Cured with Sequelae" and "Died" groups are presented in the lower section of Table 3. Glasgow coma score (OR 1.365; 90% CI 1.108–1.683, $p=0.014$ for each 1-point increase), receiving corticosteroids (OR 5.301; 90% CI 1.227–22.902, $p=0.061$), and vasopressor use (OR 0.205; 90% CI 0.068–0.625, $p=0.019$) were found to be significant risk factors in distinguishing patients with sequelae from those who died. A schematic summary of the binary multinomial logistic regression results is provided in Table 4.

DISCUSSION

PM is serious and potentially fatal disease that can lead to significant morbidity in the survivors [4]. In our study on PRSP meningitis, the median patient age was 58 years, representing a middle-aged adult population, with females accounting for 40% of the cases. Penicillin resistance is a significant risk factor for mortality in PM [4, 10], and the treatment is often complicated because of the relatively poor blood-brain barrier penetration of effective antimicrobials. Accordingly, the likelihood of neurological complications or relapse remains high, even with successful treatment [3, 11, 12]. Among adults, several factors have been associated with increased mortality, including advancing age [4, 13], ICU admissionparticularly when delayed [4, 14], mechanical ventilation [10], respiratory alkalosis [10], low GCS scores [4, 13], intracranial complications such as ischemic lesions, diffuse cerebral edema, and ventriculitis [15], low CSF glucose level [13], high CSF bacterial loads [16], concurrent pneumonia [13], thrombocytopenia [10], and overlapping systemic infections like COVID-19 [17]. In this study, we observed that one-fifth of the patients died of the disease, while another one-fifth developed sequelae. We found that a history of prior meningitis episodes and the critical status of PM patients, characterized by ICU admission, mechanical ventilation, and vasopressor use, significantly increased mortality when comparing patients who died of PM with those who fully recovered. In contrast, higher leukocyte counts in cerebrospinal fluid (CSF) (per 1,000-cell increase) and blood (per 10,000-cell increase) were associated with reduced mortality. Furthermore, when comparing patients who fully recovered to those who recovered with sequelae, factors such as mechanical ventilation, decreased platelet counts (per 1,000,000 decrease), and recurrent meningitis episodes were found to increase the likelihood of sequelae development. Lastly, when comparing patients who recovered with sequelae to those who died, each 1-point increase in the GCS was associated with a decreased risk of mortality. Corticosteroid use was linked to a reduction in mortality, favoring sequelae formation, while vasopressor use was predictive of mortality.

Table 1 Descriptive values of categorical features according to the clinical outcome

		Cured		Died		Cured with sq		*P*
		n	%	*n*	%	*n*	%	
Gender	Male	52	63.4	14	17.1	16	19.5	0.588
	Female	31	55.4	13	23.2	12	21.4	
Concurrent infection	No	24	63.2	8	21.1	6	15.8	0.718
	Yes	59	59.0	19	19.0	22	22.0	
ICU	No	47	81.0	2	3.4	9	15.5	0.001
	Yes	36	45.0	25	31.3	19	23.8	
Mechanical ventilation	No	76	76.8	7	7.1	16	16.2	0.001
	Yes	7	17.9	20	51.3	12	30.8	
Vasopressor use	No	75	75.0	6	6.0	19	19.0	0.001
	Yes	8	21.1	21	55.3	9	23.7	
Diabetes	No	69	61.6	20	17.9	23	20.5	0.573
	Yes	14	53.8	7	26.9	5	19.2	
Chronic renal failure	No	75	59.5	24	19.0	27	21.4	0.544
	Yes	8	66.7	3	25.0	1	8.3	
COPD	No	73	61.3	24	20.2	22	18.5	0.417
	Yes	10	52.6	3	15.8	6	31.6	
Pregnancy	No	82	60.7	25	18.5	28	20.7	0.107
	Yes	1	33.3	2	66.7	0	0.0	
Collagen tissue disorder	No	79	60.8	25	19.2	26	20.0	0.833
	Yes	4	50.0	2	25.0	2	25.0	
Malignancy	No	71	59.2	22	18.3	27	22.5	0.215
	Yes	12	66.7	5	27.8	1	5.6	
Splenectomy	No	81	61.4	25	18.9	26	19.7	0.390
	Yes	2	33.3	2	33.3	2	33.3	
Coronary artery disease	No	65	59.6	22	20.2	22	20.2	0.939
	Yes	18	62.1	5	17.2	6	20.7	
Burn	No	81	60.4	25	18.7	28	20.9	0.240
	Yes	2	50.0	2	50.0	0	0.0	
HIV infection	No	82	60.7	25	18.5	28	20.7	0.107
	Yes	1	33.3	2	66.7	0	0.0	
Congestive heart failure	No	75	59.5	26	20.6	25	19.8	0.582
	Yes	8	66.7	1	8.3	3	25.0	
Trauma	No	71	61.7	22	19.1	22	19.1	0.665
	Yes	12	52.2	5	21.7	6	26.1	
Cerebrovascular disease	No	77	62.1	22	17.7	25	20.2	0.239
	Yes	6	42.9	5	35.7	3	21.4	
Neurological disease	No	79	59.4	26	19.5	28	21.1	0.498
	Yes	4	80.0	1	20.0	0	0.0	
Rheumatological disease	No	83	60.1	27	19.6	28	20.3	---
Immunosuppression	No	73	58.4	25	20.0	27	21.6	0.382
	Yes	10	76.9	2	15.4	1	7.7	
Chronic liver disease	No	81	61.8	23	17.6	27	20.6	**0.036**
	Yes	2	28.6	4	57.1	1	14.3	
Ceftriaxone/Cefotaxime	not administered	25	58.1	12	27.9	6	14.0	0.174
	administered	58	61.1	15	15.8	22	23.2	
Meropenem	not administered	65	63.1	15	14.6	23	22.3	**0.037**
	administered	18	51.4	12	34.3	5	14.3	
Linezolid	not administered	81	60.0	27	20.0	27	20.0	0.644
	administered	2	66.7	0	0.0	1	33.3	
Rifampicin	not administered	82	59.9	27	19.7	28	20.4	0.716
	administered	1	100.0	0	0.0	0	0.0	
TMP-SMX	not administered	82	59.9	27	19.7	28	20.4	0.716
	administered	1	100.0	0	0.0	0	0.0	

Table 1 (continued)

		Cured		Died		Cured with sq		*P*
		n	%	*n*	%	*n*	%	
Moxifloxacin	not administered	82	60.3	27	19.9	27	19.9	0.518
	administered	1	50.0	0	0.0	1	50.0	
Ampicillin	not administered	65	58.0	24	21.4	23	20.5	0.469
	administered	18	69.2	3	11.5	5	19.2	
Chloramphenicol	not administered	79	59.8	27	20.5	26	19.7	0.407
	administered	4	66.7	0	0.0	2	33.3	
Vancomycin	not administered	12	60.0	2	10.0	6	30.0	0.336
	administered	71	60.2	25	21.2	22	18.6	
Corticosteroid treatment	No	13	52.0	9	36.0	3	12.0	0.060
	Yes	70	61.9	18	15.9	25	22.1	
Empirical BL	Rational	43	66.2	7	10.8	15	23.1	0.100
	Irrational	33	60.0	13	23.6	9	16.4	
	Unknown, if rational	6	35.3	7	41.2	4	23.5	
	BL, not received	1	100.0	0	0.0	0	0.0	
Therapeutic efficacy	Rational empirical Tx	79	59.8	26	19.7	27	20.5	0.946
	Irrational empirical tx	4	66.7	1	16.7	1	16.7	
ESC/DESC	ESC	8	53.3	3	20.0	4	26.7	0.076
	DE	20	80.0	0	0.0	5	20.0	
	None	55	56.1	24	24.5	19	19.4	
Recurrent meningitis	No	81	61.8	25	19.1	25	19.1	0.185
	Yes	2	28.6	2	28.6	3	42.9	
Penetrating skull trauma. cranial fracture and surgery	No	69	60.5	22	19.3	23	20.2	0.978
	Yes	14	58.3	5	20.8	5	20.8	

GCS: Glasgow coma score, Sq: Sequelae, Tx: Treatment

Antimicrobial therapy for PM presents significant challenges, particularly due to the emergence of antibiotic resistance, which complicates treatment options [18]. In our study, three-fourths of the patients had concurrent respiratory infections, a prevalence higher than that seen in the entire PM cohort, including both penicillin-susceptible and resistant isolates [19]. Added to that, some of these coexistent infections were chronic, suggesting frequent antibiotic exposure and an increased risk of developing multidrug resistance [20]. Consequently, the high resistance rates observed in our PRSP cohort, including ceftriaxone (44.1%), cefotaxime (35.8%), and meropenem (41%), may have further limited the efficacy of extended-spectrum beta-lactam antibiotics. Particularly, over 40% of the patients in this study were unable to receive appropriate beta-lactam therapy and instead received vancomycin as part of combination therapy. Vancomycin is effective in vitro, but it may exhibit limited penetration across the blood-brain barrier [21]. On the other hand, although there were concerns about using meropenem for penicillin or cephalosporin-resistant strains, fluoroquinolones—particularly moxifloxacin, which showed susceptibility in 98% of isolates in our study—seem to be a viable alternative for patients who do not respond to standard therapy [22].

Effective antimicrobial treatment in bacterial meningitis must possess specific characteristics to ensure adequate CSF penetration and therapeutic efficacy. Ideally, these agents should be small in molecular size, moderately lipophilic, and exhibit low plasma protein binding, allowing better passage through the blood-brain barrier [23]. In reality, the blood-brain barrier limits the penetration of many antibiotics, making treatment difficult for drugs like daptomycin, quinupristin/dalfopristin, and vancomycin [24, 25]. However, the available literature discloses that daptomycin can be a promising candidate for PRSP meningitis with minimal adverse effects [26]. Additionally, although the bacteriostatic nature of linezolid may reduce its effectiveness in meningitis, it maintains a CSF/serum ratio around 70% [27], comparable to that of ampicillin [28] provides some reassurance. Linezolid has been found to be non-inferior to vancomycin in the treatment of *Staphylococcus aureus* meningitis, too [29]. Typically, ceftriaxone and cefotaxime differ in blood-brain barrier penetration and pharmacokinetics. Cefotaxime achieves higher CSF concentrations but requires more frequent dosing due to its short half-life, while ceftriaxone, though more protein-bound, provides stable levels with less frequent dosing [30]. In our study, 67.4% of patients received ceftriaxone, while only 3.6% were given cefotaxime empirically. As a result, the probable benefit of cefotaxime, a less protein-bound drug, may have been masked in our analysis.

Table 2 Descriptive values of numerical parameters according to the clinical outcome

Clinical outcome		N	Mean	SD	Percentiles	Median	75th	P
					25th			
Age	Cured	83	54.82	15.59	42.00	58.00	66.00	0.306
	Died	27	58.96	20.60	42.00	63.00	78.00	
	Cured with sq	28	52.68	18.04	40.00	53.50	65.75	
GCS	Cured	83	10.37	3.37	8.00	10.00	14.00	0.004
	Died	27	7.81	3.43	5.00	8.00	10.00	
	Cured with sq	28	10.39	2.53	8.25	10.00	12.00	
HAMSI Score	Cured	83	3.08	1.77	2.00	3.00	4.00	0.181
	Died	27	3.89	2.15	2.00	3.00	6.00	
	Cured with sq	28	3.54	1.86	2.25	3.00	5.00	
Dutch Meningitis Score	Cured	83	45.0	20.9	29.0	40.0	64.0	0.067
	Died	27	55.6	22.1	40.0	54.0	75.0	
	Cured with sq	28	50.9	21.1	35.5	52.0	64.0	
CSF leukocyte count (/mm3)	Cured	83	5395.3	7301.7	640.0	2009.0	8046.0	0.050
	Died	27	2276.6	2839.6	321.0	1012.5	3316.8	
	Cured with sq	28	5748.5	8011.9	1125.0	3278.5	7077.8	
CSF protein level (mg/dL)	Cured	83	648.7	993.9	227.8	356.0	664.5	0.603
	Died	27	867.2	1788.8	300.3	488.0	831.3	
	Cured with sq	28	478.9	426.1	210.5	367.5	711.5	
CSF/Blood sugar	Cured	83	0.16	0.16	0.02	0.11	0.26	0.421
	Died	27	0.12	0.14	0.01	0.04	0.22	
	Cured with sq	28	0.14	0.19	0.02	0.06	0.20	
Blood leukocyte (/mm3)	Cured	83	18572.4	6918.6	14500.0	18105.0	22275.0	0.049
	Died	27	14643.2	8727.9	8000.0	14500.0	20140.0	
	Cured with sq	28	19086.3	8130.4	15585.0	17025.0	23372.5	
Platelet (/mm3)	Cured	83	232853.0	104,672	167000.0	205000.0	275000.0	0.008
	Died	27	182992.6	94311.2	110000.0	181000.0	225000.0	
	Cured with sq	28	177428.6	74269.0	122250.0	169500.0	233750.0	
Symptoms to abx. hours	Cured	76	44.97	82.02	12.00	24.00	46.50	0.553
	Died	24	45.60	48.14	12.75	24.00	66.50	
	Cured with sq	27	36.70	29.14	14.00	28.00	48.00	
Admission to abx. hours	Cured	78	12.83	51.18	1.00	3.00	6.25	0.251
	Died	26	4.88	6.45	1.00	2.00	6.50	
	Cured with sq	27	3.06	3.09	1.00	2.00	4.00	
Duration of antimicrobial tx (day)	Cured	83	5.04	4.57	4.00	4.00	5.00	0.160
	Died	27	3.67	4.07	0.00	4.00	5.00	
	Cured with sq	28	5.36	3.88	4.00	4.00	7.00	
Dosage of corticosteroid treatment	Cured	83	25.84	17.41	10.00	32.00	40.00	0.081
	Died	27	17.60	17.17	0.00	16.00	33.00	
	Cured with sq	28	27.71	14.39	18.00	32.00	40.00	

COPD: Chronic obstructive pulmonary disease, ESC: Escalation, DESC: De-escalation, BL: Beta lactam

We found that GCS, a widely used scale for assessing consciousness levels [31], showed that lower scores were linked to higher mortality. In our study group GCS was a good predictor of mortality and predicted mortality more accurately than sequelae formation. In our study cohort, there was no significant association between the HAMSI score [7], Dutch meningitis score [32] and the poor outcomes. Although PM almost always causes pleocytosis in the CSF [33], we have shown that elevated leukocyte counts in both the CSF and blood were indicative of survival in this group of patients, highlighting the amplified role of the immunity. In contrast, thrombocytopenia may indicate systemic inflammation, bone marrow suppression, or disseminated intravascular coagulation, which can worsen disease severity and outcomes [34], and should be accepted as an alarming signal in PRSP meningitis. Accordingly, recurrent meningitis suggests an underlying predisposition to repeated infections, which may result from immune dysfunction (e.g., complement or antibody deficiencies), structural abnormalities (e.g., CSF leaks, neurosurgical interventions), or chronic infections serving as reservoirs. Therefore, recurrent meningitis along with the challenges

Table 3 Results of binary multinomial logistic regression

Clinical outcome		OR	90% Confidence Interval for OR		P*
			Lower Bound	Upper Bound	
Died ***versus*** Cured	Intercept	0.128			0.070
	ICU ***(Yes versus No)***	14.886	2.167	102.256	0.021
	Mechanical ventilation ***(Yes versus No)***	7.205	1.382	37.554	0.049
	Vasopressor use ***(Yes versus No)***	8.983	1.804	44.743	0.025
	CSF leukocyte count (/mm3)	0.854	0.744	0.980	0.060
	Blood leukocyte (/mm3)	0.283	0.115	0.695	0.021
	Recurrent meningitis ***(Yes versus No)***	11.840	1.008	139.128	0.099
Cured with sequelae ***versus*** cured	Intercept	0.730			0.672
	Platelet (/mm3)	0.001	0.000	0.345	0.050
	Mechanical ventilation ***(Yes versus No)***	9.354	3.566	24.539	0.001
	Recurrent meningitis ***(Yes versus No)***	5.562	1.103	28.015	0.081
Cured with sequelae ***versus*** died	Intercept	0.039			0.046
	Glasgow coma score	1.365	1.108	1.683	0.014
	Corticosteroid treatment ***(Yes versus No)***	5.301	1.227	22.902	0.061
	Vasopressor use ***(Yes versus No)***	0.205	0.068	0.625	0.019

*: Binary logistic regression analysis, OR: Odds Ratio, $P<0.10$ accepted as statistically significant

Table 4 Descriptive values of numerical parameters according to the clinical outcome

	Fully cured	Cured with sequelae
Fully cured		
Cured with sequelae	⟨ Lower platelet counts ⟨ Mechanical ventilation ⟨ Recurrent meningitis	
Died	⟨ ICU admission ⟨ Mechanical ventilation ⟨ Vasopressor use © CSF leukocytosis © Blood leukocytosis	© Higher GCS © Steroid use ⟨ Vasopressor use

The direction of the arrows show the predicted outcome

of PRSP meningitis, underscores the critical importance of pneumococcal vaccination [35]. In addition, the favorable role of steroids is well-established in medical practice, as our findings show their ability to reduce mortality when comparing patients with poor outcomes who recovered with sequelae to those who did not survive [1, 2].

We had a couple of limitations in the study. First, although collecting prospective data for such a rare disease is almost impossible, the retrospective study design may have posed challenges in maintaining data consistency, accuracy, and completeness. Second, we could not show the efficacy of none beta-lactam antibiotics like rifampicin, TMP-SMX, moxifloxacin, chloramphenicol since they were used in very small numbers. Third, we could not show the superiority of rational empiric treatment over irrational modalities since only six (4.3%) patients received irrational empirical treatment before the availability of the culture data. Treatment escalation seemed to be driven mainly by the severity of the clinical status or by adjustments to the beta-lactam component of the combination regimen, rather than by transitioning from irrational to rational empirical therapy.

In conclusion, our findings suggest that PRSP meningitis is a severe disease, resulting in death in approximately 20% of patients and long-term complications in another 20%, leading to poor outcomes in 40% of cases overall. Headache (%86), altered mental status (%86), and neck stiffness (%76) were the most common findings in this group of patients. Clinical parameters such as ICU admission, mechanical ventilation, and vasopressor use are indicative of severe illness and hemodynamic instability, and are strongly associated with a poor prognosis. Additionally, recurrent meningitis suggests the presence of significant central nervous system comorbidity, further complicating the clinical outcome. Similarly, thrombocytopenia and lower leukocyte counts in either CSF or blood are surrogate markers of poor outcomes in drug resistant PM while lower GCS scores reflect neurological deterioration predicting poor outcomes. Finally, the absence of corticosteroid therapy being linked to poor outcomes suggests that corticosteroids provide significant protective effects. Further research is warranted to optimize antimicrobial strategies for PRSP meningitis and improve patient outcomes. Approximately 40% of penicillin-resistant isolates also exhibit resistance to carbapenems and third-generation cephalosporins, underscoring the need for alternative therapeutic options. Among these, moxifloxacin and linezolid appear promising, with susceptibility rates of 98% and 100%, respectively. Rifampicin, often used in combination regimens for meningitis, demonstrated a lower susceptibility rate of 60%, highlighting the importance of careful agent selection when designing effective treatment protocols.

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that the classification could be updated at the time of resubmission, I was not presented with that option. For your reference, the manuscript should be categorized under the RESEARCH article type.Thank you for your attention to this matter.Best wishes.

Author contributions Author contributions: HE contributed conceptualization, data curation, data analysis, investigation, methodology, writing, and supervision. Elif Dogan contributed to data curation, data analysis, and writing. Handan Ankarali contributed to conceptualization, statistical analysis, and writing. All other authors agreed the design of the study, collected and submitted data, reviewed the paper, obtained IRBs.

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Data availability We will send our database if requested.

Declarations

Consent for publication Not applicable. (Retrospective design)

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