Clinical Features and Outcomes of *Streptococcus pneumoniae* Meningitis in Children: A Retrospective Analysis of 26 Cases in China

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Abstract

**Background**  *Streptococcus pneumoniae* is an important cause of pediatric meningitis.

**Objective**  The aim of this study was to analyze the clinical features and outcomes of children with pneumococcal meningitis at our hospital in China, so as to provide basis for improving the clinical treatment effect.

**Methods**  This retrospective analysis included patients aged <16 years treated for pneumococcal meningitis at the Department of Neurology, Children’s Hospital of Shanxi (January 2014–February 2016). Clinical data were extracted from the medical records. Patients were followed up for 6 months after discharge.

**Results**  The analysis included 26 children aged 2 months to 13 years, with 17 (65.4%) aged <3 years. Presenting symptoms included fever (100%), lethargy (100%), impaired consciousness (88.5%), neck stiffness (69.2%), seizures (53.8%), and headache (50.0%). All patients had positive cerebrospinal fluid (CSF) cultures. The final treatment was vancomycin combined with a third-generation cephalosporin or other antibiotics in 25 patients. Eleven patients (42.3%) were recovered, 3 (11.5%) had neurological sequelae, and 12 (46.2%) died. Impaired consciousness (p = 0.035), cerebral hernia (p = 0.037), respiratory failure (p = 0.004), heart failure (p = 0.044), septic shock (p = 0.037), low CSF white blood cell count (p = 0.036), high CSF protein levels (p = 0.028), low white blood cell count (p = 0.036), and low blood neutrophil ratio (p = 0.016) are associated with a poor prognosis to pneumococcal meningitis.

**Conclusion**  Pneumococcal meningitis is associated with a poor prognosis in many children. Poor prognosis might be related to early ineffective antibiotic therapy, a combination of systemic failure, neurological problems, and changed inflammatory response. It is important to rapid initiation of appropriate antibiotic therapy if meningitis is suspected.

Keywords  ► *Streptococcus pneumoniae*  
► meningitis  
► children  
► infants  
► neurological complications

Introduction

Bacterial meningitis in children and infants is associated with substantial morbidity and mortality.¹ Although the incidence of bacterial meningitis has declined in Western countries following the introduction of vaccines against *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis*, the incidence rate is much higher...
in developing regions of the world such as Africa. The recognized risk factors for pneumococcal meningitis include group B Streptococcus-positive mothers, immunodeficiency, absence of opsonic bactericidal antibody, basilar skull fracture, prematurity, low birth weight, young age, living in a dormitory, lack of immunization, ear/nose/throat infections, ventriculoperitoneal shunt, cochlear implants, and neurosurgery. Bacterial meningitis classically presents with fever, headache, signs of meningeal irritation, and altered level of consciousness, but these symptoms and signs may be hard to detect or absent in some cases, especially in neonates and infants. Neurological complications of bacterial meningitis include cerebral infarction, cerebral abscess, subdural empyma, cerebritis, and intracerebral bleeding, and these can lead to long-term sequelae such as focal neurological deficits, hearing loss, cognitive impairment, and epilepsy. Bacterial meningitis is potentially fatal, and the mortality rate is 10% to 15% in neonates.

Streptococcus pneumoniae is a major cause of invasive diseases such as pneumonia, sepsis, and meningitis. Although the introduction of the pneumococcal conjugate vaccine has greatly reduced the global burden of invasive pneumococcal disease during the past two decades, it has been estimated that S. pneumoniae was responsible for 3.7 million cases of severe disease and more than 300,000 deaths in 2015. Pneumococcal meningitis is more frequently associated with worse outcomes than meningococcal meningitis, with a mortality rate of 35% and neuropsychological sequelae in 25% of those who survive. In China, 85% of pneumococcal diseases occur in children younger than 5 years, and antibiotic resistance is common in those with an invasive disease. Indeed, it is acknowledged that inappropriate use of antibiotics remains a problem in China and that increased access to pneumococcal vaccination is needed to reduce the incidence of pneumococcal meningitis in children and adults. During 2012 to 2015, S. pneumoniae was the second most common pathogen isolated from the cerebrospinal fluid (CSF) of children with acute bacterial meningitis in Yunnan Province and the most commonly isolated pathogen in infants aged >3 months, highlighting the importance of this bacterium as a cause of pediatric bacterial meningitis in China. However, data are limited regarding the clinical characteristics and outcomes of children with pneumococcal meningitis in China.

The aim of this retrospective analysis was to analyze the clinical features and outcomes of children with pneumococcal meningitis treated at the Department of Neurology, Children’s Hospital of Shanxi, China, between January 2014 and February 2016. It was anticipated that our findings might help clinicians identify patients at risk of poor outcomes such as neurological complications.

**Methods**

**Patients**

This was a retrospective analysis of all children (patients <16 years of age) who were treated for pneumococcal meningitis at the Department of Neurology, Children’s Hospital of Shanxi (a 1,000-bed medical center) between January 2014 and February 2016. The inclusion criteria, based on the diagnostic criteria for pneumococcal meningitis, were as follows: (1) clinical manifestations of purulent meningitis in children; (2) the results of routine CSF tests, including biochemical investigations, were consistent with a diagnosis of purulent meningitis; and (3) S. pneumoniae was isolated on blood culture or CSF culture, and other pathogens were excluded. Patients were excluded from the study if the data required for the analysis were missing. This study was approved by the ethics committee of the Children’s Hospital of Shanxi and the Women’s Health Center of Shanxi, and the requirement for informed consent was waived.

**Collection of Clinical Data**

The following clinical information was extracted from the medical records: (1) age, sex, home location (urban or rural), vaccination status, age at onset, time from onset to admission, previous treatment received at a different hospital, hospital department to which first admitted, season of year in which the patient was admitted, and cause of death; (2) symptoms and signs, including fever, headache, vomiting, convulsions, and meningeal irritation; (3) results of blood tests on the day of admission (all within 8 days of disease onset), including routine blood tests, C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), procalcitonin level, and blood culture; (4) results of CSF investigations during the first 3 days of admission (all within 11 days of disease onset), including routine CSF tests and CSF culture; (5) computed tomography (CT), magnetic resonance imaging (MRI), and electroencephalography (EEG) findings; (6) results of pathogen susceptibility tests; (7) presence of acute complications, including subdural effusion, hydrocephalus, and other neurological complications; and (8) clinical outcome at discharge, rated as 1 (death), 2 (persistent vegetative state), 3 (severe disability), 4 (moderate disability), or 5 (good recovery) using the Glasgow outcome scale (GOS). A GOS score of 5 was regarded as a good prognosis, and a GOS score of 0 to 4 was considered a poor prognosis.

**Follow-up**

All patients were followed up by telephone at 6 months after discharge. The data collected at the follow-up included the frequency of any seizures, locomotor, cognitive, auditory, and visual function, and medication history.

**Statistical Analysis**

SPSS 17 (SPSS Inc., Chicago, Illinois, United States) was used to analyze the data. A descriptive statistical method was used. Continuous data are presented as median (range), and count data are presented as n/N (%). Continuous data were analyzed by the Kruskal–Wallis test. Categorical data were analyzed by Fisher’s exact test. A p < 0.05 was considered statistically significant.

**Results**

**Demographic Characteristics of the Study Participants and Clinical Manifestations of Pneumococcal Meningitis**

Among 525 children diagnosed with bacterial meningitis during the study period, 26 children (5.0%) were confirmed...
to have meningitis caused by *S. pneumoniae*. The demographic characteristics and clinical features of meningitis in these 26 cases (18 males, 69.2%) are presented in Table 1 and Supplementary Table S1. The median age at onset was 1.5 years (range, 2 months–13 years), with 17 children (65.4%) aged <3 years and 10 children (38.5%) aged <1 year. None of the patients had been vaccinated against *S. pneumoniae*. The median duration from disease onset to admission was 2.5 days (range, 1–8 days), and 12 patients had received antibiotics at other hospitals. The hospital’s department to which the patient was first admitted was the neurology department in 12 cases, the pediatric intensive care unit (PICU) in 10 cases, cardiology department in 2 cases, and hematology department in 2 cases, and 9 patients were subsequently transferred to the PICU due to their critical clinical condition during treatment. The season of the year in which the patient was admitted was autumn (September–November) in 11 cases (42.3%), winter (December–February) in 8 cases (30.8%), spring (March–May) in 5 cases (19.2%), and summer (June–August) in 2 cases (7.7%).

### Table 1 Demographic characteristics and clinical features for the 26 children with pneumococcal meningitis

|                               | Good prognosis (n = 11) | Poor prognosis (n = 15) | p-Value |
|-------------------------------|------------------------|-------------------------|---------|
| Age, y, median (range)        | 1.4 (0.2, 13)          | 1.8 (0.3, 13)           | 0.979   |
| Male, n (%)                   | 6 (54.5)               | 12 (80.0)               | 0.218   |
| Source, n (%)                 |                        |                         |         |
| City                          | 2 (18.2)               | 10 (66.7)               | 0.658   |
| Country                       | 9 (81.8)               | 5 (33.3)                |         |
| Time from onset to admission, d, median (range) | 2 (1, 8)               | 3 (1, 7)                | 0.671   |
| Antibiotics within 3 d of onset, n (%) | 5 (45.4)               | 1 (6.7)                 | 0.054   |
| Dexamethasone, n (%)          | 10 (90.9)              | 11 (73.3)               | 0.356   |

| Clinical feature, n (%)       |                       |                         |         |
|-------------------------------|------------------------|-------------------------|---------|
| Fever                         | 11 (100)               | 15 (100)                | >0.99   |
| Lethargy                      | 11 (100)               | 15 (100)                | >0.99   |
| Impaired consciousness        | 8 (72.7)               | 15 (100)                | 0.035   |
| Headache and vomiting         | 6 (54.5)               | 7 (46.7)                | 0.697   |
| Convulsions within 3 d of onset| 6 (54.5)               | 9 (60)                  | 0.785   |
| Hemiplegia                    | 0                      | 3 (20)                  | 0.122   |
| Meningeal irritation signs     | 8 (72.7)               | 9 (60)                  | 0.509   |
| Cerebral hernia               | 0                      | 5 (33.3)                | 0.037   |
| DIC                           | 0                      | 3 (20)                  | 0.122   |
| Respiratory failure           | 0                      | 8 (53.3)                | 0.004   |
| Heart failure                 | 1 (9.0)                | 7 (46.7)                | 0.044   |
| Renal failure                 | 0                      | 1 (6.7)                 | 0.392   |
| Septic shock                  | 0                      | 5 (33.3)                | 0.037   |
| Bacteremia                    | 9 (81.8)               | 10 (71.4)               | 0.554   |

Cerebrospinal fluid tests, median (range)

|                             | Good prognosis (n = 11) | Poor prognosis (n = 15) | p-Value |
|-----------------------------|------------------------|-------------------------|---------|
| White blood cell count      | 990 (20, 4,700)        | 148 (1, 9,600)          | 0.036   |
| Protein (g/L)               | 2.7 (1.6, 4.7)         | 8.7 (1.0, 22.7)         | 0.028   |
| Glucose (mmol/L)            | 0.3 (0.2, 1.1)         | 0.7 (0.1, 3.5)          | 0.454   |

Blood tests, median (range)

|                             | Good prognosis (n = 11) | Poor prognosis (n = 15) | p-Value |
|-----------------------------|------------------------|-------------------------|---------|
| White blood cell count (10^9/L) | 22.7 (5.4, 49.9)     | 11.3 (1.7, 29.3)        | 0.036   |
| Neutrophil ratio (%)        | 85.4 (58.0, 92.2)      | 68.8 (19.0, 91.6)       | 0.016   |
| Hemoglobin (g/L)            | 116.0 (70.0, 121.0)    | 115 (91, 176.8)         | 0.516   |
| Platelet count (10^9/L)      | 246 (71, 609)          | 170 (22, 547)           | 0.287   |
| Creative protein (mg/L)      | 153.0 (26.0, 242.0)    | 200.0 (68.2, 200.0)     | 0.225   |
| Procalcitonin (ng/mL)        | 14.9 (4.0, 31.6)       | 26.6 (0.1, 200.0)       | 0.186   |

Abbreviation: DIC, disseminated intravascular coagulation.
The significance of bold used in Table 1, means p < 0.05, statistical significance.
All patients presented with respiratory tract infection, fever, and lethargy. Headache and vomiting were present in 13 cases (50.0%) and were more common in patients aged ≥1 year than in those aged <1 year. Anterior fontanelle bulging was evident in all 10 patients aged <1 year. Impaired consciousness was a clinical manifestation in 23 cases (88.5%). Seizures occurred in 14 patients (53.8%), including 6 patients with seizures at disease onset; 6 patients had partial seizures, and 8 patients had generalized tonic-clonic seizures. Neck stiffness was present in 18 cases (69.2%).

Blood and CSF Tests
The results of blood tests and CSF tests are shown in supplementary Table S2 and S3. Blood leukocyte count and platelet count were elevated in 14 cases (53.8%) and 4 cases (15.4%), respectively. All patients had high levels of procalcitonin and CRP, and 12 patients (46.2%) had an elevated ESR (>50 mm/h). CSF leukocyte count was elevated in 23 cases (88.5%), and the neutrophil ratio ranged from 45 to 98%. The CSF protein level exceeded 0.5 g/L in all cases and was >2.0 g/L in 22 cases (84.6%). The CSF glucose level was between 0.07 and 2.27 mmol/L in 25 cases (96.2%), and a slight decline in CSF chloride level was detected in 8 cases (30.8%). CSF cultures were positive in all 26 cases, and 13 cases had a positive Gram stain in the CSF. Blood cultures were positive in 18 cases (69.2%).

Neuroimaging and EEG Findings
Among 22 patients who received cranial MRI or CT, there were 11 cases (50.0%) of intracranial multiple inflammatory lesions, 9 cases (34.6%) of subdural effusion, 7 cases (31.8%) of hydrocephalus, 4 cases (18.2%) of diffuse cerebral edema, 4 cases (18.2%) of brain atrophy, 2 cases (9.1%) of focal cerebral hemorrhage, 2 cases (9.1%) of cerebral softening, and 1 case (4.5%) of dural venous sinus thrombosis (supplementary Table S4). In most cases, MRI suggests inflammatory or infectious lesions in various parts of the brain. Among the 26 patients, 16 (61.5%) underwent cranial MRI. Among the 10 patients who did not receive MRI, 4 could not undergo any imaging at all because of a severe condition, and 6 only received skull CT examination. Among the 16 patients with MRI, 2 had normal results, 14 showed inflammatory changes (including 1 patient with local cortical hemorrhage and 1 with ischemic foci). The cerebral cortex was involved in all 14 patients. In addition, the ventricular system was involved in four patients, two patients had basal ganglia involvement, two patients had cerebellum involvement, two patients had diffuse cerebral atrophy, one patient had cerebral stem involvement, and one patient showed venous sinus and local venous thrombosis. Eight patients underwent an EEG examination: six cases showed slow background activity, and one case showed a large number of high-amplitude slow waves and sharp slow-wave bursts (supplementary Table S4).

Acute Neurological Complications
There were nine cases (34.6%) of subdural effusion, seven cases (26.9%) of hydrocephalus, six cases (23.1%) of seizures, five cases (19.2%) of cerebral hernia, four cases (15.4%) of brain atrophy, three cases (11.5%) of hemiplegia, two cases (7.7%) of peripheral facial paralysis, and one case (3.8%) each of subdural empyema, ependymitis, and dural venous sinus thrombosis.

Nonneurological Complications
There were nine cases (34.6%) of bronchopneumonia, eight cases (30.8%) of heart failure, eight cases (30.8%) of respiratory failure, five cases (19.2%) of septic shock, three cases (11.5%) of diffuse intravascular coagulation, and one case (3.8%) each of renal failure and suppurative otitis media.

Treatment
Twelve patients (46.2%) were administered antibiotics prior to admission, including third-generation cephalosporins in eight cases (66.7%), amoxicillin in two cases (16.7%), erythromycin in one case (8.3%), and cefotaxime in one case (8.3%). All patients were treated with antibiotics on admission to our hospital. One patient (untreated before admission) was given cefoperazone monotherapy but died within 10 hours. The remaining 25 patients were initially treated with a third-generation cephalosporin, and the regimen was then switched to a vancomycin-containing regimen according to the results of drug sensitivity tests and therapeutic effects. The vancomycin-containing regimen included meropenem in 8 cases, cefotaxime in 9 cases, ceftriaxone in 1 case, cefoperazone/subactam in 17 cases, and ampicillin and cloxacillin in 2 cases. Susceptibility tests (supplementary Table 2) revealed very high resistance rates to erythromycin (100%) and clindamycin (95.8%) as well as substantial resistance to penicillin (53.8%), cefotaxime (34.6%), and ceftriaxone (34.6%). However, all strains were susceptible to vancomycin, meropenem, levofloxacin, and linezolid (supplementary Table 2). In addition to the rational use of antibiotics, albumin was coadministered in 16 patients, and large-dose gamma globulin was used in 12 cases. All children received mannitol infusion to reduce intracranial pressure as well as other symptomatic and supportive treatments. Steroids were used in 21 patients (dexamethasone 0.3–0.5 mg/kg/d, every 12 hours).

Outcomes
Univariable analyses were used to explore the factors associated with prognosis. They suggest that impaired consciousness (p = 0.035), cerebral hernia (p = 0.037), respiratory failure (p = 0.035), and clinical manifestations (p = 0.037) are associated with poor outcomes. The results of univariable analyses are shown in supplementary Table 4.

Table 2 Results of CSF test for drug susceptibility tests

| Antibiotic drug | Drug-resistant strains/all cases | Resistance rate (%) |
|-----------------|---------------------------------|--------------------|
| Clindamycin     | 23/24                           | 95.8%              |
| Ceftriaxone     | 9/26                            | 34.6%              |
| Erythromycin    | 24/26                           | 100%               |
| Levofloxacin    | 0/26                            | 0%                 |
| Linezolid       | 0/26                            | 0%                 |
| Penicillin      | 14/26                           | 53.8%              |
| Cefotaxime      | 9/26                            | 34.6%              |
| Vancomycin      | 0/26                            | 0%                 |
| Meropenem       | 0/2                             | 0%                 |

Abbreviation: CSF, cerebrospinal fluid.
Seven of the patients treated with vancomycin recovered within 1 week (GOS = 5). Further, four patients showed marked improvement (conscious and without fever, but with some abnormal CSF parameters) and left the hospital voluntarily; at the 6-month follow-up, all four of these patients underwent CSF reexamination to verify whether the previous abnormalities were still present but had normal results for CSF tests and CSF protein and glucose levels should also be assessed. Notably, less than half the patients had a high white blood cell count in peripheral blood, indicating that this may be a less reliable indicator of pneumococcal meningitis. On the other hand, low CSF and blood leukocyte counts do not rule out the diagnosis of pneumococcal meningitis. On the other hand, both factors are also associated with poor prognosis which might point to a problem with the immune response or consumption of leukocytes in the course of septicemia.

An important finding of the present study was that neurological complications were common in children with pneumococcal meningitis and included subdural effusion (34.6%), hydrocephalus (26.9%), epilepsy (23.1%), cerebral hernia (19.2%), brain atrophy (15.4%), hemiplegia (11.5%), peripheral facial paralysis (7.7%), subdural empyema (3.8%), ependymitis (3.8%), and dural venous sinus thrombosis (3.8%). Previous studies also reported high rates in such patients. The mortality rate among the children in our study was 46.2%, somewhat higher than the rates reported previously, and 7 of these 12 patients (58.3%) were <2 years of age. The reasons underlying the higher mortality rate in our study are not known, although one contributing factor may be the high proportion of patients (46.2%) treated with antibiotics at other hospitals prior to admission to our institution: ineffective therapy at other hospitals may have delayed the initiation of appropriate antibiotic therapy and thus resulted in poorer outcomes. Poor prognosis might also be related to a combination of systemic failure, neurological problems, and chronic inflammatory response. In a previous study, the factors associated with a poor prognosis included younger age, lengthy fever, low CSF cell count, very low CSF glucose, low neutrophil count, resistance to penicillin, low GOS, organ failure, and early admission to intensive care unit. Systemic factors might be important regarding mortality, but neurological problems might be more important regarding the outcomes in survivors. This will have to be examined in future studies with larger sample sizes. Nevertheless, our findings and previous studies emphasize the need to institute appropriate treatment as early as possible to minimize the risks of poor outcomes.

The vancomycin/rifampin combination is an alternative for patients with allergy to penicillin or cephalosporins, and other drugs such as meropenem or chloramphenicol can be considered. The antibiotic regimen is then adjusted once the CSF culture and sensitivity results are known. The recommended empiric regimen for children aged >1 month is ceftriaxone or cefotaxime plus vancomycin or rifampicin. In this study, 25 patients were treated empirically with
vancomycin after admission; in 24 patients, vancomycin was combined with a third-generation cephalosporin, as recommended, and in 7 patients, vancomycin was subsequently administered with meropenem because of poor initial efficacy, critical clinical condition, and/or the results of susceptibility tests. One patient was not given vancomycin because of death 10 hours after admission. The resistance of *S. pneumoniae* to cephalosporins showed an increasing trend in China, and the highest sensitivities were observed with levofloxacin, moxifloxacin, and vancomycin. Ceftriaxone might also be a good choice. This cephalosporin resistance of *S. pneumoniae* is not exclusive in China. In the present study, 14 patients (53.8%) had penicillin-resistant strains who were also resistant to erythromycin, but all strains were sensitive to vancomycin. Previous studies have reported penicillin resistance rates of 31 to 89%, ceftriaxone resistance rates of 14 to 52%, and erythromycin resistance rates approaching 100%, but full susceptibility to vancomycin. On account of the high mortality and morbidity associated with pneumococcal meningitis, the high level of penicillin resistance in our pneumococcal meningitis isolates leads us to believe that it would be prudent to add vancomycin to ceftriaxone for initial treatment of acute bacterial meningitis till culture reports become available, after which antibiotics can be administered based on results of susceptibility testing. Local antibiotic prescribing patterns affect the local resistance patterns, highlighting the need for susceptibility testing in each case.

In this study, the mortality rate of pneumococcal meningitis was 46.2% (12/26). Reported mortality rates were 20.3% (65/321) in New York (United States), 20.1% (41/204) in Chicago (United States), 12.7% (107/841) in the Netherlands, 13.1% (704/5,374) in Denmark, 1.1% (3/264) in Germany, 5.5% (3/55) in 2003 to 2015 versus 24.1% (21/87) in 1984 to 2002 in Germany, 13.7% (42/306) in Turkey, and 21.4% (6/28) in Gambia. A meta-analysis indicated that the mortality rate varied according to the serotype of *S. pneumoniae*, but the present study did not examine the exact serotype. This study has some limitations. This was a retrospective analysis, so the results may be prone to information bias and selection bias. The generalizability of the findings is not known because this was a single-center study with a small sample size. *Streptococcus pneumoniae* serotyping was not performed, so the causative serotypes and their possible associations with outcomes were not evaluated. Due to the small sample size, multivariable analysis of factors independently associated with poor outcomes could not be performed.

**Conclusion**

In conclusion, pneumococcal meningitis was associated with neurological sequelae or death in a majority of children in China. Poor prognosis might be related to early ineffective antibiotic therapy, a combination of systemic failure, neurological problems, and changed inflammatory response. Furthermore, the resistance rates of *S. pneumoniae* to penicillin were high, and this emphasizes the need for rapid initiation of using appropriate empiric antibiotic therapy such as combination therapy with vancomycin added to cefotaxime or ceftriaxone if meningitis is suspected and adjustment of the antibiotic regimen once the results of susceptibility tests are known.

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**Conflict of Interest**

None declared.

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