International Journal of Infectious Diseases 74 (2018) 47–53

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Clinical characteristics and etiology of bacterial meningitis in Chinese children >28 days of age, January 2014–December 2016: A multicenter retrospective study

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ARTICLE INFO

Article history:
Received 16 April 2018
Received in revised form 8 June 2018
Accepted 30 June 2018
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Bacterial meningitis
Children
Pathogen
Antibiotic susceptibility

ABSTRACT

Objective: To explore the clinical characteristics and etiology of bacterial meningitis (BM) in Chinese children.
Method: BM cases in children 28 days to 18 years old were collected from January 2014–December 2016 and screened according to World Health Organization standards. Clinical features, pathogens, and resistance patterns were analyzed.
Results: Overall, 837 cases were classified into five age groups: 28 days–2 months (17.0%), 3–11 months (27.8%), 12–35 months (24.0%), 3–6 years (13.9%), and >6 years (17.3%). Major pathogens were *Streptococcus pneumoniae* (*S. pneumoniae,* n = 136, 46.9%), group B *Streptococcus* (GBS, n = 29, 10.0%), and *Escherichia coli* (*E. coli,* n = 23, 7.9%). In infants <3 months old, GBS (46.5%) and *E. coli* (23.3%) were most common; in children >3 months old, *S. pneumoniae* (54.7%), which had a penicillin non-susceptibility rate of 55.4% (36/65), was most frequent. The resistance rates of *S. pneumoniae* and *E. coli* to cefotaxime and ceftriaxone were 14.0%/40.0% and 11.3%/68.4%, respectively. All GBS isolates were sensitive to penicillin.
Conclusions: The occurrence of BM peaked in the first year of life, while *S. pneumoniae* was the predominant pathogen in children >3 months of old. The antibiotic resistance of *S. pneumoniae* was a concern.

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https://doi.org/10.1016/j.ijid.2018.06.023

Introduction

Bacterial meningitis (BM), an infection of the meninges by bacteria, is an emergency and critical disease. Historically, the most common causes of BM have been *Streptococcus pneumoniae* (*S. pneumoniae*), *Neisseria meningitidis* (*N. meningitidis*), and *Haemophilus influenzae* type b (Hib) in children worldwide (Chávez-Bueno and McCracken, 2005). Without treatment, the mortality of BM approaches 100% (Kim, 2010). Prompt and accurate diagnosis and aggressive antibiotic treatment are essential. With prompt and adequate antibiotic therapy, case fatality rates have been reduced to 4.2% in children (Mongelluzzo et al., 2008). However, the rate of abnormalities in survivors remains high (56% of group B *streptococcus*, and 63% of S. *pneumoniae*) (Libster et al., 2012; Stockmann et al., 2013).

Due to the universal use of conjugated vaccines targeting *S. pneumoniae*, *N. meningitidis*, and Hib, the incidence of BM caused by these pathogens has been reduced sharply in developed countries (Chávez-Bueno and McCracken, 2005). In the United States, the incidence of BM in 2006–2007 dropped to 1.38 cases per 100,000 population. However, the case fatality rate did not change and was 14.3% at that time (Thigpen et al., 2011). In China, the incidence of BM in 2006–2009 ranged from 6.95 to 22.3 cases per 100,000 population for children aged under 5 years (Li et al., 2014), and the case fatality rate was 18.42% for children under 5 years of age (Dong et al., 2004). The positive rate of pathogen detection was only 2.2% (Li et al., 2014). Meanwhile, the penicillin resistance rate of *S. pneumoniae* rose sharply during those years, and multidrug-resistant *S. pneumoniae* appeared (Yao and Zhang, 2011). Therefore, BM remains a challenge in China in the present day.

Many single-center reports about BM in children in China are available for these years. However, few multicenter reports exist about BM in children aged over 28 days, and thus, we do not completely understand the status of this disease throughout China. Therefore, we performed this study, which involved 12 hospitals throughout China, from 2014 to 2016. The clinical data, etiology and pathogen resistance patterns in these hospitals were analyzed to yield a database for prospective multicenter studies in the future.

Methods

Study design and setting

We conducted a national multicenter retrospective study in China. To complete this study, we set two inclusion criteria for hospital selection: (1) a hospital must have adequate research capabilities and facilities to conduct the study, especially laboratory facilities for bacterial culture and the ability to assess susceptibility to antimicrobials; and (2) a hospital must have enough time to devote to this study and be willing to participate in this research. Twelve hospitals (nine tertiary hospitals and three secondary ones) joined our study. The selected hospitals consisted of 4 in North China, 4 in East China, 2 in South China, 1 in the southwest, and 1 in the northwest. Demographic data, clinical features, and laboratory findings of all patients with clinical or confirmed diagnoses of BM in these hospitals from 2014 to 2016 were collected by local researchers.

Study population

Inclusion criteria: (1) The admission day was between January 1, 2014 and December 31, 2016. (2) Hospitalized children between 28 days and 18 years old with suspected or confirmed BM in selected hospitals.

The diagnostic criteria was based on the recommended case definition of the World Health Organization (WHO) (WHO, 2003): (1) a sudden onset of fever (>38.5 °C rectal or >38.0 °C axillary); (2) one of the following symptoms or signs: headache, meningeal irritation, or altered consciousness; (3) cerebrospinal fluid (CSF) examination showing either of the following: leukocytosis ($>100 \times 10^6$ cells/l) or leukocytosis ($10–100 \times 10^6$ cells/l) with an elevated protein (>100 mg/dl) or decreased glucose (<40 mg/dl); (4) positive culture, positive Gram stain, or positive bacterial antigen in the CSF. A case meeting diagnostic criteria 1, 2, and 3 at the same time was considered a probable case. A probable case meeting criterion 4 was considered a confirmed case.

Exclusion criteria: (1) viral encephalitis or meningitis; (2) tuberculous meningitis; (3) fungal encephalitis or meningitis; (4) involvement of the central nervous system in patients with definitive diagnosis of neoplasm; (5) patients with definitive diagnosis of autoimmune encephalitis. The case should be excluded if any exclusion criteria was met.

Clinical outcomes

We considered clinical status on the day of discharge as the clinical outcome, and the outcome was graded with the Glasgow outcome scale (GOS): (1) death; (2) persistent vegetative state; (3) severe disability; (4) moderate disability; and (5) good recovery. A good outcome was defined as a score of five, and a poor outcome as a score of one to four (Mourvillier et al., 2013; Van de Beek et al., 2004).

Antimicrobial susceptibility testing

To rule out repeated strains, only one representative strain from each case was included. When both the blood and CSF cultures were positive in a case, we used only the strain from the CSF sample for antimicrobial susceptibility testing. According to the performance standards for antimicrobial susceptibility testing of the Clinical and Laboratory Standards Institute in 2008, we determined the penicillin susceptibility of *S. pneumoniae* by the minimum inhibition concentration. If an *S. pneumoniae* strain was isolated from blood, we defined its penicillin susceptibility by the parenteral non-meningitis breakpoint (susceptible, 2 mg/l; intermediate, 4 mg/l; resistant, 8 mg/l). If the *S. pneumoniae* strain was isolated from CSF, we defined its penicillin susceptibility by the parenteral meningitis breakpoint (susceptible, 0.06 mg/l; resistant, 0.12 mg/l).

Ethics analysis

This study was reviewed and approved by the Ethics Committee of Beijing Children's Hospital Affiliated to Capital Medical University and the Medical Ethical Committees of the selected hospitals.

Data management and statistical analysis

According to our inclusion criteria, a total of 2660 BM cases were collected. Ruling out the cases that met any exclusion criteria and confirming the remaining cases according to the WHO standard, we finally obtained 837 cases. These cases were input into a computer database by EpiData. All the data were statistically analyzed by SPSS 24.0 (SPSS Inc. Chicago, IL, USA).

Results

Demographic data

There were 837 cases included in this study. The numbers of annual meningitis cases were 297 in 2014, 284 in 2015, and 256 in