Original Article

Changes in pathogens of neonatal bacterial meningitis over the past 12 years: a single-center retrospective study

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Background: Bacterial meningitis is a serious central nervous system infection associated with high morbidity and mortality during the neonatal period, while the pathogen distribution was rarely reported on a large scale in China. This study aimed to investigate the distribution and change trends of neonatal bacterial meningitis pathogens in Children's Hospital of Fudan University over the past 12 years.

Methods: This retrospective study included all cases diagnosed with neonatal bacterial meningitis and admitted to our hospital from 2009 to 2020.

Results: Totally 231 cases were enrolled, including 128 (55.4%) for male, 72 (31.2%) for premature infants, 48 (20.8%) for early-onset meningitis. The most common pathogens were *Escherichia coli* (*E. coli*) (39.0%) and Group *B Streptococcus* (*GBS*) (22.1%). Gram-negative bacteria were more common in preterm infants than in full-term infants (P=0.005). *GBS* was more common in term infants (P=0.000); *Klebsiella pneumoniae* (P=0.000) and *Enterobacter cloacae* (P=0.034) were more common in preterm infants. Gram-positive bacteria were more frequent in early-onset meningitis than in late-onset meningitis (P=0.002). Both *E. coli* (46.3% *vs.* 30.9%, P=0.017) and *GBS* (29.8% *vs.* 13.6%, P=0.003) increased, and *Enterococcus* (3.3% *vs.* 12.7%, P=0.008) decreased significantly in the epoch from 2015 to 2020 compared with the epoch from 2009 to 2014.

Conclusions: *GBS* and *E. coli* are the most common pathogens of neonatal bacterial meningitis in our hospital, and both have shown an upward trend over the past 12 years.

Keywords: Neonates; bacteria; meningitis; pathogen; trend

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Introduction

Bacterial meningitis is a serious central nervous system infection that more commonly occurs in the neonatal period than in any other age group. Despite reported decreases in mortality, the incidence of neurological sequelae, including hearing impairment, blindness, epilepsy, cerebral palsy, and intellectual disability, remains high and ranges from 32% to 44% (1,2). Moreover, the prognosis of neonatal bacterial meningitis may be associated with the type of pathogen responsible. Nevertheless, the pathogen distribution may change over time and vary in different populations depending on gestational age, hospital setting and the level of care given (3). *Group B Streptococcus* (*GBS*) and *Escherichia coli* (*E. coli*) are the most common pathogens causing neonatal bacterial meningitis in most developed countries; however, the neonatal bacterial meningitis pathogen distribution varies geographically in developing countries. With the development of maternal prenatal *GBS* screening and intrapartum antibiotic prophylaxis for pregnant women,

the morbidity of neonatal bacterial meningitis has declined in developed countries (4,5). However, some recent studies have shown an increasing trend in morbidity due to the variation in pathogen serotypes and increase in antibiotic resistance (6-8). Overall, exploring the pathogen distribution and change trends in neonatal bacterial meningitis will help to improve the rational use of antibiotics to decrease the incidence of neurological sequelae and mortality, but there have been very few large-scale studies on the pathogen distribution and change trends in neonatal bacterial meningitis in China to date.

Therefore, in this study, we retrospectively collected clinical data for all patients who were diagnosed with neonatal bacterial meningitis and hospitalized at Children's Hospital of Fudan University from 2009 to 2020 and analyzed the distribution characteristics and change trends of pathogens during the last 12 years. We present the following article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-103/rc).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by The Ethics Committee of the Children's Hospital of Fudan University [Ethics approval No. (2019)314] and individual consent for this retrospective analysis was waived.

Study design

All neonates diagnosed with bacterial meningitis and admitted to Children's Hospital of Fudan University between 2009 and 2020 were included in this study. We retrospectively analyzed the clinical data of these neonates, and investigated the distribution characteristics and change trends of pathogens. Children's Hospital of Fudan University is a tertiary pediatric hospital and one of three national children's medical centers, and it has one of the largest neonatal wards in eastern China.

Selection and description of participants

The inclusion criteria for this study were as follows: (I) term infants within 28 days after birth and premature infants within 28 days after expected date of delivery; (II) infants with clinical manifestations of infection and meningitis with nonspecific symptoms including abnormal body temperature, lethargy, poor milk feeding, cyanosis, and apnea and neurological symptoms including seizures, dystonia, irritability, abnormal primitive reflexes and bulging fontanelle; and (III) results of cerebrospinal fluid (CSF) examination meeting one or two of the following: (i) isolation of a bacterial pathogen from CSF culture; or (ii) isolation of a bacterial pathogen from blood culture, with CSF pleocytosis (>20×10^6/L) (9,10). When traumatic lumbar punctures occur, the CSF white blood cell (WBC) count is corrected due to the contamination of CSF by blood. Predicted CSF WBCs were calculated as (peripheral WBC count/peripheral red blood cell count) × CSF red blood cell count (11).

The exclusion criteria were as follows: (I) congenital malformations of the nervous system; (II) placement of a reservoir or ventricle-peritoneal shunt due to hydrocephalus or ventricular dilatation before lumbar puncture; or (III) missing data.

Data collection

The following data were abstracted from computer-documented hospital information systems: age, sex, gestational age, birth weight, mode of delivery, clinical symptoms and signs, CSF routine and culture results, and bacterial species from blood cultures. All data collection followed standard operations and definitions.

Definitions

Early-onset meningitis was defined as diagnosis at ≤3 days of age; late-onset meningitis was defined as diagnosis at >3 days of age (12-14). The patients were divided into two groups according to admission time: the first epoch, which was admitted from 2009 to 2014, and the second epoch, which was admitted from 2015 to 2020. The criteria of antibiotic susceptibility testing referred to the 31st edition of Performance Standards for Antimicrobial Susceptibility Testing (15).

Statistical analysis

Measurement data conforming to a normal distribution are represented by the mean ± standard deviation, and the independent-sample *t*-test was used for comparison. Measurement data not conforming to a normal distribution are represented by the interquartile range, and the rank

sum test was used for comparison. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. In all analyses, a P value of <0.05 was considered statistically significant. The statistical analysis was performed using Stata 15.0 (StataCorp, College Station, Texas, USA).

Results

Basic characteristics of the patients

A total of 58,507 newborns were admitted to our hospital during the 12-year study period, among whom 249 (0.4%) were diagnosed with neonatal bacterial meningitis. Among the 249 neonates with bacterial meningitis, 118 neonates (out of 28,415) were from the first epoch and 131 neonates (out of 30,092) were from the second epoch. Nine cases were excluded for incomplete clinical data, 6 cases for congenital malformations of the nervous system, and 3 cases for placement of a ventricle-peritoneal shunt due to hydrocephalus before meningitis. Therefore, 231 cases were enrolled in our study, including 128 boys and 103 girls (159 term and 72 preterm). The median gestational age was 38.6 weeks, the median birth weight was 3,100 grams, and the median onset age was 9 days. Of the 231 neonates, 76 (32.9%) were born by cesarean section, 48 (20.8%) were early-onset infections, and 110 (47.6%) from the first epoch and 121 (52.4%) from the second epoch.

Pathogen distribution

Among the 231 cases of neonatal bacterial meningitis, 80 patients were positive based on both CSF and blood culture and with same bacteria, 50 were positive based on CSF culture alone, and 101 were positive based on blood culture alone. All of pathogens are shown in *Table 1*. The most common pathogens were *E. coli* (39.0%) and *GBS* (22.1%). Gram-negative bacteria accounted for the majority (57.1%).

As indicated in *Table 2*, both preterm and term infants were primarily infected by gram-negative bacteria, though gram-negative bacteria were significantly more frequent in preterm infants (P=0.005). *GBS* was significantly more frequent in term infants (P=0.000), while *Klebsiella pneumoniae* (P=0.000) and *Enterobacter cloacae* (P=0.034) were more frequent in preterm infants.

The pathogen distribution results of early-onset and late-onset bacterial meningitis were also analyzed. Gram-positive bacteria were more common in early-onset meningitis (P=0.002), *GBS* was the leading pathogen in early-onset meningitis (29.2%), and *E. coli* was the leading pathogen in late-onset bacterial meningitis (42.1%). *Listeria monocytogenes* was more frequent in early-onset meningitis than in late-onset meningitis (P=0.036).

Antibiotic susceptibility

Antibiotic susceptibility testing records were available for 110 cases (*Table 3*). *E. coli* showed high sensitivity to piperacillin/tazobactam, cefoperazone/sulbactam, cefepime, and meropenem (97.8%, 91.3%, 89.6%, and 100%, respectively) and a varying sensitivity to ampicillin/sulbactam, cefuroxime, cefotaxime, ceftazidime, gentamicin, and ciprofloxacin (34.8%, 53.3%, 56.4%, 71.7%, 60.0%, and 60.9%, respectively). All *GBS* strains were sensitive to penicillin, cefuroxime, cefotaxime, vancomycin, and linezolid. *Listeria monocytogenes* also showed full sensitivity to penicillin, ampicillin/sulbactam, gentamicin, vancomycin, and linezolid. The drug resistance rates of *Enterococcus* and *CONS* to most antibiotics were very high, but they were generally sensitive to vancomycin and linezolid. *Klebsiella pneumoniae* exhibited low sensitivity to most antibiotics, and three strains resistant to carbapenems were isolated.

Trends in pathogen changes

Comparing the demographic characteristics of the infants in the two epochs, there were no significant differences in terms of sex, gestational age, birth weight, or age of onset, except for a decrease in the rate of cesarean section in the second epoch (25.6% *vs.* 40.9%, P=0.014). *Table 4* shows the trends for the most common pathogens: *E. coli*, *GBS*, *Enterococcus*, *Klebsiella pneumoniae*, *CONS*, and *Listeria monocytogenes*. Obviously, *E. coli* (46.3% *vs.* 30.9%, P=0.017) and GBS (29.8% *vs.* 13.6%, P=0.003) infections increased significantly in the second epoch compared with the first epoch, whereas *Enterococcus* infections decreased significantly in the second epoch (3.3% *vs.* 12.7%, P=0.008). The proportion of common pathogens in each year is provided in Figure S1.

As shown in *Table 5*, early-onset *E. coli* infection accounted for 14.4% (13/90) of cases of *E. coli* meningitis; early-onset *GBS* infection accounted for 27.5% (14/51) of cases of *GBS* meningitis. There was a significant increase in the proportions of both early-onset and late-onset *GBS* meningitis. The proportion of late-onset *E. coli* meningitis also increased in the second epoch, but the proportion of early-onset *E. coli* meningitis was similar between the two

Table 1 Pathogen distribution of all cases

Pathogens	All cases (N=231), n (%)	Cerebrospinal fluid culture (N=130), n (%)	Blood culture (N=181), n (%)
Gram-positive bacteria	99 (42.9)	53 (40.8)	76 (42.0)
Group B Streptococcus	51 (22.1)	31 (23.8)	44 (24.3)
Enterococcus faecalis/faecium	18 (7.8)	14 (10.8)	7 (3.9)
Coagulase-negative staphylococci	13 (5.6)	3 (2.3)	10 (5.5)
Listeria monocytogenes	7 (3.0)	2 (1.5)	6 (3.3)
Bacillus cereus	2 (0.9)	0	2 (1.1)
Staphylococcus aureus	2 (0.9)	1 (0.8)	1 (0.6)
Streptococcus uberis	1 (0.4)	1 (0.8)	1 (0.6)
Streptococcus bovis	1 (0.4)	0	1 (0.6)
Streptococcus constellatus	1 (0.4)	0	1 (0.6)
Uncategorized Gram-positive bacteria	3 (1.3)	1 (0.8)	3 (1.7)
Gram-negative bacteria	132 (57.1)	77 (59.2)	105 (58.0)
Escherichia coli	90 (39.0)	56 (43.1)	74 (40.9)
Klebsiella pneumoniae	15 (6.5)	7 (5.4)	12 (6.6)
Enterobacter cloacae	5 (2.2)	2 (1.5)	3 (1.7)
Flavobacterium meningosepticum	4 (1.7)	4 (3.1)	3 (1.7)
Stenotrophomonas maltophilia	4 (1.7)	1 (0.8)	4 (2.2)
Acinetobacter baumannii	4 (1.7)	3 (2.3)	3 (1.7)
Haemophilus influenzae	1 (0.4)	0	1 (0.6)
Enterobacter aerogenes	1 (0.4)	0	1 (0.6)
Citrobacter freundii	1 (0.4)	0	1 (0.6)
Alcaligenes xylosoxidans	1 (0.4)	0	1 (0.6)
Pseudomonas aeruginosa	1 (0.4)	1 (0.8)	0
Burkholderia cepacia	1 (0.4)	0	1 (0.6)
Serratia liquefaciens	1 (0.4)	1 (0.8)	0
Salmonella group D	1 (0.4)	0	1 (0.6)
Uncategorized Gram-negative bacteria	2 (0.9)	2 (1.5)	0

epochs. According to antibiotic susceptibility testing of *E. coli* in late-onset meningitis, sensitivity to third- generation cephalosporins increased significantly during the second epoch (Table S1).

Discussion

Due to the immature immune system and the poor function of the blood-brain barrier, neonates are more susceptible to bacterial meningitis than older children. Indeed, data show that almost half of all bacterial meningitis cases occur in the neonatal period (16). With the development of perinatology and neonatology, the incidence of neonatal bacterial meningitis, especially early-onset infection, has declined in recent years, but the trends of different pathogens are inconsistent (13,17). Moreover, the pathogen distribution of neonatal bacterial meningitis reported in different countries also differs. In this study, the distribution characteristics and

Table 2 Differences of pathogen distribution between preterm and full-term infants, early-onset and late-onset infection

Pathogens	Infants, n (%)			Infection, n (%)		
	Preterm (N=72)	Term (N=159)	P value*	Early-onset (N=48)	Late-onset (N=183)	P value**
Gram-positive bacteria	21 (29.2)	78 (49.1)	0.005	30 (62.5)	69 (37.7)	0.002
Group B Streptococcus	2 (2.8)	49 (30.8)	0.000	14 (29.2)	37 (20.2)	0.183
Enterococcus faecalis/faecium	7 (9.7)	11 (6.9)	0.461	6 (12.5)	12 (6.6)	0.222
Coagulase-negative staphylococci	4 (5.6)	9 (5.7)	1.000	4 (8.3)	9 (4.9)	0.478
Listeria monocytogenes	4 (5.6)	3 (1.9)	0.208	4 (8.3)	3 (1.6)	0.036
Other Gram-positive bacteria[†]	4 (5.6)	6 (3.8)	–	2 (4.2)	8 (4.4)	–
Gram-negative bacteria	51 (70.8)	81 (50.9)	0.005	18 (37.5)	114 (62.3)	0.002
Escherichia coli	28 (38.9)	62 (39.0)	0.988	13 (27.1)	77 (42.1)	0.058
Klebsiella pneumoniae	12 (16.7)	3 (1.9)	0.000	3 (6.3)	12 (6.6)	1.000
Enterobacter cloacae	4 (5.6)	1 (0.6)	0.034	0	5 (2.7)	0.586
Other Gram-negative bacteria[†]	7 (9.7)	15 (9.4)	–	2 (4.2)	20 (10.9)	–

[†], the total of other Gram-positive or Gram-negative bacteria was not calculated; –, no information. *, P value shows the differences of pathogen distribution between preterm and full-term infants; Fisher's exact test for *Coagulase-negative staphylococci, Listeria monocytogenes*, *Klebsiella pneumoniae*, *Enterobacter cloacae*; Chi-square test for the other categorical variables. **, P value shows the differences of pathogen distribution between early-onset and late-onset infection; Fisher's exact test for *Enterococcus faecalis/faecium*, *Coagulase-negative staphylococci*, *Listeria monocytogenes*, *Klebsiella pneumoniae*, *Enterobacter cloacae*; Chi-square test for the other categorical variables.

Table 3 *In vitro* antimicrobial susceptibility testing of common pathogens

Antibiotics	*Escherichia coli* (N=48), n/N (%)	*Group B Streptococcus* (N=28), n/N (%)	*Listeria monocytogenes* (N=5), n/N (%)	*Enterococcus faecalis/faecium* (N=13), n/N (%)	*Coagulase-negative staphylococci* (N=6), n/N (%)	*Klebsiella pneumoniae* (N=10), n/N (%)
Penicillin	–	28/28 (100.0)	5/5 (100.0)	–	1/6 (16.7)	–
Ampicillin	–	–	–	5/13 (38.5)	–	–
Ampicillin/sulbactam	16/46 (34.8)	–	5/5 (100.0)	–	2/5 (40.0)	1/10 (10.0)
Piperacillin/tazobactam	45/46 (97.8)	–	–	–	–	5/10 (50.0)
Clindamycin	–	8/24 (33.3)	1/5 (20.0)	–	1/4 (25.0)	–
Gentamicin	27/45 (60.0)	–	5/5 (100.0)	7/12 (58.3)	3/6 (50.0)	9/10 (90.0)
Ciprofloxacin	28/46 (60.9)	–	–	1/12 (8.3)	–	4/8 (50.0)
Levofloxacin	–	22/24 (91.7)	4/5 (80.0)	7/13 (53.8)	–	–
Cefuroxime	24/45 (53.3)	28/28 (100.0)	2/5 (40.0)	–	2/5 (40.0)	1/10 (10.0)
Cefotaxime	22/39 (56.4)	28/28 (100.0)	–	–	–	1/9 (11.1)
Ceftazidime	33/46 (71.7)	–	–	–	–	3/10 (30.0)
Cefoperazone/sulbactam	42/46 (91.3)	–	–	–	–	4/10 (40.0)
Cefepime	43/48 (89.6)	–	–	–	–	4/10 (40.0)
Vancomycin	–	28/28 (100.0)	5/5 (100.0)	13/13 (100.0)	5/5 (100.0)	–
Linezolid	–	28/28 (100.0)	5/5 (100.0)	13/13 (100.0)	5/5 (100.0)	–
Meropenem	48/48 (100.0)	28/28 (100.0)	–	–	–	7/10 (70.0)

–, no information, this antibiotic has not been tested for sensitivity to this drug.

Table 4 Differences of pathogen distribution between the two epochs

Pathogens	First epoch [2009–2014], (N=110), n (%)	Second epoch [2015–2020], (N=121), n (%)	P value
Escherichia coli	34 (30.9)	56 (46.3)	0.017
Group B Streptococcus	15 (13.6)	36 (29.8)	0.003
Enterococcus faecalis/faecium	14 (12.7)	4 (3.3)	0.008
Klebsiella pneumoniae	8 (7.3)	7 (5.8)	0.647
Coagulase-negative staphylococci	8 (7.3)	5 (4.1)	0.301
Listeria monocytogenes	4 (3.6)	3 (2.5)	0.711*

*, Fisher's exact test for *Listeria monocytogenes*.

Table 5 Differences of *Escherichia coli* and *Group B Streptococcus* between the two epochs

Pathogens	Early-onset infection, n (%)			Late-onset infection, n (%)		
	First epoch [2009–2014], (N=27)	Second epoch [2015–2020], (N=21)	P value	First epoch [2009–2014], (N=83)	Second epoch [2015–2020], (N=100)	P value
Escherichia coli	7 (25.9)	6 (28.6)	0.838	27 (32.5)	50 (50.0)	0.017
Group B Streptococcus	4 (14.8)	10 (47.6)	0.013	11 (13.3)	26 (26.0)	0.033

change trends of pathogens in neonatal bacterial meningitis in our hospital during the last 12 years were retrospectively analyzed.

Among 231 patients, we found that the most common bacteria were *E. coli* (39.0%) and GBS (22.1%). *E. coli* was the predominant bacterium among cases of neonatal bacterial meningitis, which was different from studies in developed countries. For example, *GBS* is the most common bacterium in developed countries, accounting for 52% of cases from the United Kingdom (≤90 days of age) (18), 59% of cases from France (≤28 days of age) (19), 31% of cases from Canada (<90 days of age) (20), and 39% of cases from Japan (<90 days of age) (21). However, current studies in China on the pathogen distribution of neonatal bacterial meningitis are inconsistent among hospitals. Most studies have found *E. coli* and *CONS* to predominate (22,23). Moreover, rates of *GBS* colonization in pregnant women vary by region, with a low prevalence of *GBS* in China (24-26). Additionally, *Klebsiella pneumoniae* and *Enterobacter cloacae*, which usually cause nosocomial infections (27,28), were more common in preterm infants in our study. Due to their immature development, longer hospital stays and higher likelihood of exposure to invasive mechanical ventilation and central venous catheters, preterm infants are more likely to have nosocomial infections than term infants. Onset age was associated with the bacterial epidemiology of neonatal meningitis. *E. coli* was more common in late-onset meningitis than in early-onset meningitis, while there was no statistically significant difference. *Listeria monocytogenes* was more frequent in early-onset than in late-onset meningitis. In developed countries, *Listeria monocytogenes* is the third most common pathogen responsible for neonatal bacterial meningitis, second only to *GBS* and *E. coli* (29), but the incidence of *Listeria monocytogenes* meningitis is not high in China. Pregnant women are infected by *Listeria monocytogenes* mainly through contaminated food (30), and *Listeria monocytogenes* can transfer through the placenta or be acquired from the vaginal tract during birth, mainly causing early-onset infection in neonates (31).

Our analysis of antibiotic susceptibility revealed that third-generation cephalosporins can be used for the treatment of *E. coli* meningitis. When these drugs are ineffective, they should be replaced with fourth-generation cephalosporins or carbapenem antibiotics as soon as possible. In our study, penicillin was still the first choice for the treatment of *GBS* meningitis. *Enterococcus*, *CONS* and *Klebsiella pneumoniae*, which are common pathogens of nosocomial infections, displayed a high rate of resistance to most antibiotics. In recent years, the increase in the detection rate of carbapenem-resistant *Klebsiella pneumonia* has brought severe challenges to clinical treatment worldwide (32); many experts consider that the combination of carbapenems and

other antibiotics is an effective treatment for carbapenem-resistant *Klebsiella pneumoniae* (33).

Pathogen distribution changes over time, as do numerous other factors, including prenatal maternal vaginal bacterial screening, application of prevention and treatment measures, preterm birth rates, mutation of bacterial species, and improvement in detection methods. In our study, infection by both *GBS* and *E. coli* increased significantly in the second epoch, whereas *Enterococcus* decreased significantly in this epoch. Nonetheless, the causes of these changes are unclear. Changes in *GBS* and *E. coli* infections may be related to the increase in vaginal delivery in our study, leading to an increased chance of infection by bacteria colonizing the mother's vagina. In our study, there was an obvious increase in the proportion of *GBS* meningitis in the second epoch, either for early-onset or late-onset infection. In general, preventive measures and recommendations have a significant impact on the incidence of *GBS* infection, mainly leading to a decrease in early-onset infection in many countries (2,4,5). *GBS* prenatal screening and intrapartum antibiotic prophylaxis have also increased, and national guidelines of prevention have been issued in the United States and Europe since the 1990s. In China, however, screening and prevention programs have not been implemented nationwide, which may have led to the increase in *GBS* infection in this country. In addition, some studies have shown that the increase in antibiotic resistance leads to an increase in *GBS* infection rates (6,7). In our study, however, all cases of *GBS* infection were sensitive to penicillin, cefuroxime, cefotaxime, vancomycin, and linezolid, with no difference between the two epochs. Furthermore, we speculate that such an increase may also result from an increase in the detection rate of bacteria due to the improvement of detection technology over the past 12 years.

In our study, *E. coli* meningitis also increased from 30.9% in 2009–2014 to 46.3% in 2015–2020, consistent with investigations in the Netherlands and Taiwan (6,16). A significant increase in late-onset infection, not in early-onset infection, was noted during the second epoch. The causes of this increase may also be associated with a decrease in antibiotic susceptibility, mutations in bacteria, and increased bacterial detection, among others. Regardless, our research showed that the sensitivity to third-generation cephalosporins increased during the second epoch, which may be related to the rational application of antibiotics in our hospital in recent years. Therefore, the causes of observed changes remain unclear. In contrast, *Enterococcus* infection decreased significantly in the second epoch. With the application of the improved quality program in our hospital in recent years, the incidence of nosocomial infections has gradually decreased (34,35). Nevertheless, further research is needed to explore the causes of pathogen distribution changes.

To our knowledge, this is the largest single-center study of neonatal bacterial meningitis regarding the pathogen distribution and change trends over the past 12 years in China. This study provides valuable data for understanding the pathogenic epidemiology and changes of neonatal bacterial meningitis in China. However, because our study is retrospective, some records of clinical data were incomplete, for example, the incidence of maternal chorioamnionitis, maternal *GBS* status, maternal prenatal use of antibiotics, antibiotic susceptibility tests for some patients transferred from other hospitals, and whether CSF was obtained before or after antibiotics use. In the future, we will conduct further prospective multicenter studies to investigate the epidemiology of neonatal bacterial meningitis in China.

Conclusions

In summary, this study investigated the distribution characteristics and change trends of pathogens in our hospital over the last 12 years. It is very helpful to choose antibiotics empirically, which can reduce the development of drug-resistant bacteria and improve the clinical outcomes of patients. *GBS* and *E. coli* were the most common pathogens associated with neonatal bacterial meningitis in our hospital, and both have exhibited an upward trend over the past 12 years. The causes of the changes in pathogen distribution need to be explored by further research. Standardized prenatal *GBS* screening and prevention, early detection of pathogens, and rational application of antibiotics are very important for decreasing morbidity and mortality in neonatal bacterial meningitis.

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Footnote

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Ethics Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by The Ethics Committee of the Children's Hospital of Fudan University [Ethics approval No. (2019)314] and individual consent for this retrospective analysis was waived.

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Supplementary

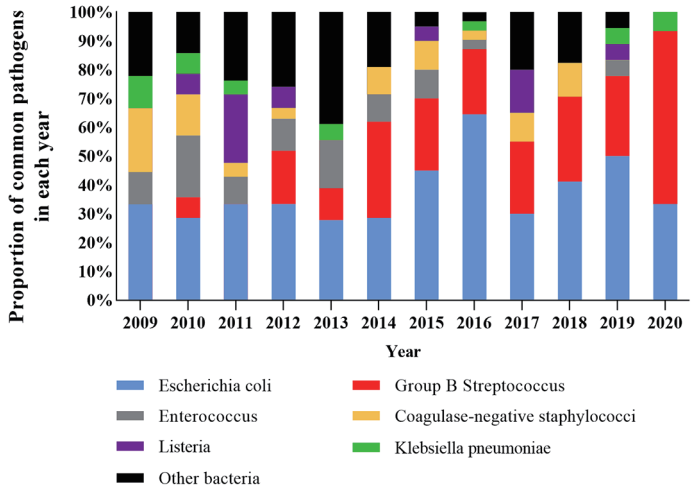

Figure S1 Proportion of common pathogens in each year

Table S1 Differences of antibiotic susceptibility of *Escherichia coli* in late-onset infection between the two epochs

	First epoch (2009–2014), (N=20), n/N (%)	Second epoch (2015–2020), (N=21), n/N (%)	P value
Ampicillin/Sulbactam	6/20 (30.0)	8/19 (42.1)	0.431
Piperacillin/Tazobactam	19/20 (95.0)	19/19 (100.0)	1.000*
Gentamicin	12/20 (60.0)	12/18 (66.7)	0.671
Ciprofloxacin	14/20 (70.0)	11/19 (57.9)	0.431
Cefuroxime	7/20 (35.0)	14/18 (77.8)	0.008
Cefotaxime	7/20 (35.0)	12/13 (92.3)	0.001
Ceftazidime	10/20 (50.0)	17/19 (89.5)	0.008
Cefoperazone/Sulbactam	17/20 (85.0)	19/19 (100.0)	0.231*
Cefepime	16/20 (80.0)	20/21 (95.2)	0.184*

* Fisher's exact test for Piperacillin/Tazobactam, Cefoperazone/Sulbactam, Cefepime.

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