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Pathogen Distribution of Neonatal Bacterial Meningitis in the Era of Multidrug-Resistant Bacteria: A Single-Center Experience

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Purpose: Neonatal bacterial meningitis (NBM) is a serious disease with high morbidity and mortality. This study aimed to establish a foundation for the selection of empirical antibiotics for NBM through an analysis of pathogen distribution and shift in antimicrobial resistant pattern.

Patients and Methods: A retrospective cohort study on culture confirmed NBM from 2005 to 2022.

Results: A total of 191 cases were enrolled, 48 for premature infants and 70 for early-onset meningitis. The incidence of NBM in first half and last half period was 0.2‰ and 0.24‰, while the mortality was 12.0% and 5.6% respectively. The top two pathogens were *Escherichia coli* (*E. coli*) (40.3%) and *Group B Streptococcus* (GBS) (29.8%). *E. coli* was the most common pathogen in both periods, *Enterococcus* (13.3% vs 0.9%, $P < 0.05$) and *Staphylococcus aureus* (8.4% vs 1.9%, $P < 0.05$) decreased, while GBS increased significantly in the periods [16.9% vs 39.8%, $P < 0.001$]. Gram-positive bacteria were more common in full term infants (53.8% vs 27.1%, $P = 0.001$), while gram-negative bacteria were more common in preterm infants (72.9% vs 46.2%, $P = 0.001$). All isolated GBS strains were susceptible to penicillin. On the other hand, less than 60% of *E. coli* were susceptible to third generation of cephalosporins, and were only susceptible to carbapenem or amikacin. This was mainly due to production of extended-spectrum beta-lactamase (ESBLs) which was higher in late-onset group than that in early-onset group (45.1% vs 19.2%, $P = 0.026$).

Conclusion: Incidence of NBM has not changed significantly over the last 2 decades. *E. coli* remains as the most common pathogen of NBM despite that GBS has increased in recent 9 years, especially in full-term infants. While all isolated GBS are susceptible to penicillin, over a third of *E. coli* strains are multidrug resistant due to production of ESBLs.

Keywords: infant, newborn, bacteria, meningitis, pathogen, drug resistance

Introduction

Neonatal bacterial meningitis (NBM) is a serious infectious disease associated with high mortality and morbidity rates in newborn infants. The incidence of culture-confirmed NBM is estimated at 0.3 per 1000 live births, with potentially higher numbers in developing countries.[1] Despite advances in neonatal intensive care, the mortality of NBM remains high. Furthermore, a significant number of NBM survivors have long-term neurological sequelae such as hearing loss, blindness, epilepsy, and even cerebral palsy,[1–3] which places substantial psychological and socioeconomic burdens on families and society. Prompt diagnosis and treatment are essential to achieving good outcomes in affected infants.

Selection of the appropriate initial empiric antibiotics is based mainly on the sensitivity patterns of the most common pathogenic organisms in NBM. For several decades, group B *Streptococcus* (GBS), *Escherichia coli* (*E. coli*), and *Listeria* have been among the common microbes responsible for NBM in developed countries.[4–6] In developing countries, *E. coli* is usually the most common pathogen for NBM.[7,8] In eastern Asia, GBS and *E. coli* are also reported

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as the most common microbes responsible for NBM.[9–11] Moreover, pathogen distribution may change over time and vary among different populations. Very few studies on NBM epidemiology or pathogen changes over time have been published, especially in low- and middle-income regions where multidrug-resistant bacteria have become epidemic. This is the case in China, in which dramatic socioeconomic changes have occurred in the last two decades due to industrialization. Our recent studies have shown that approximately 50% of all *E. coli* bloodstream isolates from the neonatal intensive care unit (NICU) are now multidrug-resistant due to extended-spectrum beta-lactamase (ESBL) production.[12,13] Therefore, the present study aimed to investigate the epidemiology, changes in pathogen distribution, and antimicrobial resistance patterns of NBM in a tertiary NICU in China to inform empirical antibiotic guidance in the era of multidrug-resistant bacteria.

Materials and Methods

Study Population

The medical records of all newborn infants admitted to the NICU of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University between 2005 and 2022 were screened. Cases with a medical diagnosis of meningitis were carefully reviewed, and those that met the following selection criteria were included in this retrospective cohort study.

Inclusion Criteria (All Four Had to Be Met)

1. Onset of disease within 28 days of birth for term infants or 44 weeks of corrected postmenstrual age for premature infants.
2. Clinical signs of infection were present, and spinal tap for suspected meningitis was performed.
3. Results of cerebrospinal fluid (CSF) examination met the diagnostic criteria for meningitis, defined as a white blood cell count > 20×10^6 /L in the CSF.[14]
4. Bacterial pathogens were isolated from either blood or CSF culture.

Exclusion Criteria

1. Contamination was identified, such as isolation of any *coagulase negative staphylococci* (CoNS).
2. Presence of congenital malformations of the nervous system or known genetic metabolic disorders.
3. History of previous neurosurgical procedures.

Bacterial Identification and Antimicrobial Susceptibility Testing

The clinical laboratory at our hospital employs routine microbiological tests according to the standards set by the Clinical & Laboratory Standards Institute (CLSI).[15] Bacteria were identified using a matrix-assisted laser desorption/ionization-time-of-flight mass spectrometer (Brück, Germany). Bacterial drug-susceptibility testing was conducted using the VITEK 2 Compact automated drug-susceptibility analyzer (bioMérieux, Marcy-l'Étoile, France) or disk diffusion method (British OXOID). The Gram-negative Susceptibility card (bioMérieux) was utilized to determine the antibiotic susceptibility of Gram-negative bacterial isolates. Additionally, ESBL-producing strains were identified using the double-disk synergy method.[16] Results were interpreted following the recommendations and definitions of the CLSI.

Data Collection and Statistical Analysis

Demographics, clinical characteristics, and outcomes were obtained from the hospital medical records. To calculate the incidence of NBM, data on the total number of live births in the hospital during the two time periods were also collected. Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Normally distributed data are presented as the mean ± standard deviation and were analyzed using a Student's *t*-test. Non-normally distributed data are described as median (25–75 percentile) and were assessed using the Mann–Whitney *U*-test. Categorical variables were compared using chi-square or Fisher's exact tests. The incidences of NBM were calculated by dividing the number of inborn infants with culture-confirmed NBM by the number of live births at the hospitals. The significance level was set at

$P < 0.05$. All statistical analyses and graph creation were performed using SPSS 27.0 (IBM, Armonk, NY, USA) and GraphPad Prism (GraphPad, La Jolla, CA, USA), respectively.

The study protocol was approved by the Institutional Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (protocol code 2021-K-371-01). The committee waived the need for patient parental consent to review medical records. The handling of patient data confidentiality strictly followed the institutional rules, and the study procedures complied with the Declaration of Helsinki.

Results

Basic Demographic and Clinical Characteristics of Neonates with NBM

Between 2005 and 2022, 52,700 newborns were admitted to the NICU of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University Hospital, of which 553 were clinically diagnosed with meningitis based on spinal tap results. Of the 553 meningitis cases, 208 were culture-confirmed NBM. After careful review, 17 patients were excluded (2 cases of congenital neural tube defects, 1 case of infection after Ommaya capsule implantation, and 14 cases with CoNS in blood culture). The remaining 191 cases were included in the analysis, as shown in the flow diagram in Figure 1.

Cases were arbitrarily divided into two epochs of 9 years each (2005–2013 and 2014–2022) for analysis. There were 83 culture-confirmed NBM cases in the first period and 108 in the second. The demographic and clinical characteristics of the neonates with NBM were not statistically different between the two epochs (Table 1). Most cases were full-term infants, with approximately one-third of these classified as early-onset NBM which was defined as infection occurring within 1 week of life.

We calculated the incidence of NBM based on inborn infants only, since most cases were transferred from other hospitals. Of the 191 total cases, 31 infants were inborn, with 11 and 20 cases in the two epochs, respectively. The numbers of live births in the study hospital in these periods were 54,938 and 84,325, respectively. Therefore, the overall incidence of NBM for inborn infants was 0.22 per 1000 live births (0.22‰), and the rate increased slightly from 0.20‰ in the first period to 0.24‰ in the second. Sixteen patients died in the hospital, resulting in a mortality rate of 8.4%. Although the mortality of NBM decreased from 12% in the first period to 5.6% in the second, this difference was not statistically significant.

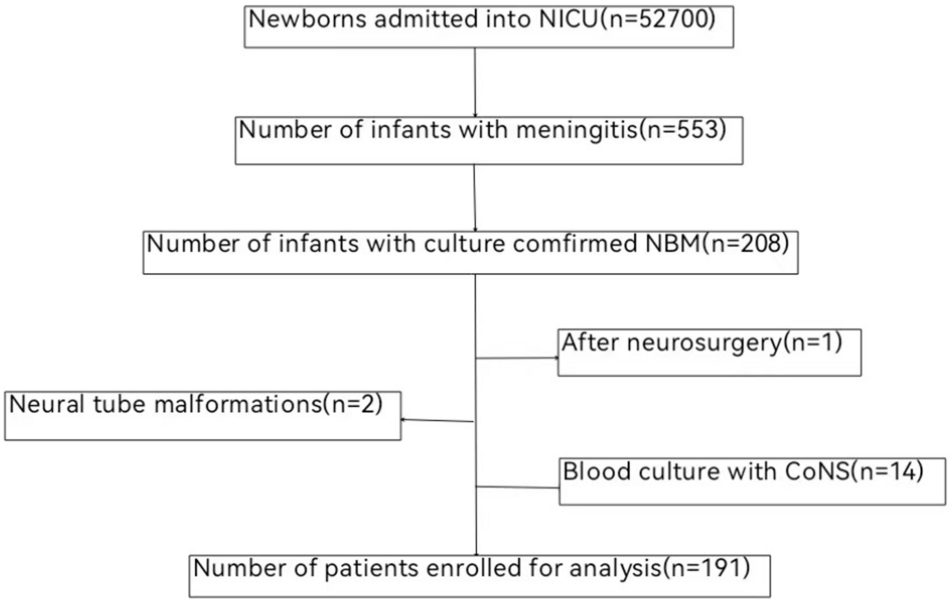

Figure 1 Screening flowchart of research subjects.

Table 1 The Basic Clinical Characteristics of the Neonates with NBM

	2005–2013 (n =83)	2014–2022 (n =108)
Male gender	47 (56.6%)	57 (52.8%)
Gestational age (w), M (IQR)#	39.0 (37.0–40.0)	38.4 (36.7–39.6)
<37 w	20 (24.1%)	28 (25.9%)
Birth weight (kg), M (IQR)	3.10 (2.40–3.50)	3.14 (2.52–3.50)
<2.50 kg	22 (26.5%)	28 (25.9%)
Vaginal delivery	59 (71.7%)	78 (72.2%)
Inborn	11 (13.3%)	20 (18.5%)
Incidence of NBM	11/54,938 (0.20‰)	20/84,325 (0.24‰)
Early onset	30 (36.1%)	40 (37.0%)
Mortality	10 (12.0%)	6 (5.6%)

Note: #IQR: interquartile range.

Pathogen Distribution of NBM

Table 2 shows the main pathogen distribution of NBM based on culture results. Among the 191 children with culture-confirmed NBM, 75 had positive CSF cultures, while 166 had positive blood cultures. Furthermore, 50 cases were positive for the same bacterial pathogen in both CSF and blood cultures. We identified 90 cases of Gram-positive bacteria and 101 of Gram-negative bacteria. The top five pathogens were *E. coli* (40.3%), GBS (29.8%), *Enterococcus* (6.3%), *Staphylococcus aureus* (4.7%) and *Klebsiella pneumonia* (4.2%). Additionally, 16 cases of other Gram-negative bacilli and 12 of other Gram-positive bacteria were observed. Notably, although we had seven cases of *Listeria* bacteremia in our NICU during the study period, none of these met our inclusion criteria for NBM cases.

Table 3 illustrates the comparison of early-onset and late-onset NBM pathogens. The proportion of early-onset non-GBS streptococcus was higher than that of late-onset streptococcus (8.6% vs 0.8%, $P < 0.05$), and there was no significant difference among other pathogens. Regarding differences in pathogen distribution between term and preterm infants, Gram-negative bacteria were more common in premature infants (72.9% vs 46.2%, $P = 0.001$), with *Klebsiella pneumonia* more often seen in preterm patients (12.5% vs 1.4%, $P = 0.004$). Conversely, Gram-positive bacteria occurred more frequently in full-term infants (53.8% vs 27.1%, $P = 0.001$), with GBS as the leading pathogen in term infants (36.4%) (Table 4). Furthermore, as shown in Table 5, the proportion of GBS increased in the second epoch (16.9% vs 39.8%, $P < 0.001$), whereas those of *enterococci* and *Staphylococcus aureus* decreased significantly (13.3% vs 0.9%, $P < 0.001$; 8.4% vs 1.9%, $P = 0.042$).

Table 2 Pathogen Distribution of NBM (2005–2022) [n (%)]

Pathogens	Blood n=166	CSF n=75	Blood & CSF n=50	Total n=191
Gram-negative bacterium	90 (54.2)	32 (42.7)	21 (42.0)	101 (52.9)
E. coli	71 (42.8)	24 (32.0)	18 (36.0)	77 (40.3)
Klebsiella pneumonia	8 (4.8)	0	0	8 (4.2)
Other *enterobacteriaceae**	4 (2.4)	4 (5.3)	1 (2.0)	7 (3.7)
Miscellaneous	7 (4.2)	4 (5.3)	2 (4.0)	9 (4.7)
Gram-positive bacterium	76 (45.8)	43 (57.3)	29 (58.0)	90 (47.1)
GBS	47 (28.3)	36 (48.0)	26 (52.0)	57 (29.8)
*Enterococcus***	11 (6.6)	1 (1.3)	0	12 (6.3)
Staphylococcus aureus	9 (5.4)	1 (1.3)	1 (2.0)	9 (4.7)
Other *streptococci****	5 (3.0)	3(4.0)	1 (2.0)	7 (3.7)
Miscellaneous	4 (2.4)	2 (2.7)	1 (2.0)	5 (2.6)

Notes: *: *Enterobacter cloacae* (2), *Salmonella esseni* (1), *Proteus mirabilis* (1), *Enterobacter hodginsii* (1), *Serratia marcescens* (1), *other Enterobacter* (1). **: *Enterococcus faecalis* (5), *Enterococcus faecium* (5), *Enterococcus avium* (1), *Enterococcus casei* (1). ***: *Streptococcus bovis* (3), *Streptococcus avium* (1), *Streptococcus constellatus* (1), *Streptococcus non-lactose* (1), *Streptococcus pyogenes* (1).

Table 3 Pathogen Distribution of Early-Onset and Late-Onset NBM [n (%)]

Pathogens	Early-onset* N=70	Late-onset N=121	χ^2	*P*
Gram-negative bacterium	38 (54.3)	63 (52.1)		
E. coli	26 (37.1)	51 (42.1)		
Klebsiella pneumonia	4 (5.7)	4 (3.3)		
Other *enterobacteriaceae*	4 (5.7)	3 (2.5)		
Others	4 (5.7)	5 (4.1)		
Gram-positive bacterium	32 (45.7)	58 (47.9)		
GBS	21 (30.0)	36 (29.8)		
Enterococcus	2 (2.9)	10 (8.3)		
Staphylococcus aureus	2 (2.9)	7 (5.8)		
Other *streptococci*	6 (8.6)	1 (0.8)**		0.01
Others	1 (1.4)	4 (3.3)		

Notes: *: Infection occurs within 7 days after birth. **: Fisher Exact probability method.

Table 4 Pathogen Distribution of NBM in Term and Preterm Infants [n (%)]

Pathogens	< 37 weeks n=48	≥37 weeks n=143	χ^2	*P*
Gram-negative bacterium	35 (72.9)	66 (46.2)	10.33	0.001
E. coli	23 (47.9)	54 (37.8)		
Klebsiella pneumonia	6 (12.5)	2 (1.4)*		0.004
Other *enterobacteriaceae*	4 (8.3)	3 (2.1)		
Miscellaneous	2 (4.2)	7 (4.9)		
Gram-positive bacterium	13 (27.1)	77 (53.8)	10.33	0.001
GBS	5 (10.4)	52 (36.4)	11.56	<0.001
Enterococcus	3 (6.3)	9 (6.3)		
Staphylococcus aureus	4 (8.3)	5 (3.5)		
Other *streptococci*	1 (2.1)	6 (4.2)		
Miscellaneous	0 (0.0)	5 (3.5)		

Note: *: Fisher Exact probability method.

Table 5 Pathogen Distribution of NBM in Two Stages [n (%)]

Pathogens	2005–2013 n=83	2014–2022 n=108	χ^2	*P*
Gram-negative bacterium	44 (53.0)	57 (52.8)		
E. coli	29 (34.9)	48 (44.4)		
Klebsiella pneumonia	4 (4.8)	4 (3.7)		
Other enterobacteriaceae	5 (6.0)	2 (1.9)		
Miscellaneous	6 (7.2)	3 (2.8)		
Gram-positive bacterium	39 (47.0)	51 (47.2)		
GBS	14 (16.9)	43 (39.8)	11.804	<0.01
Enterococcus	11 (13.3)	1 (0.9)	12.112	<0.01
Staphylococcus aureus	7 (8.4)	2 (1.9)*		0.042
Other streptococci	3 (3.6)	4 (3.7)		
Miscellaneous	4 (4.8)	1 (0.9)		

Note: *: Fisher Exact probability method.

Antimicrobial Susceptibility of the Common Pathogens of NBM

The antimicrobial susceptibility of the five most common pathogens for NBM is summarized in Table 6. Almost all isolated GBS strains were susceptible to penicillin or ampicillin, and approximately 20–30% of the isolated enterococci were resistant to penicillin or ampicillin. Seven of the nine cultured strains of *Staphylococcus aureus* were methicillin-resistant (MRSA). However, the isolated Gram-positive bacteria were all susceptible to vancomycin or linezolid. For the two most frequent Gram-negative pathogens, 35.9% of *E. coli* and 87.5% of *Klebsiella pneumonia* were ESBL (+), therefore exhibiting multidrug resistance. Our results indicate that the selection of appropriate antibiotics for Gram-negative NBM was limited; they were all only susceptible to carbapenems and amikacin. Figure 2 shows the results of antibiotic-susceptibility testing on *E. coli* causing NBM for term vs preterm infants. The *E. coli* isolates from premature infants had a slightly greater chance of being more resistant to common antibiotics (Ampicillin: 9.5% vs 33.3%, $P = 0.043$; Cefuroxime: 23.1% vs 62.2%, $P = 0.025$). Further, Figure 3 shows the results of antibiotic-susceptibility testing on *E. coli* for early- vs late-onset NBM. *E. coli* ESBL positivity was significantly higher in the late- than in the early-onset group (19.2% vs 45.1%, $P = 0.026$).

Discussion

Once infected, neonates are more prone to meningitis than any other age group because of their immature blood-brain barrier. The incidence of NBM is estimated at 0.3% of live births, with higher incidences and mortality seen in developing countries and great regional variability.[17–19] Accurately reporting the incidence of NBM in China is difficult due to the lack of monitoring system and corresponding large database. The current study uses data from a tertiary general hospital with many annual newborn deliveries and a level 4 provincial neonatal referral center, enabling us to calculate NBM incidence. We showed that the overall incidence of NBM for inborn infants was 0.22 per 1000 live births, which is similar to that reported in developed countries. We also demonstrated that the incidence of culture-confirmed NBM in our hospital has not changed significantly in the last 18 years. In addition, the mortality of culture-confirmed NBM decreased by approximately half, from 12.0% in 2005–2013 to 5.6% in 2014–2022. However, this difference was not statistically significant.

The diagnosis of NBM is usually complicated by nonspecific clinical manifestations that are similar to neonatal sepsis. Clinicians commonly postpone lumbar puncture until a positive blood culture is obtained. In addition, many

Table 6 Antimicrobial Susceptibility of the Common Pathogens of NBM [n/n (%)]

	GBS	***Enterococcus***	***Staph aureus***	***E. coli***	***Klebsiella pneumonia***
Penicillin	57/57 (100.0)	8/12 (66.7)	0/7 (0.0)		
Ampicillin	24/25 (96.0)	7/9 (77.8)	0/6 (0.0)	19/72 (26.4)	0/8 (0.0)
Clindamycin	6/50 (12.0)		2/9 (22.2)		
SMZ			9/9 (100.0)	30/68 (44.1)	3/6 (50.0)
Gentamicin		6/12 (50.0)	7/7 (100.0)	43/70 (61.4)	6/7 (85.7)
Amikacin				74/74 (100.0)	8/8 (100.0)
Levofloxacin	37/49 (75.5)	8/12 (66.7)	7/9 (77.8)	34/60 (56.7)	2/4 (50.0)
Ciprofloxacin	6/11 (54.5)	6/9 (66.7)	7/8 (87.5)	45/70 (64.3)	5/7 (71.4)
Vancomycin	52/52 (100.0)	12/12 (100.0)	9/9 (100.0)		
Linezolid	48/48 (100.0)	9/9 (100.0)	4/4 (100.0)		
Cefuroxime			0/7 (0.0)	31/58 (53.4)	0/5 (0.0)
Cefotaxime			0/6 (0.0)	32/59 (54.2)	1/6 (16.7)
Cefepime			2/9 (22.2)	52/72 (72.2)	7/8 (87.5)
Imipenem			9/9 (100.0)	77/77 (100.0)	8/8 (100.0)
Ampicillin/sulbactam				17/37 (45.9)	3/6 (50.0)
Piperacillin/tazobactam			7/7 (100.0)	68/70 (97.1)	6/7 (85.7)
Cefoperazone/sulbactam				11/11 (100.0)	1/3 (33.3)
MRSA (+)			7/9 (77.8)		
ESBLs (+)				28/77 (36.4)	7/8 (87.5)

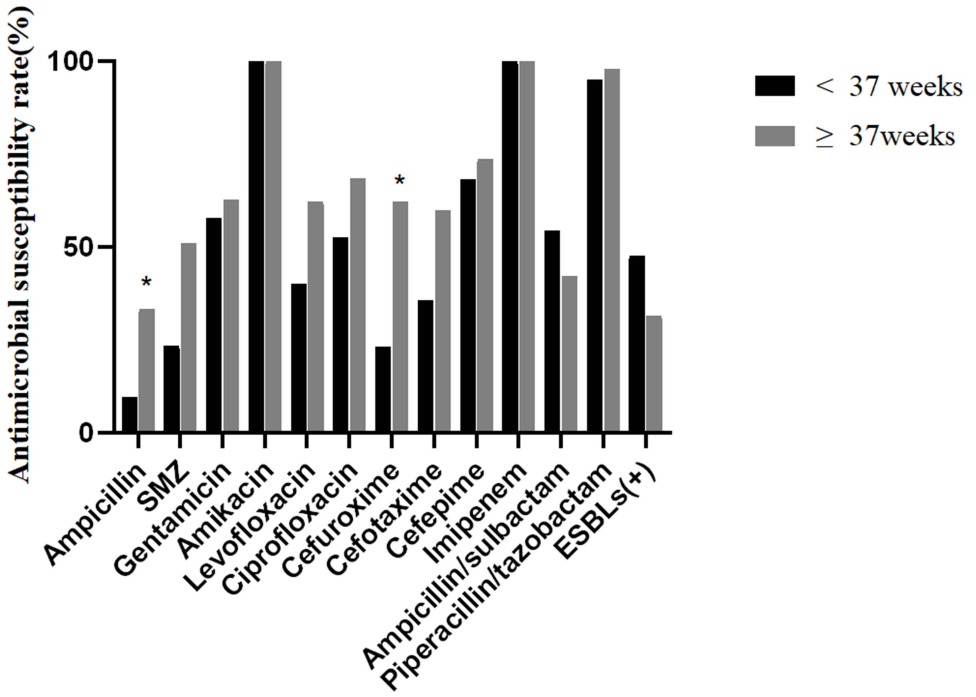

Figure 2 Antimicrobial susceptibility of all isolated *E. coli* from term and preterm infants. *$P < 0.05$.

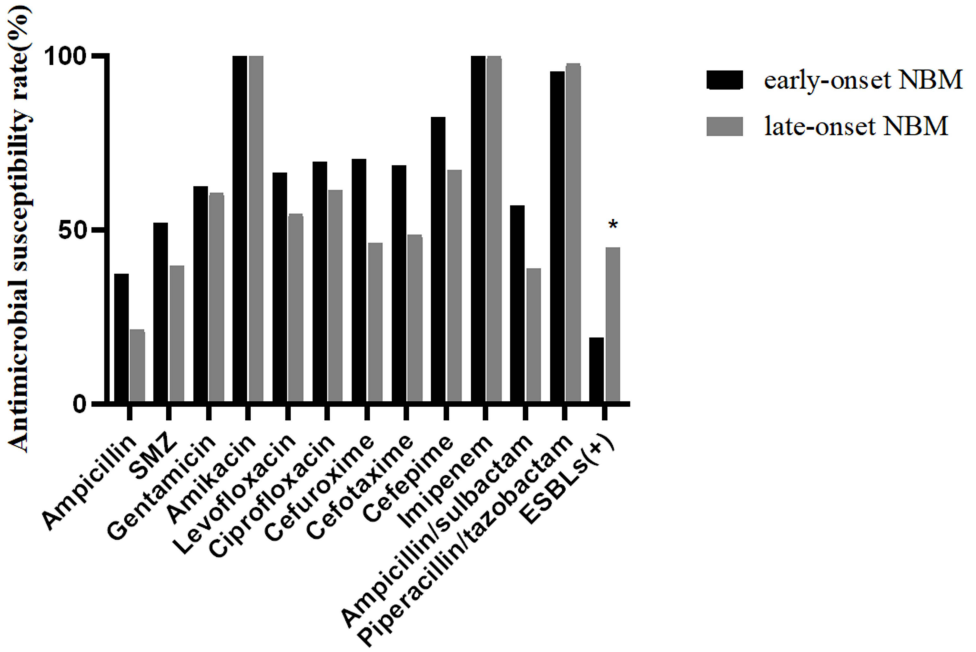

Figure 3 Antimicrobial susceptibility of all isolated *E. coli* from early-onset and late-onset NBM. *$P < 0.05$.

neonates receive antibiotics before the lumbar puncture is performed, potentially decreasing the positive CSF culture yield. Consequently, the detection rate of NBM pathogens in CSF is relatively low.[20,21] In this study, we classified those with CSF cell counts consistent with meningitis and a positive blood or CSF culture as confirmed NBM cases.[14] Our analysis revealed that the top five pathogens for NBM were *E. coli* (40.3%), GBS (29.8%), *Enterococcus* (6.3%), *Staphylococcus aureus* (4.7%), and *Klebsiella pneumonia* (4.2%). *E. coli* remains the most common pathogen for NBM.

While *E. coli* remains the most common pathogen for NBM in developing countries, GBS is the most prevalent in developed countries. In previous reports in China, *E. coli* has always been the most common pathogen for NBM; however, the microbiology of NBM varies geographically.[20–25] The pathogen distribution of NBM might have changed with the rapid industrialization in China in the last two decades. Our study demonstrates that GBS-induced NBM has increased significantly in the last 9 years compared with the previous 9, and has surpassed *E. coli* in both early- and late-onset NBM in full-term infants. At present, GBS and *E. coli* are the two most common pathogens of NBM in our hospital, with the same trend occurring in early-onset neonatal sepsis.[26] The increased incidence of GBS infection seems to have correlated with economic development in the region.

Our data show that meningitis due to Gram-negative enterobacteriaceae such as *E. coli* and *Klebsiella pneumonia* was more common in premature infants, which is consistent with previous reports.[14,27,28] Premature infants are at much higher risk of Gram-negative bacterial infection due to an immature immune system, underdeveloped intestinal barrier, and low diversity of intestinal flora.[29] *Klebsiella pneumonia* is usually reported as the most common Gram-negative pathogen for nosocomial infections in NICU. Longer hospital stays, the presence of central venous lines, higher exposure to mechanical ventilation, and wide use of broad-spectrum antibiotics are typically considered risk factors for nosocomial infections, including late-onset NBM in premature infants.[30]

Regarding antimicrobial susceptibility of the common pathogens, all GBS strains isolated from our region were susceptible to penicillin, while approximately two-thirds of enterococci were susceptible to penicillin. For *Staphylococcus aureus*, most isolated strains were MRSA. All Gram-positive bacteria were sensitive to vancomycin and linezolid, and no vancomycin-resistant enterococci were isolated. Among the Gram-negative bacteria, 36.4% of *E. coli* strains were ESBL positive and therefore multidrug-resistant. The susceptibility rate of *E. coli* to ampicillin and cefuroxime was lower in premature infants, and ESBL positivity was higher in the late-onset group. However, no statistically significant difference in ESBL positivity of *E. coli* strains was identified between the two epochs. In this study, eight cases of meningitis were related to *Klebsiella pneumonia* infection, six of which occurred in premature infants. Almost all *Klebsiella pneumonia* isolates (7/8 strains) were ESBL-positive and multidrug-resistant. These bacteria were only susceptible to carbapenem and amikacin, which is similar to findings in a previous report from China.[13,23] Of note, Antimicrobial resistance is spreading in the neonatal population globally. In recent studies, Gram-negative strains that causing neonatal sepsis were resistant to cephalosporins in up to 84% of cases in low-income and middle-income countries across Africa and Asia.[31,32]

As proposed by us and others,[12,13,23] the abuse of third-generation cephalosporins and other broad-spectrum β-lactam antibiotics may be the primary reason for the extremely high rate of ESBL production in Gram-negative enterobacteriaceae in China. Due to the high rates of ESBL-positive enterobacteriaceae, the abuse of empirical carbapenem antibiotics has resulted in the emergence of plasmid-mediated resistance to carbapenems. Data obtained from the China Antimicrobial Resistance Surveillance Report in 2022 showed that the rate of carbapenem resistance in clinical *E. coli* and *Klebsiella pneumonia* strains in newborns in China was around 1 and 11%, respectively.[33] Fortunately, no Gram-negative pathogens isolated from this cohort were resistant to carbapenems. If the abuse of carbapenems in NICUs continues, we will inevitably see NBM cases caused by carbapenem-resistant enterobacteriaceae.

This study has some limitations. First, it was a retrospective observational cohort study conducted at a single center, there were significant limitations in terms of data collection, including missing or inadequately reported data. Second, while all CoNS were excluded as potential contaminants, some may have represented a true infection, although the numbers were low. Third, as a regional perinatal medical center, many of our NBM cases were transferred from other hospitals, making the calculation of true incidence difficult and the description of clinical characteristics non-comprehensive. Conducting a more representative multi-center study in the future is warranted.

Conclusion

In summary, the incidence of NBM has not changed significantly over the last 2 decades. *E. coli* remains as the most common pathogen of NBM despite that GBS has increased in recent 9 years, especially in full-term infants. While all isolated GBS are susceptible to penicillin, over a third of *E. coli* strains are multidrug resistant due to production of ESBLs.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analysis, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

1. Kohli-Lynch M, Russell NJ, Seale AC, et al. Neurodevelopmental impairment in children after group B streptococcal disease worldwide: systematic review and meta-analyses. *Clin Infect Dis*. 2017;65(suppl_2):S190–s199. doi:10.1093/cid/cix663
2. Horváth-Puhó E, van Kassel MN, Gonçalves BP, et al. Mortality, neurodevelopmental impairments, and economic outcomes after invasive group B streptococcal disease in early infancy in Denmark and the Netherlands: a national matched cohort study. *Lancet Child Adolesc Health*. 2021;5(6):398–407. doi:10.1016/S2352-4642(21)00022-5
3. Haffner DN, Machie M, Hone E, et al. Predictors of neurodevelopmental impairment after neonatal bacterial meningitis. *J Child Neurol*. 2021;36(11):968–973. doi:10.1177/08830738211026053
4. Di Mauro A, Cortese F, Laforgia N, et al. Neonatal bacterial meningitis: a systematic review of European available data. *Minerva Pediatr*. 2019;71(2):201–208. doi:10.23736/S0026-4946.17.05124-6
5. El-Naggar W, Afifi J, McMillan D, et al. Epidemiology of meningitis in Canadian neonatal intensive care units. *Pediatr Infect Dis J*. 2019;38(5):476–480. doi:10.1097/INF.0000000000002247
6. Erickson TA, Munoz FM, Troisi CL, et al. The epidemiology of meningitis in infants under 90 days of age in a large pediatric hospital. *Microorganisms*. 2021;9(3):526. doi:10.3390/microorganisms9030526
7. Furyk JS, Swann O, Molyneux E. Systematic review: neonatal meningitis in the developing world. *Trop Med Int Health*. 2011;16(6):672–679. doi:10.1111/j.1365-3156.2011.02750.x
8. Oordt-Speets AM, Bolijn R, van Hoorn RC, et al. Global etiology of bacterial meningitis: a systematic review and meta-analysis. *PLoS One*. 2018;13(6):e0198772. doi:10.1371/journal.pone.0198772
9. Wong CH, Duque JR, Wong JSC, et al. Epidemiology and trends of infective meningitis in neonates and infants less than 3 months old in Hong Kong. *Int J Infect Dis*. 2021;111:288–294. doi:10.1016/j.ijid.2021.06.025
10. Hsu MH, Hsu JF, Kuo HC, et al. Neurological complications in young infants with acute bacterial meningitis. *Front Neurol*. 2018;9:903. doi:10.3389/fneur.2018.00903
11. Rhie K, Choi EH, Cho EY, et al. Etiology of invasive bacterial infections in immunocompetent children in Korea (2006-2010): a retrospective multicenter study. *J Korean Med Sci*. 2018;33(6):e45. doi:10.3346/jkms.2018.33.e45
12. Zhu M, Wang L, Zhuge Z, et al. Risk factors associated with multi-drug resistance in neonatal sepsis caused by Escherichia coli. *Infect Drug Resist*. 2023;16:2097–2106. doi:10.2147/IDR.S403135
13. Li JY, Chen SQ, Yan YY, et al. Identification and antimicrobial resistance of pathogens in neonatal septicemia in China-A meta-analysis. *Int J Infect Dis*. 2018;71:89–93. doi:10.1016/j.ijid.2018.04.794
14. Kestenbaum LA, Ebberson J, Zorc JJ, et al. Defining cerebrospinal fluid white blood cell count reference values in neonates and young infants. *Pediatrics*. 2010;125(2):257–264. doi:10.1542/peds.2009-1181
15. CLSI, ed. *Performance Standards for Antimicrobial Susceptibility Testing(M100)*. 29th. Wayne, PA, USA: Clinical and Laboratory Standards Institute; 2019.
16. Dong L, Zhang XY, Li CC, et al. Characteristics of epidemiology and antimicrobial resistance of gram-negative bacterial bloodstream infections in children. *Zhonghua Er Ke Za Zhi*. 2017;55(9):683–688. doi:10.3760/cma.j.issn.0578-1310.2017.09.012
17. Ku LC, Boggess KA, Cohen-Wolkowiez M. Bacterial meningitis in infants. *Clin Perinatol*. 2015;42(1):29–45. doi:10.1016/j.clp.2014.10.004
18. Mashau RC, Meiring ST, Dramowski A, et al. Culture-confirmed neonatal bloodstream infections and meningitis in South Africa, 2014-19: a cross-sectional study. *Lancet Glob Health*. 2022;10(8):e1170–e1178. doi:10.1016/S2214-109X(22)00246-7
19. Barichello T, Rocha Catalão CH, Rohlwink UK, et al. Bacterial meningitis in Africa. *Front Neurol*. 2023;14:822575. doi:10.3389/fneur.2023.822575
20. Liu CQ, Liu C-Q; The Collaborative Group For Neonatal Meningitis Study, TC. Epidemiology of neonatal purulent meningitis in Hebei Province, China: a multicenter study. *Zhongguo Dang Dai Er Ke Za Zhi*. 2015;17(5):419–424.

21. Collaborative Study Group for Neonatal Bacterial Meningitis. A multicenter epidemiological study of neonatal bacterial meningitis in parts of South China. *Zhonghua Er Ke Za Zhi*. 2018;56(6):421–428. doi:10.3760/cma.j.issn.0578-1310.2018.06.004
22. Zhao Z, Yu JL, Zhang HB, et al. Five-year multicenter study of clinical tests of neonatal purulent meningitis. *Clin Pediatr*. 2018;57(4):389–397. doi:10.1177/0009922817728699
23. Xu M, Hu L, Huang H, et al. Etiology and clinical features of full-term neonatal bacterial meningitis: a multicenter retrospective cohort study. *Front Pediatr*. 2019;7:31. doi:10.3389/fped.2019.00031
24. Zhu M, Hu Q, Mai J, et al. Analysis of pathogenic bacteria and drug resistance in neonatal purulent meningitis. *Zhonghua Er Ke Za Zhi*. 2015;53(1):51–56.
25. Shen H, Zhu C, Liu X, et al. The etiology of acute meningitis and encephalitis syndromes in a sentinel pediatric hospital, Shenzhen, China. *BMC Infect Dis*. 2019;19(1):560. doi:10.1186/s12879-019-4162-5
26. Zhu M, Jin Y, Duan Y, et al. Multi-drug resistant Escherichia coli causing early-onset neonatal sepsis - a single center experience from China. *Infect Drug Resist*. 2019;12:3695–3702. doi:10.2147/IDR.S229799
27. Gaschignard J, Levy C, Romain O, et al. Neonatal bacterial meningitis: 444 cases in 7 Years. *Pediatr Infect Dis J*. 2011;30(3):212–217. doi:10.1097/INF.0b013e3181fab1e7
28. Zhai Q, Li S, Zhang L, et al. Changes in pathogens of neonatal bacterial meningitis over the past 12 years: a single-center retrospective study. *Transl Pediatr*. 2022;11(10):1595–1603. doi:10.21037/tp-22-103
29. Birchenough GM, Johansson ME, Stabler RA, et al. Altered innate defenses in the neonatal gastrointestinal tract in response to colonization by neuropathogenic Escherichia coli. *Infect Immun*. 2013;81(9):3264–3275. doi:10.1128/IAI.00268-13
30. Wang L, Du KN, Zhao YL, et al. Risk factors of nosocomial infection for infants in neonatal intensive care units: a systematic review and meta-analysis. *Med Sci Monit*. 2019;25:8213–8220. doi:10.12659/MSM.917185
31. Li G, Bielicki JA, Ahmed ASMNU, et al. Towards understanding global patterns of antimicrobial use and resistance in neonatal sepsis: insights from the NeoAMR network. *Arch Dis Child*. 2020;105(1):26–31. doi:10.1136/archdischild-2019-316816
32. Sands K, Carvalho MJ, Portal E, et al. Characterization of antimicrobial-resistant Gram negative bacteria that cause neonatal sepsis in seven low and middle-income countries. *Nat Microbiol*. 2021;6(4):512–523. doi:10.1038/s41564-021-00870-7
33. National monitoring report on bacterial resistance in 2022 (brief edition). China Antimicrobial Resistance Surveillance.