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Original Article

Antibiotic resistance in neonates in China 2012—2019: A multicenter study

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KEYWORDS
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Abstract *Background:* To investigate antibiotic resistance of pathogens responsible for neonatal invasive bacterial infections (IBIs) in China.
Methods: Cross-sectional study of neonates with IBI evaluated in nine hospitals in China (January 2012—August 2019). Antibiotic resistance patterns of pathogens responsible for neonatal IBIs were analyzed.
Results: Of 3770 full-term neonates who were subjected to lumbar puncture and a blood culture, IBIs were diagnosed in 460 neonates (12.2%). *Escherichia coli* and Group B *Streptococcus* (GBS) were the leading pathogens, followed by *Enterococcus* spp, and *Staphylococcus aureus*. *E. coli* expressed high resistance to ampicillin (72.0%) and third-generation cephalosporins (cefotaxime, 34.8%; ceftriaxone, 38.1%). The prevalence of extended spectrum beta-lactamase (ESBL)-producing *E. coli* was 34.1%. The proportions of *E.* spp resistant to penicillin and ampicillin were 60% and 54.1%. All *S. aureus* showed resistance to ampicillin and penicillin. The

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resistance rate of *S. aureus* to methicillin was 50%. Although all GBS were susceptible to penicillin and ampicillin, the proportions of GBS resistant to erythromycin and clindamycin were 75.9% and 77.3%. Antibiotic susceptibility appeared to improve in 2019. Susceptibility of *E. coli* to ampicillin, cefotaxime, and ceftriaxone improved to 42.9%, 76.9%, and 71.4% in 2019, compared with 12.5%, 37.5%, and 50% in 2012. The prevalence of ESBL-producing *E. coli* declined to 20% in 2019, lower than 100% in 2012. Susceptibility of GBS to erythromycin and clindamycin improved from 0% in 2012 to 28.6% and 25% in 2019.

Conclusions: The prevalence of antibiotic resistance is high in neonates in China, although there is a favorable declining trend in recent years.

Introduction

Antibiotic resistance is a serious global public health issue.[1,2] The prevalence of antibiotic resistance is relatively high in China,[3] which may be due to the overuse of antibiotics.[4–6] In China, nearly 70% of inpatients and about 20% of outpatients in hospital settings are prescribed with antibiotics, and both double the WHO's expected rates.[5]

Overuse of antibiotics in children may be more severe than that in adults,[7] since children more often come into contact with pathogens from foods and environment,[8] and children are more vulnerable to infections,[9] which leads to widespread social concern on antibiotic resistance in children. A study on the epidemiology and antibiotic resistance of bacteremia in infants aged 1 week to 3 months in the United States reported that nearly half of all strains of *Escherichia coli* and 86% of *Staphylococcus aureus* are resistant to ampicillin, higher than those reported in adults.[10,11] However, in China, there is a lack of nationwide study data on antibiotic resistance in children.

The emergence of antibiotic resistance threatens our capacity to treat patients with infectious diseases. The proportion of neonatal deaths among the under-five deaths rose from 37% in 1990 to 44% in 2012, and an important cause of death is due to the increasing prevalence of antibiotic resistance in neonatal infections.[12] It is reported that 56,524 neonates die each year from resistance-attributable neonatal sepsis caused by bacteria resistant to first-line antibiotics in India.[13] Thus, antibiotic resistance in neonates is an important issue deserving significant concern, especially in low-income countries where neonatal mortality is high and antibiotic resistance is growing.[14,15]

Therefore, we conducted a large, multicenter investigation on the predominant bacterial pathogens isolated from neonatal invasive bacterial infections (IBIs, comprising bacteremia and/or bacterial meningitis), and antibiotic resistance patterns were evaluated over an 8-year period (2012—2019).

Methods

We identified neonates with IBI evaluated in the neonatal intensive care units (NICUs) of nine hospitals in China, including Xinhua Hospital, Shanghai Children's Medical Center, Children's Hospital of Shanghai, Children's Hospital of Fudan University, the First Affiliated Hospital of Zhengzhou University, the Affiliated Hospital of Southwest Medical University, Children's Hospital of Nanjing Medical University, the Maternal and Child Health Hospital of Jiaxing, and the Affiliated Wuxi Maternal and Child Health Care Hospital of Nanjing Medical University from January 2012 to August 2019. The Medical Ethical Committees of each hospital approved the study and the subsequent data sharing with the coordinating center (Approval number: XHEC-C-2017-084).

Study population

We searched the electronic medical record system at each hospital to identify all neonates who underwent lumbar punctures (LPs) and blood cultures. The eligibility criteria were: 1) previously healthy full-term neonates who underwent LPs and blood cultures; 2) diagnosed infection onset at age $\leq$28 days; 3) no history of severe neurological disease or ventricular drainage; and 4) no traumatic LP [$>1000 \times 10^6$/L red blood cells in cerebrospinal fluid (CSF)]. The investigations including blood cultures and LPs were left to the discretion of the pediatricians. Bacterial cultures in blood and CSF were requested for each patient suspected with invasive infection according to clinical appearance, including unexplained toxic, limp, unresponsive, fever, gray, cyanotic, apnea, weak cry, poorly perfused, grunting, listless, lethargic, seizures, or irritable, and laboratory investigations, including tests for complete blood cell (CBC) parameters and C-reactive protein (CRP) and procalcitonin (PCT) levels. The methods including bacteria culture and antimicrobial susceptibility test were consistent in all the hospitals.

Data collection

For each eligible neonate, we recorded the following data: demographic information (sex, age, mode of delivery, and birth weight), medical history, clinical symptoms, signs, laboratory data (CBC parameters, PCT, and CRP), bacterial culture results (blood and CSF), and antimicrobial susceptibilities.

Pathogens surveillance

Bacteremia and bacterial meningitis were defined as the growth of a single pathogen in blood and CSF cultures, respectively. We recorded bacterial culture results in blood and CSF. Organisms, including coagulase-negative staphylococci, *Bacillus* non-*cereus*/non-*anthracis*, *Lactobacillus*, diphtheroids, viridans group streptococci, and *Micrococcus*, were classified as contaminants.[10,16] We defined early-onset neonatal IBIs as infections in neonates within 7 days of birth.[17–19]

Antimicrobial susceptibility test

Antimicrobial susceptibility testing was carried out according to a unified protocol using Kirby Bauer method or automated Systems. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of an antibiotic that inhibited the growth of bacteria. The interpretation criteria were in accordance with the Clinical and Laboratory Standards Institute to define resistance, intermediate resistance, or susceptibility to an antibiotic.[20] Resistant and intermediate resistant categories were combined. Extended spectrum beta-lactamase (ESBL) identification was performed by the double disk synergy test as described by the Clinical and Laboratory Standards Institute.[20]

Statistical analyses

We calculated the frequency for categorical variables and mean and standard deviation for continuous variables. The proportions of categorical variables between bacteremia without meningitis group and bacterial meningitis group (bacterial meningitis with or without bacteremia) were compared by Chisq test. The means of continuous variables between bacteremia without meningitis group and bacterial meningitis group (bacterial meningitis with or without bacteremia) were compared by t-test. Statistical analyses were conducted using SPSS software (version 16.0).

Results

Main demographic and clinical characteristics of the neonates with IBIs

During the 8-year study reference period, 3770 neonates were included (Fig. 1), and IBIs were diagnosed in 460 neonates (12.2%), including 343 with bacteremia without meningitis, and 117 with bacterial meningitis (bacterial meningitis with or without bacteremia). The characteristics of the neonates with IBI (including early-onset and late-onset IBIs) are presented in Table 1.

The comparison of the characters between bacteremia without meningitis group and bacterial meningitis group (bacterial meningitis with or without bacteremia) was shown in Supplementary Table1. Fever, lethargy, and poor feeding were more common in neonates with bacterial meningitis. The percentage of fever, lethargy, and poor feeding in neonates with bacterial meningitis (84.6%, 41.0%, and 40.2%) was higher than that in neonates with bacteremia without meningitis (68.2%, 26.5%, and 24.5%). P value was <0.05.

Pathogens

The proportions of *E. coli*, Group B *Streptococcus* (GBS), *Enterococcus* spp, and *S. aureus* IBI remained stable from 2012 to 2019. In the 460 IBI cases, *E. coli* (n = 166, 36.1%) and GBS (n = 148, 32.2%) were the leading pathogens, followed by *E.* spp (n = 46, 10.0%), and *S. aureus* (n = 29, 6.3%) (Fig. 2A). In the 177 early-onset IBI cases, *E. coli* accounted for 47 cases (26.6%), GBS accounted for 65 cases (36.7%), *S. aureus* accounted for 17 cases (9.6%), and *E.* spp accounted for 13 cases (7.3%). Early-onset GBS infection was found to be more likely in bacterial meningitis, and GBS accounted for 16 cases (50%) in bacterial meningitis cases (Fig. 2B). In the 283 late-onset IBI cases, *E. coli* accounted for 119 cases (42.0%), GBS accounted for 83 cases (29.3%), *E.* spp accounted for 33 cases (11.7%), and *S. aureus* accounted for 12 cases (4.2%) (Fig. 2C).

Antibiotic resistance

Overall, antibiotic resistance of leading pathogens was common. The proportions of *E. coli* resistant to ampicillin, gentamicin, cefotaxime, and ceftriaxone were 72.0%, 37.2%, 34.8%, and 38.1% respectively. 41 of 166 *E. coli* had ESBL identification, and the prevalence of ESBL-producing *E. coli* was 34.1%. All GBS strains were susceptible to meropenem, cefotaxime, linezolid, vancomycin, penicillin, and ampicillin. However, the proportions of GBS resistant to erythromycin and clindamycin were 75.9% and 77.3%, respectively. The proportions of *E.* spp resistant to penicillin and ampicillin were 60% and 54.1%, respectively. All *E.* spp strains were sensitive to vancomycin and linezolid, and the proportions of *E.* spp resistant to gentamicin was 27.8%. All *S. aureus* strains showed resistance to ampicillin and penicillin. The resistance rate of *S. aureus* to methicillin was 50%.

Trends in antibiotic resistance

Fig. 3 presents the trends in antibiotic resistance from 2012 to 2019. Antibiotic susceptibility appeared to improve in 2019. Antimicrobial susceptibility of *E. coli* to ampicillin, gentamicin, cefotaxime, and ceftriaxone showed marked improvements from 12.5%, 50%, 37.5%, and 50% in 2012 to 42.9%, 76.9%, 76.9%, and 71.4%, respectively in 2019. In 2019, the prevalence of ESBL-producing *E. coli* was 20%, which was much lower than that (100%) in 2012 (Fig. 3A). Antimicrobial susceptibility of GBS to erythromycin and clindamycin improved to 28.6% and 25% in 2019, compared with 0% in 2012 (Fig. 3B). However, the improvement in antimicrobial susceptibility was not observed for *E.* spp and *S. aureus* (Fig. 3C and D).

Discussion

Our surveillance data indicated that antibiotic resistance of leading pathogens in neonatal IBIs was common in China.

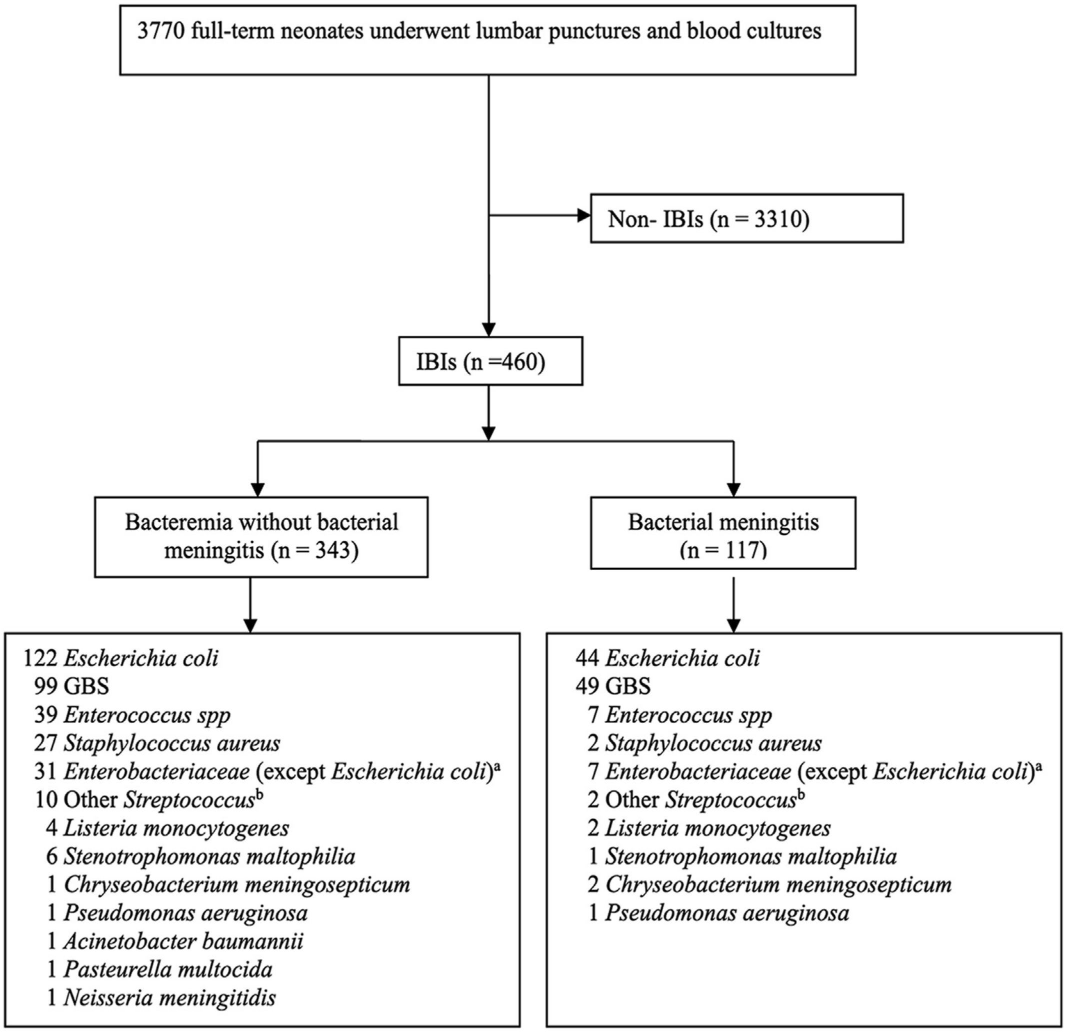

Figure 1. Patient flow chart. IBIs = invasive bacterial infection, GBS = Group B *Streptococcus*. [a] includes *Salmonella species*, *Klebsiella species*, *Serrattia*, *Proteus species*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Enterobacter asburiae*, and *Enterobacter sakazakii*. [b] includes *hemolytic Streptococcus*, *Streptococcus gallolyticus*, *Streptococcus constellatus*, *Streptococcus pneumoniae*, and *Streptococcus bovis*.

However, antibiotic susceptibility seemed to improve from 2012 to 2019.

In the present study, although all GBS strains were sensitive to penicillin and ampicillin, the proportions of GBS resistant to erythromycin and clindamycin were much higher than those reported in the United States (75.9% vs 32%; 77.3% vs 15%, respectively).[21] Among all *E. coli* isolates from neonates with IBIs in 2012—2019, the proportions of *E. coli* resistant to ampicillin and third-generation cephalosporins were much higher than those reported in the United States.[10,22,23] Stoll et al. (2011) reported that only 3% of *E. coli* isolates were resistant to third-generation cephalosporin,[22] and Greenhow et al. (2012) reported that 44% of *E. coli* isolates were resistant to ampicillin.[10] On the other hand, the prevalence of ESBL-producing *E. coli* in our study was higher than that reported in Korea (34.1% vs 6.7%).[24] ESBL-producing isolates among *E. coli* have been found globally with increasing numbers,[25,26] which is mainly due to a dramatic increase in CTX-M-type enzymes (a ESBL group).[27,28] ESBLs, a group of beta lactamases, could cause resistance to various types of the newer beta-lactam antibiotics by hydrolysis, including the expanded-spectrum (or third-generation) cephalosporins (eg, cefotaxime, ceftriaxone).[29] Thus, the high prevalence of ESBL-producing *E. coli* might partly explain the high resistance of *E. coli*.

There are two possible reasons which might explain the high prevalence of antibiotic resistance in neonates in China. Contrary to developed countries where there are clinical guidelines more strictly implemented to restrict antibiotic misuse, antibiotic misuse or overuse is almost universal in China owning to weak national clinical practice policies on antibiotic use.[30] Since the awareness of the problems associated with antibiotic resistance used to be low among the general public before 2011, antibiotics were freely available in China, either online or over the counter, resulting in overuse self-medication.[31] Such unrestricted usage of antibiotics may have exerted strong selective pressure in the environment for resistant bacteria, especially for *E. coli*.[32] Another explanation for the high prevalence of antibiotic resistance in China may be the routine feeding of antibiotics to healthy farm animals,

Table 1 Characteristics of neonates with invasive bacterial infections.

Characteristic	Total n (%) n = 460	Bacteremia without bacterial meningitis n (%) n = 343	Bacterial meningitis[a] n (%) n = 117
Total			
Gestational age (days), mean ± SD	274 ± 8	274 ± 8	274 ± 9
Gender, n (%)			
Male	271 (58.9)	215 (62.7)	56 (47.9)
Female	189 (41.1)	128 (37.3)	61 (52.1)
Birth weight (g), mean ± SD	3342 ± 480	3346 ± 491	3330 ± 450
Age group			
< 7 d	177 (38.5)	145 (42.3)	32 (27.4)
≥ 7 d	283 (61.5)	198 (57.7)	85 (72.6)
Mode of delivery, n (%)			
Cesarean	105 (22.8)	84 (24.5)	21 (17.9)
Vaginal	355 (77.2)	259 (75.5)	96 (82.1)
Fever			
Yes	333 (72.4)	234 (68.2)	99 (84.6)
No	127 (27.6)	109 (31.8)	18 (15.4)
Lethargy			
Yes	139 (30.2)	91 (26.5)	48 (41.0)
No	321 (69.8)	252 (73.5)	69 (59.0)
Poor feeding			
Yes	131 (28.5)	84 (24.5)	47 (40.2)
No	329 (71.5)	259 (75.5)	70 (59.8)
Vomit			
Yes	27 (5.9)	19 (5.5)	8 (6.8)
No	433 (94.1)	324 (94.5)	109 (93.2)
Cyanosis			
Yes	52 (11.3)	40 (11.7)	12 (10.3)
No	408 (88.7)	303 (88.3)	105 (89.7)
Early- onset			
Gestational age (days), mean ± SD	275 ± 8	274 ± 8	278 ± 8
Gender, n (%)			
Male	102 (57.6)	86 (59.3)	16 (50.0)
Female	75 (42.4)	59 (40.7)	16 (50.0)
Birth weight (g), mean ± SD	3329 ± 471	3323 ± 483	3361 ± 416
Mode of delivery, n (%)			
Cesarean	37 (20.9)	31 (21.4)	6 (18.8)
Vaginal	140 (79.1)	114 (78.6)	26 (81.2)
Fever			
Yes	84 (47.5)	62 (42.8)	22 (68.8)
No	93 (52.5)	83 (57.2)	10 (31.2)
Lethargy			
Yes	37 (20.9)	27 (18.6)	10 (31.2)
No	140 (79.1)	118 (81.4)	22 (68.8)
Poor feeding			
Yes	35 (19.8)	25 (17.2)	10 (31.2)
No	142 (80.2)	120 (82.8)	22 (68.8)
Vomit			
Yes	10 (5.6)	8 (5.5)	2 (6.2)
No	167 (94.4)	137 (94.5)	30 (93.8)
Cyanosis			
Yes	32 (18.1)	28 (19.3)	4 (12.5)
No	145 (81.9)	117 (80.7)	28 (87.5)
Late- onset			
Gestational age (days), mean ± SD	274 ± 8	274 ± 8	272 ± 9
Gender, n (%)			
Male	169 (59.7)	129 (65.2)	40 (47.1)
Female	114 (40.3)	69 (34.8)	45 (52.9)

Table 1 (*continued*)

Characteristic	Total n (%) n = 460	Bacteremia without bacterial meningitis n (%) n = 343	Bacterial meningitis[a] n (%) n = 117
Birth weight (g), mean ± SD	3349 ± 487	3362 ± 498	3319 ± 463
Mode of delivery, n (%)			
Cesarean	68 (24.0)	53 (26.8)	15 (17.6)
Vaginal	215 (76.0)	145 (73.2)	70 (82.4)
Fever			
Yes	249 (88.0)	172 (86.9)	77 (90.6)
No	34 (12.0)	26 (13.1)	8 (9.4)
Lethargy			
Yes	102 (36.0)	64 (32.3)	38 (44.7)
No	181 (64.0)	134 (67.7)	47 (55.3)
Poor feeding			
Yes	97 (34.3)	60 (30.3)	37 (43.5)
No	186 (65.7)	138 (69.7)	48 (56.5)
Vomit			
Yes	18 (6.4)	12 (6.1)	6 (7.1)
No	265 (93.6)	186 (93.9)	79 (92.9)
Cyanosis			
Yes	20 (7.1)	12 (6.1)	8 (9.4)
No	263 (92.9)	186 (93.9)	77 (90.6)

[a] Neonates with bacterial meningitis with or without bacteremia.

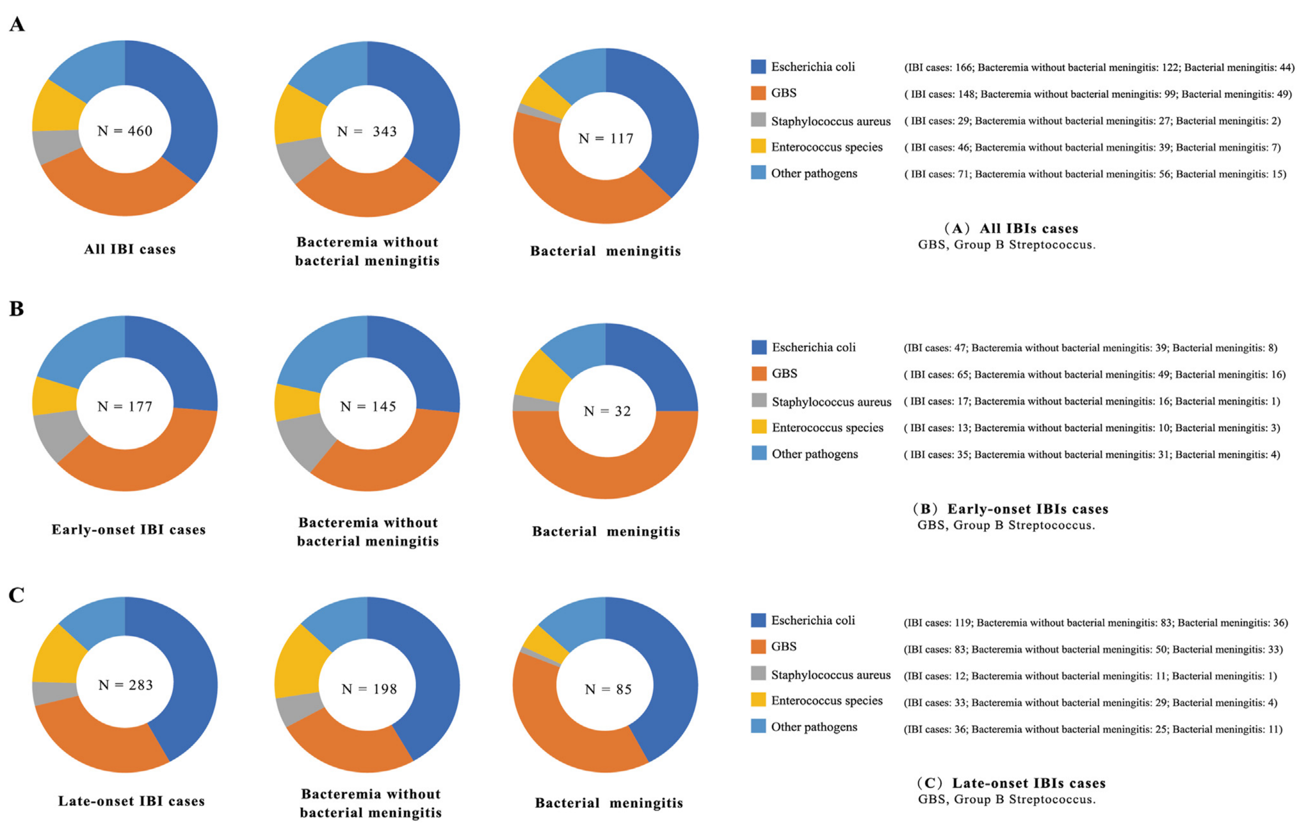

Figure 2. Distribution of pathogens causing IBIs in neonates in China 2012—2019. IBI = invasive bacterial infection, GBS = Group B *Streptococcus*. (A) All IBI cases. (B) Early-onset IBI cases. (C) Late-onset IBI cases.

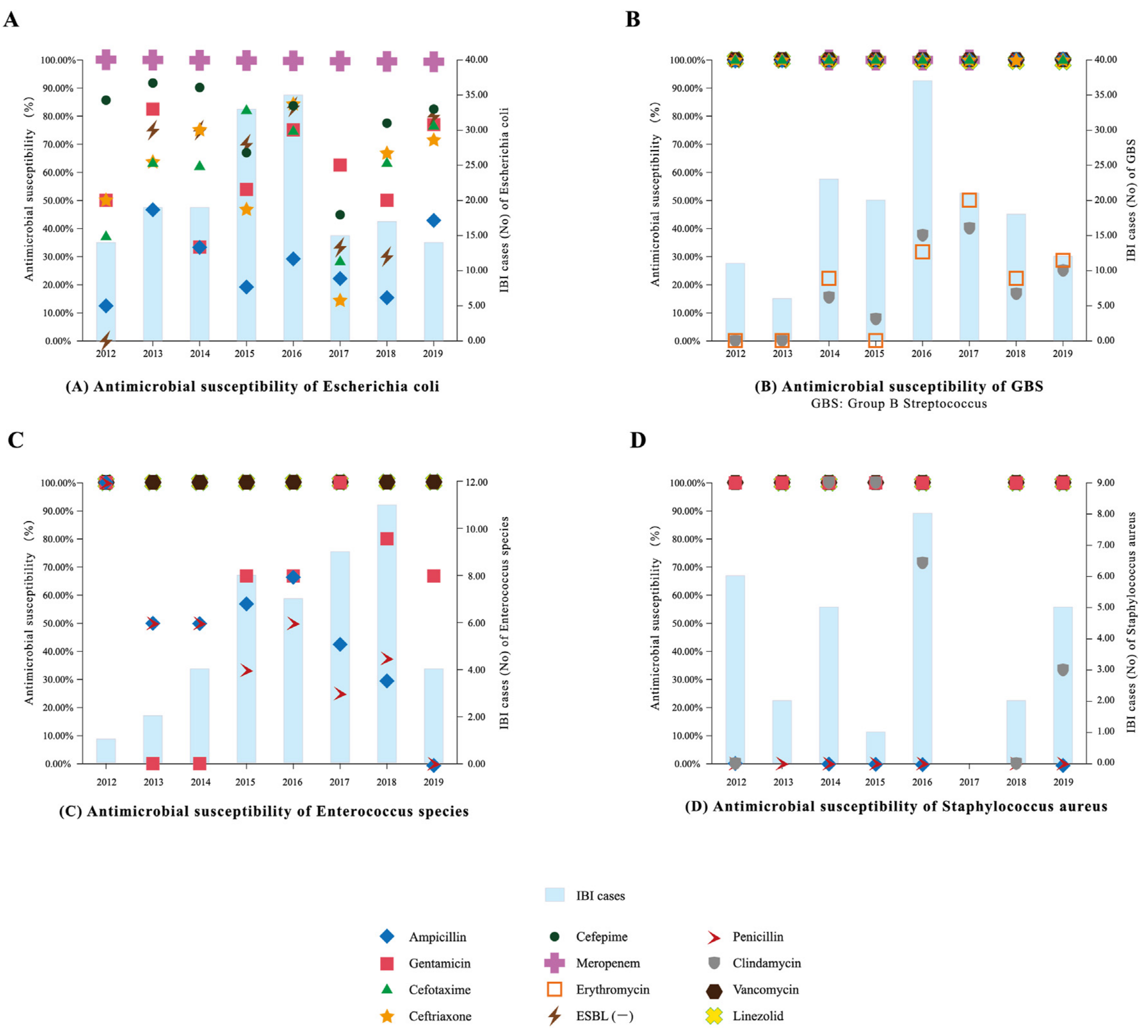

Figure 3. In vitro antimicrobial susceptibility testing of the common pathogens from neonates with IBIs. IBI = invasive bacterial infection, GBS = Group B *Streptococcus*, ESBL = extended spectrum beta-lactamase. (A) Antimicrobial susceptibility of *Escherichia coli*. (B) Antimicrobial susceptibility of GBS. (C) Antimicrobial susceptibility of *Enterococcus spp*. (D) Antimicrobial susceptibility of *Staphylococcus aureus*.

which promotes the development of antibiotic-resistant bacteria that can be transferred to humans through food products, environment, or by contact with livestock.[33–35] Thus, maternal exposure to antibiotics could alter both the maternal and offspring's bacterial profiles, and might in favor of resistant pathogens in neonates.[23]

Although the dramatic increase in antibiotic resistance is likely to continue to emerge as one of the main global health care threats in the 21st century,[36] the antimicrobial susceptibility of *E. coli* seemed to improve in 2019 in our study, which was likely due to new policies to promote the rational use of antibiotics in China. In 2012, China formally implemented a decree issued by the Ministry of Health on regulations for clinical use of antibiotics to ensure rational use and prevent resistance.[37] After the rational use of antibiotics in China, the proportion of antibiotic prescriptions decreased in outpatients (from 19.4% to 9.4%) and in inpatients (from 67.3% to 39.1%) nationwide from 2010 to 2015.[38] One study retrospectively evaluated the antibiotic resistance in a tertiary hospital in China during 2010–2016, and found that the resistance rates of *E. coli* to fluoroquinolones decreased, the incidence rate of methicillin-resistant *S. aureus* also decreased after the rational use of antibiotics.[39] Furthermore, the Chinese government issued a 5-year national action plan in 2016 to promote rational use of antibiotics and contain resistance, curbing non-prescription sales of antibiotics at community pharmacies with the goal to eliminate this problem by 2020.[40] The 5-year national action plan included strengthening the construction of antimicrobial application and drug resistance control system; improving the application of antibiotics and bacterial resistance monitoring system; improving the ability of professionals to prevent and control bacterial resistance; strengthening the prevention and control of environmental pollution of antibiotics; and increasing public publicity and education. These policies might contribute to decrease antibiotic resistance in China. In 2017, the proportion of antibiotic prescriptions decreased to 7.7% in outpatients, and decreased to 36.8% in inpatients.[41] One recently published study collected data from neonatal units worldwide in 2017 and reported that the proportion of Gram-negative bacteria resistant to at least one third-generation cephalosporin agent in China was 42%, which was lower than that in India (51%), Cambodia (67%), and Greece (62%).[42]

Our study provided a profile of the pathogenic features and antibiotics resistance in neonates in China. Our study has limitations. First, we did not have information on maternal antibiotic exposure prior to delivery, thus limiting the ability to evaluate a potential relationship between exposure and the risk of infection with antibiotic-resistant pathogens. Intrapartum antibiotic prophylaxis might have changed the maternal and neonate bacterial flora, and selected for antibiotic-resistant pathogens. Some studies have found a relationship between intrapartum antibiotics and the risk of bacterial infections and ampicillin-resistant pathogens.[23,43] Second, our study was limited to NICUs, rendering our findings less generalizable to other clinical settings. Third, although we defined resistance, intermediate, or susceptibility in accordance with the Clinical and Laboratory Standards Institute, MIC of antibiotics were not further determined by the agar dilution method.

Conclusions

To our knowledge, this is the first national study on antibiotic resistance patterns in neonates in China. Our findings indicated the high prevalence of antibiotic resistance in Chinese neonates, although with some encouraging improvements from 2012 to 2019. Future efforts are needed, to promote the proper use of antibiotics and avoid overuse of antibiotic in China. Furthermore, the bacterial profiles of preterm and full-term neonates are inconsistent, it is necessary to study the bacterial profile and antibiotic resistance in preterm neonates in the future.

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Declaration of competing interest

None declared.

Acknowledgments

None.

References

1. WHO. *Global antimicrobial resistance surveillance system (GLASS) report*. *Early implementation 2017—2018*. 2018. https://apps.who.int/iris/bitstream/handle/10665/279656/9789241515061-eng.pdf?ua=1. [Accessed 16 April 2019].
2. Xiao Y, Zhang J, Zheng B, Zhao L, Li S, Li L. Changes in Chinese policies to promote the rational use of antibiotics. *PLoS Med* 2013;**10**:e1001556.
3. Xiao YH, Shen P, Wei ZQ, Chen YB, Kong HS, Yang Q, et al. Mohnarin report of 2011: monitoring of bacterial resistance in China [in Chinese]. *Chin J Nosocomiol* 2012;**22**:4946—52.
4. Zhang R, Eggleston K, Rotimi V, Zeckhauser RJ. Antibiotic resistance as a global threat: evidence from China, Kuwait and the United States. *Glob Health* 2006;**2**:6.
5. Li YB, Xu J, Wang F, Wang B, Liu LQ, Hou WL, et al. Overprescribing in China, driven by financial incentives, results in very high use of antibiotics, injections, and corticosteroids. *Health Aff* 2012;**31**:1075—82.
6. Xiao YH, Giske CG, Wei ZQ, Shen P, Heddini A, Li LJ. Epidemiology and characteristics of antimicrobial resistance in China. *Drug Resist Updates* 2011;**14**:236—50.
7. Wang H, Wang B, Zhao Q, Zhao Y, Fu C, Feng X, et al. Antibiotic body burden of Chinese school children: a multisite biomonitoring-based study. *Environ Sci Technol* 2015;**49**:5070—9.
8. Landrigan PJ, Carlson JE. Environmental policy andchildren's health. *Future Child* 1995;**5**:34—52.
9. Tregoning JS, Schwarze J. Respiratory viral infections ininfants: causes, clinical symptoms, virology, and immunology. *Clin Microbiol Rev* 2010;**23**:74—98.
10. Greenhow TL, Hung YY, Herz AM. Changing epidemiology of bacteremia in infants aged 1 week to 3 months. *Pediatrics* 2012;**129**:e590—6.
11. Kerrn MB, Klemmensen T, Frimodt-Møller N, Espersen F. Susceptibility of Danish Escherichia coli strains isolated from urinary tract infections and bacteraemia, and distribution of sul genes conferring sulphonamide resistance. *J Antimicrob Chemother* 2002;**50**:513—6.
12. UNICEF, WHO. *World bank, UN population division: levels and trends inchild mortality report 2014*: *estimates developed by the inter-agency groupfor child mortality estimation*. 2014. http://www.unicef.org/media/files/%20Levels_and_Trends_in_Child_Mortality_2014.pdf.
13. Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen JA, Klugman K, et al. Access to effective antimicrobials: a worldwide challenge. *Lancet* 2016;**387**:168—75.
14. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000—13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2015;**385**:430—40.
15. WHO. *Antimicrobial resistance: global report on surveillance 2014*. Geneva: World Health Organization; 2014.
16. Cruz AT, Mahajan P, Bonsu BK, Bennett JE, Levine DA, Alpern ER, et al. Accuracy of complete blood cell counts to identify febrile infants 60 Days or younger with invasive bacterial infections. *JAMA Pediatr* 2017;**171**:e172927.
17. Heath PT, Nik Yusoff NK, Baker CJ. Neonatal meningitis. *Arch Dis Child Fetal Neonatal Ed* 2003;**88**:F173—8.
18. Seale AC, Mwaniki M, Newton CR, Berkley JA. Maternal and early onset neonatal bacterial sepsis: burden and strategies for prevention in sub-Saharan Africa. *Lancet Infect Dis* 2009;**9**:428—38.
19. Bekker V, Bijlsma MW, van de Beek D, Kuijpers TW, van der Ende A. Incidence of invasive group B streptococcal disease and pathogen genotype distribution in newborn babies in The Netherlands over 25 years: a nationwide surveillance study. *Lancet Infect Dis* 2014;**14**:1083—9.
20. Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing: twenty-third informational supplement*. *M100-S23*. Wayne (Pennsylvania): Clinical and Laboratory Standards Institute; 2013.
21. Phares CR, Lynfield R, Farley MM, Mohle-Boetani J, Harrison LH, Petit S, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999-2005. *J Am Med Assoc* 2008;**299**:2056—65.
22. Stoll BJ, Hansen NI, Sánchez PJ, Faix RG, Poindexter BB, Van Meurs KP, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. *Pediatrics* 2011;**127**:817—26.

23. Glasgow TS, Young PC, Wallin J, Kwok C, Stoddard G, Firth S, et al. Association of intrapartum antibiotic exposure and late-onset serious bacterial infections in infants. *Pediatrics* 2005; **116**:696—702.
24. Park SH, Choi SM, Lee DG, Kim J, Choi JH, Kim SH, et al. Emergence of extended-spectrum β-lactamase-producing escherichia coli as a cause of community-onset bacteremia in South Korea: risk factors and clinical outcomes. *Microb Drug Resist* 2011;**17**:537—44.
25. Livermore DM. Current epidemiology and growing resistance of Gram-negative pathogens. *Korean J Intern Med (Korean Ed)* 2012;**27**:128—42.
26. da Costa PM, Loureiro L, Matos AJ. Transfer of multidrug-resistant bacteria between intermingled ecological niches: the interface between humans, animals and the environment. *Int J Environ Res Public Health* 2013;**10**:278—94.
27. Paterson DL, Bonomo RA. Extended-spectrum β-lactamases: a clinical update. *Clin Microbiol Rev* 2005;**18**:657—86.
28. Livermore DM, Canton R, Gniadkowski M, Nordmann P, Rossolini GM, Arlet G, et al. CTX-M: changing the face of ESBLs in Europe. *J Antimicrob Chemother* 2007;**59**:165—74.
29. Bradford PA. Extended-spectrum β-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. *Clin Microbiol Rev* 2001;**14**:933—51.
30. Quan J, Zhao D, Liu L, Chen Y, Zhou J, Jiang Y, et al. High prevalence of ESBL-producingEscherichia coli and Klebsiella pneumoniae in community-onset bloodstream infections in China. *J Antimicrob Chemother* 2017;**72**:273—80.
31. Dong L, Yan H, Wang D. Antibiotic prescribing patterns in village healthclinics across 10 provinces of Western China. *J Antimicrob Chemother* 2008;**62**:410—5.
32. Zhu M, Jin Y, Duan Y, He M, Lin Z, Lin J, et al. Escherichia coliMulti-drug resistant CausingEarly-onset neonatal sepsis - a single center experience from China. *Infect Drug Resist* 2019; **12**:3695—702.
33. Goldman E. Antibiotic abuse in animal agriculture: exacerbating drug resistance in human pathogens. *Hum Ecol Risk Assess* 2004;**10**:121—34.
34. Alsan M, Schoemaker L, Eggleston K, Kammili N, Kolli P, Bhattacharya J. Out-of-pocket health expenditures and antimicrobial resistance in low-income and middle-income countries: an economic analysis. *Lancet Infect Dis* 2015;**15**: 1203—10.
35. Van Boeckel TP, Brower C, Gilbert M, Grenfell BT, Levin SA, Robinson TP, et al. Global trends in antimicrobialuse in food animals. *Proc Natl Acad Sci USA* 2015;**112**:5649—54.
36. Littmann J, Viens AM. The ethical significance of antimicrobial resistance. *Publ Health Ethics* 2015;**8**:209—24.
37. Ministry of Health. *People's Republic of China. Administrative regulations for clinical use of antibacterial agents. Beijing*. May, 2012.
38. State Health and Family Planning Commission. *The clinical utilization rate and average cost of antibiotics decreased in China*. in Chinese. 2016. http://www.gov.cn/xinwen/2016—11/25/content_5137540.htm.
39. Wang H, Wang H, Yu X, Zhou H, Li B, Chen G, et al. Impact of antimicrobial stewardship managed by clinical pharmacists on antibiotic use and drug resistance in a Chinese hospital, 2010-2016: a retrospective observational study. *BMJ Open* 2019;**9**: e026072.
40. National Health and Family Plan Commission of China. *National Development and Reform Commission of China, Ministry of Education of China, et al. National action plan for the containment of antibacterial resistance (2016—2020)*. in Chinese. 2016. http://www.gov.cn/xinwen/2016—08/25/content_5102348.htm.
41. in Chinese *The utilization rate of antibiotics in outpatient in China dropped to 7.7 percent*. 2018. http://www.gov.cn/xinwen/2018-06/17/content_5299356.htm.
42. Li G, Bielicki JA, Ahmed ASMNU, Islam MS, Berezin EN, Gallacci CB, et al. Towards understanding global patterns of antimicrobial use and resistance in neonatal sepsis: insights from the NeoAMR network. *Arch Dis Child* 2020;**105**:26—31.
43. Bizzarro MJ, Dembry LM, Baltimore RS, Gallagher PG. Changing patterns in neonatal Escherichia coli sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis. *Pediatrics* 2008;**121**:689—96.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2021.05.004.