

Incidence, Bacterial Profiles, And Antimicrobial Resistance Of Culture-Proven Neonatal Sepsis In South China

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Background: Neonatal sepsis (NS) is one of the leading causes of infant morbidity and mortality, but little is known about pathogen incidence and distribution in China.

Methods: In this retrospective study (January 2012 to December 2016), culture-proven cases aged less than 28 days with diagnosed NS in the Guangzhou Women and Children's Medical Center, South China, were analyzed for pathogen incidence and antimicrobial resistance.

Results: A total of 620 isolates were identified from 597 NS cases. Gram-negative bacteria (n=371, 59.8%) dominated over Gram-positive bacteria (n=218, 35.2%) and fungi (n=30, 4.8%). *Klebsiella pneumoniae* (21.9%), *Escherichia coli* (21.9%), group B *Streptococcus* (GBS, 13.2%), and *Staphylococcus aureus* (6.8%) were the four most predominant pathogens. In early-onset sepsis (EOS), GBS (30.0%) and *E. coli* (20.0%) were dominant, whereas in late-onset sepsis (LOS), *K. pneumoniae* (25.6%) and *E. coli* (22.4%) were dominant. *E. coli* (25.2%) and GBS (17.7%) were the most frequently isolated from term patients, whereas *K. pneumoniae* was the most frequently isolated from preterm patients (34.9%). Of the infected infants, 9.5% died from sepsis, most commonly by *E. coli* infection (16.2%). Among 91,215 live births (LBs) delivered in the study hospital (2012–2016), 252 infants developed sepsis infection (2.76 per 1000 LBs, 95% CI 2.4–3.1), including EOS (0.78 per 1000 LBs) and LOS (2.13 per 1000 LBs). All GBS isolates were susceptible to β -lactam antibiotics, and *S. aureus*, including methicillin-resistant isolates, were susceptible to vancomycin. An extended-spectrum β -lactamase producer was identified in 37.3% of *E. coli* and 50.4% of *K. pneumoniae*.

Conclusion: *K. pneumoniae* was the most frequent pathogen in culture-proven NS in South China, primarily associated with LOS in preterm, whereas GBS was the dominant pathogen in EOS. *E. coli* was common in both episodes with the highest mortality.

Keywords: neonatal sepsis, incidence, antimicrobial resistance, *Escherichia coli*, group B *Streptococcus*, *Klebsiella pneumoniae*

Introduction

Neonatal sepsis (NS) is one of the leading causes of morbidity and mortality in infants worldwide.¹ It is classically divided into early-onset sepsis (within the first 72 h of life, EOS) and late-onset sepsis (3–28 days after birth, LOS), depending on the age at the onset of the sepsis episode. Neonatal sepsis can result from infections by bacteria, viruses, or fungi. Early-onset sepsis is usually the result of vertical maternal transmission before or during delivery, whereas LOS is acquired from interaction with the environment of the communities.¹ A general method to diagnose pathogens of this systemic condition is to examine the culture of blood or sterile body fluids such as cerebrospinal fluid (CSF). The incidence and distribution of pathogens, as well as their

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responses to antimicrobial agents, may vary temporally and geographically, which can affect the decisions for local preventive policy and clinical management.

Group B *Streptococcus* (GBS) and *Escherichia coli* are considered historically as the dominant pathogens of EOS.¹ By comparison, in LOS, GBS, *E. coli* or other Gram-negative aerobes, or *Listeria monocytogenes* may cause infection.² Invasive GBS infections in Chinese infants have been supposed to be very rare because of the lower rate of GBS colonization in pregnant women and the higher protective antibody concentrations in mothers, so that preventive measurements have been suspended.³ However, the results of a study in China are not consistent with these observations,⁴ and in recent years, the trend of neonatal GBS cases from mainland China is increasing. Moreover, in a previous multicenter study of infants aged less than 3 months, the overall incidence of invasive GBS infection of 0.55/1000 live births was higher than the global mean.⁵ In particular, the incidence of early-onset GBS disease increased significantly from 2011 to 2014. With the increase, the incidence is almost two times that in the USA where universal culture-based screening of pregnant women and intrapartum antibiotic prophylaxis for GBS-colonized women have been widely employed.⁶ Nevertheless, the disease burden caused by GBS infection remains unclear when compared with other pathogens in NS. It is also unclear whether preventive measures are required in China because studies are limited, the data from certain departments in hospitals such as neonatal intensive care units (NICU) are insufficient, some studies extend the neonates to 1 year of age, and compared with international definitions, EOS and LOS groups are vaguely defined.⁷⁻⁹

In this retrospective study, culture-proven cases diagnosed with NS in a South China hospital were analyzed for microorganism profiles and the antimicrobial resistance of bacterial pathogens from 1 January 2012 to 31 December 2016. The study included many cases, and therefore, sufficient evidence may be provided to implement preventive measures and empirical antimicrobial treatment for neonates suffering from sepsis in the future.

Materials And Methods

Study Design And Population

Culture-positive results of blood or CSF from neonates aged less than 28 days were extracted from the microbiology laboratory database at the Guangzhou Women and Children's Medical Center (GWCMC), Guangzhou,

Guangdong Province, China. The microbiological and clinical data of neonates with culture-proven sepsis were reviewed from 1 January 2012 to 31 December 2016, and information was collected on antimicrobial resistance of isolated organisms, gestational age, birth weight, and outcomes when discharged from the hospital. Whether the infants were born in the study hospital or were born outside the study hospital but transferred to the hospital was also recorded.

The study protocol was reviewed and approved by the ethical committees of the GWCMC, and the study was conducted in accordance with the principles of Good Pharmacoepidemiological Practice and the Declaration of Helsinki. The records of patients remained anonymous during data collection and analysis. Written parental consent was not required.

The GWCMC is the largest medical center in South China and has three tertiary hospitals that provide labor service and neonatal and pediatric health care. The GWCMC has 15,000–22,000 annual deliveries and has 300 beds for neonatal hospitalization, of which 120 are designated for intensive care.

Culture And Identification

Microorganism identification and culture were conducted according to the routine diagnostic standard operation procedure used by the clinical laboratory in the study hospital: for any infant presenting with clinical signs or symptoms of sepsis, meningitis, or pneumonia, 1–3 mL of blood or 0.5–3 mL of CSF sample was inoculated into a commercial culture bottle exclusively for newborns and analyzed using an automated monitoring system for bacterial detection (BD BACTEC™; Franklin Lake, NJ, USA or BioMérieux Bact/ALERT, Marcy L'Étoile, France). Incubation was continued until a positive result was observed or up to a maximum of 7 days. The microorganisms were identified to species level by conventional biochemical techniques or automated methods with the VITEK system (BioMérieux). The bacterial isolates were tested for susceptibility to antibiotics using VITEK 2 Compact (BioMérieux) or the manual Kirby–Bauer disc diffusion method, as per interpretive standards established by the Clinical Laboratory Standards Institute (USA).

Definitions

Culture-proven NS was defined as one or more blood or CSF culture obtained at 0–28 days of life growing a recognized pathogenic bacterium or fungus and a clinical diagnosis of

sepsis.^{10,11} Coagulase-negative staphylococci (CoNS), micrococci, propionibacteria, corynebacteria, or diphtheroids grown alone in a single sample were considered contaminants and excluded. CoNS were included only when cultivated in two or more blood/CSF samples. Repeatedly positive samples were considered to represent the same episode of infection, unless they occurred more than 21 days after the last positive culture result. The date of sepsis onset was the date of collection of the first blood sample yielding a pathogenic strain. Early-onset sepsis was defined as infection occurring less than 72 h after birth, whereas episodes thereafter (3–28 days after birth) were classified as LOS.

Preterm was defined as <37 weeks of gestation. The preterms were categorized by birth weight: very low birth weight (VLBW), <1500 g; low birth weight (PLBW), 1500–2499 g; normal, 2500–3999 g; overweight, ≥4000 g.

Only neonates born in the study hospital were included in the incidence estimation to ensure a constant denominator, and those cases born outside the study hospital were excluded from the calculation. The statistical department of the study hospital provided the total numbers of live births per year from 2012 to 2016. The incidence rates were calculated as cases per 1000 live births (LBs), and the 95% confidence intervals (CIs) for the incidence rates were based on the assumption that the annual case count followed a Poisson distribution.

Statistical Analyses

SPSS 20.0 (IBM, Armonk, NY, USA) was used for data analyses. Discrete data are presented as frequencies, which were compared with a χ^2 test or Fisher exact test. $P < 0.05$ was considered significant. The case fatality rate of a certain organism was defined as the percentage (%) of the cases with diagnosed sepsis caused by the organism in which the neonates died before discharge. The incidence per 1000 LBs of a certain organism was calculated as the total number of cases diagnosed with the organism-caused sepsis born in the study hospital divided by the total number of infants in the study hospital birth cohort, multiplied by 1000.

Results

Characteristics Of Infants

Between 1 January 2012 and 31 December 2016, 597 infants with positive cultures of samples obtained at ≤28 days of age and diagnosed with NS were identified, including 382 boys (64.0%) and 215 girls (36.0%). The median

age was 10 days. Of these infants, seven neonates (1.2%) experienced more than one episode of infection caused by different pathogens. Multiple organisms were isolated from the same culture in 2.0% (n=12) of episodes.

According to the time of onset, 97 cases were classified as EOS and 502 cases as LOS. Two neonates developed NS in EOS and LOS with different pathogens. All of the patients were collected from the general neonatal unit, NICU, cardiac ICU, surgical ICU, or emergency department set in the study hospital. Of the infants, 388 (65.0%) were born at term, 206 (34.5%) were preterm, and 3 (0.5%) had no gestational age records because they were foundlings without any information at birth. Of the 206 preterms, 71 (11.9%) were categorized as PLBW and 54 (9.0%) as VLBW.

Fifty-seven (9.5%) patients died from sepsis before being discharged from the hospital. *Escherichia coli* infection was the leading cause of mortality at 16.2% (22/136), followed by *Klebsiella pneumoniae* at 8.8% (12/136), GBS at 4.9% (4/82), and *Staphylococcus aureus* at 4.8% (2/42). The death rate between neonates with EOS (9.0%) and LOS (9.2%) was not different ($P > 0.05$).

Organisms Causing Neonatal Sepsis

A total of 620 isolates were identified (Table 1). Sepsis was primarily caused by Gram-negative bacteria (n=371, 59.8%), compared with Gram-positive bacteria (n=218, 35.2%) and fungi (n=31, 5.0%). The most frequent pathogens were *K. pneumoniae* (n=136, 21.9%) and *E. coli* (n=136, 21.9%), followed by GBS (n=82, 13.2%) and *S. aureus* (n=42, 6.8%). Other pathogens included Enterococcus species at 4.9%, CoNS at 4.0%, *Acinetobacter baumannii* at 1.1%, *Pseudomonas aeruginosa* at 0.6%, and *L. monocytogenes* at 0.3%. Fungal pathogens were at 5.0%, and *Candida* was the most prevalent. The profiles of the microorganisms isolated from the terms and preterms are shown in Figure 1. The most common bacteria isolated from the terms were *E. coli* (n=98, 25.2%), GBS (n=69, 17.7%), *K. pneumoniae* (n=58, 15.0%), and *S. aureus* (n=29, 7.5%). Of the infections in terms, GBS caused 86.6% (71/82), *E. coli* 74.2% (101/136), and *S. aureus* 69.0% (29/42). Compared with term neonates, *K. pneumoniae* (34.9%) rather than *E. coli* (15.8%) was the most common bacteria in preterm NS neonates ($P < 0.001$), including in both VLBW (35.1% vs 15.8%, $P < 0.001$) and PLBW (32.0% vs 13.3%, $P < 0.001$) neonates. GBS was also less commonly isolated in preterm (5.1%) than in term (17.7%) neonates ($P = 0.000$). Fungi were more

Table 1 Distribution Of Organisms Causing Neonatal Sepsis

Organism	Total (n%)	Early Onset Sepsis (n%)	Late Onset Sepsis (n%)
Gram-negative bacteria	371/59.8	44/44.0	327/63.0
<i>Klebsiella pneumoniae</i>	136/21.9	3/3.0	133/25.6
<i>Escherichia coli</i>	136/21.9	20/20.0	116/22.3
<i>Serratia marcescens</i>	16/2.6	5/5.0	11/2.1
<i>Enterobacter cloacae</i>	12/1.9	1/1.0	11/2.1
<i>Ochrobactrum anthropi</i>	12/1.9	5/5.0	7/1.3
<i>Acinetobacter baumannii</i>	7/1.1	1/1.0	6/1.2
<i>Stenotrophomonas maltophilia</i>	6/1.0	5/5.0	1/0.2
<i>Enterobacter aerogenes</i>	6/1.0	0/0.0	6/1.2
<i>Alcaligenes xylosoxidans</i>	5/0.8	1/1.0	4/0.8
<i>Chryseobacterium meningosepticum</i>	5/0.8	0/0.0	5/1.0
Other Gram-negative bacteria	30/4.8	8/8.0	27/5.2
Gram-positive bacteria	218/35.2	54/54.0	164/31.5
Group B <i>Streptococcus</i>	82/13.2	30/30.0	52/10.0
<i>Staphylococcus aureus</i>	42/6.8	2/2.0	40/7.7
Coagulase-negative <i>Staphylococcus</i>	25/4.0	5/5.0	20/3.8
<i>Enterococcus faecalis</i>	19/3.1	2/2.0	17/3.3
<i>Enterococcus faecium</i>	11/1.8	1/1.0	10/1.9
<i>Streptococcus mitis</i>	8/1.3	3/3.0	5/1.0
<i>Streptococcus pasteurianus</i>	3/0.5	2/2.0	1/0.2
<i>Streptococcus gallolyticus</i>	3/0.5	1/1.0	2/0.4
<i>Streptococcus milleri</i>	3/0.5	3/3.0	0/0.0
Other Gram-positive bacteria	22/3.6	5/5.0	17/3.3
Fungi	31/5.0	2/2.0	29/5.6
<i>Candida albicans</i>	13/2.1	0/0.0	13/2.5
<i>Candida parapsilosis</i>	8/1.3	1/1.0	7/1.3
<i>Candida guilliermondii</i>	3/0.5	0/0.0	3/0.6
Other fungi	7/1.1	1/1.0	6/1.2
Total	620/100	100/100.0	520/100.0

commonly isolated in preterm (7.9%) than in term (3.2%) neonates ($P=0.03$).

Pathogens In EOS And LOS

In EOS patients, Gram-positive bacteria (n=54, 54.0%) were the main pathogens (Table 1). The most frequent pathogen was GBS (n=30, 30.0%), followed by *E. coli* (n=20, 20.0%). The prevalence of GBS was always greater than that of *E. coli* in each year of study, but the trends in variation were synchronous for these two bacteria from

2012 to 2016 (Figure 2A). *Serratia marcescens* (n=5, 5.0%), *Ochrobactrum anthropi* (n=5, 5.0%), and CoNS (n=5, 5.0%) were also recorded.

In LOS patients, Gram-negative bacteria were the main pathogens (n=327, 63.0%). The prominent pathogens during the study period were *K. pneumoniae* (n=133, 25.6%) and *E. coli* (n=116, 22.3%) (Figure 2B), followed by GBS (n=52, 10.0%) and *S. aureus* (n=40, 7.7%).

Incidence

Of the 597 NS neonates, 252 (42.0%) were born in the GWCMC: 69 with EOS and 185 with LOS, including four neonates who experienced both EOS and LOS, and some had multiple organisms isolated from the same culture. Of the 265 isolates from the in-born patients, *K. pneumoniae* (n=72, 27.2%), *E. coli* (n=43, 16.2%), GBS (n=42, 15.8%), and *S. aureus* (n=19, 7.2%) remained the main pathogens, with GBS (27/71, 38.0%) dominating in EOS and *K. pneumoniae* (71/194, 36.6%) dominating in LOS. In EOS, *K. pneumoniae* (1/71) and *S. aureus* (2/71) infections seldom occurred, whereas the infection rate by *E. coli* was similar in EOS (10/71) and LOS (33/194, $\chi^2=0.327$, $P>0.05$).

During the study period, a total of 91,215 LBs were delivered in the GWCMC. The overall incidence rate of NS was 2.76 per 1000 LBs (252/91,215; 95% CI 2.4–3.1). The incidence of EOS was 0.78 per 1000 LBs (71/91,215; 95% CI 0.61–0.97) and that of LOS was 2.13 per 1000 LBs (185/91,215; 95% CI 1.75–2.33). The average incidence of infection in NS for the four predominant pathogens was as follows: *K. pneumoniae*, 0.79 per 1000 LBs (72/91,215; 95% CI 0.62–0.98); *E. coli*, 0.47 per 1000 LBs (43/91,215; 95% CI 0.34–0.62); GBS, 0.46 per 1000 LBs (42/91,215; 95% CI 0.33–0.61); and *S. aureus*, 0.21 per 1000 LBs (19/91,215; 95% CI 0.13–0.31). In EOS, GBS had the highest incidence (0.30 per 1000 LBs; 95% CI 0.20–0.42) among the four major bacteria over the five study years, followed by *E. coli* (0.11 per 1000 LBs; 95% CI 0.05–0.19; Figure 3). In LOS, *K. pneumoniae* (0.78 per 1000 LBs; 95% CI 0.61–0.97) and *E. coli* (0.36 per 1000 LBs; 95% CI 0.25–0.50) were the major bacteria. *Streptococcus aureus* (0.19 per 1000 LBs; 95% CI 0.11–0.29) and GBS (0.16 per 1000 LBs; 95% CI 0.09–0.26) were also common in LOS.

Antimicrobial Resistance

Antibiotic susceptibility of Gram-positive GBS and *S. aureus* was selected as shown in Table 2. All GBS isolates tested were sensitive to penicillin, ampicillin, and vancomycin;

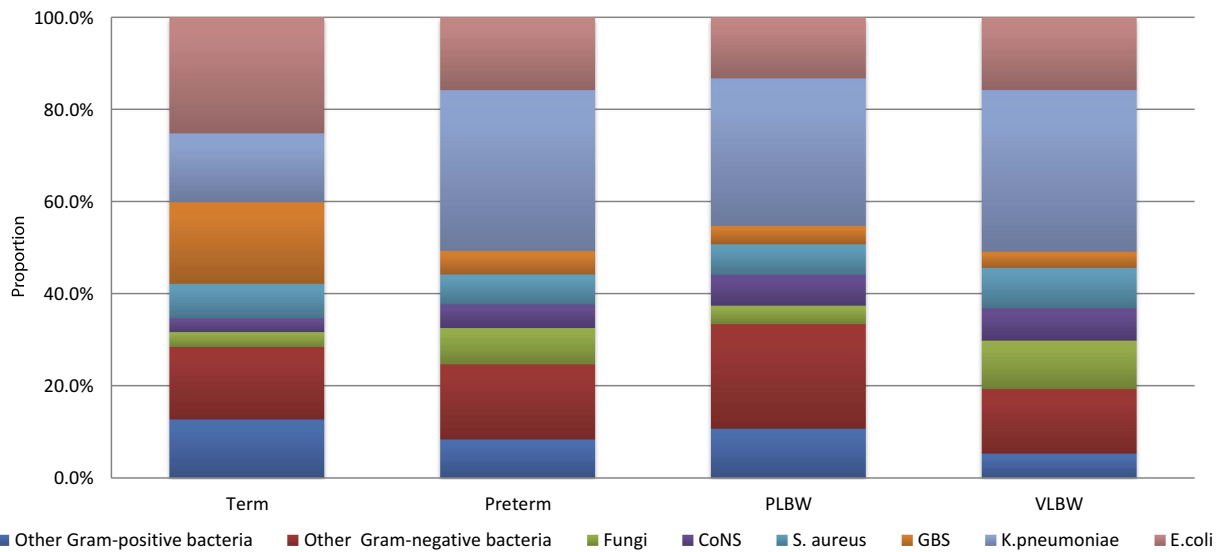


Figure 1 Proportions of term and preterm neonates, including very low birth weight (VLBW) and preterm low birth weight (PLBW), infected by different bacteria. CoNS, Coagulase-negative *Staphylococcus*; *S. aureus*, *Staphylococcus aureus*; GBS, Group B *Streptococcus*; *K. pneumoniae*, *Klebsiella pneumoniae*; *E. coli*, *Escherichiacoli*.

however, many were highly resistant to erythromycin (70.9%), clindamycin (64.0%), and tetracycline (88.4%). Of the 42 *S. aureus* isolates, nine (21.4%) were considered methicillin-resistant *S. aureus* (MRSA). β -Lactamase was produced in 80.8% of *S. aureus* (26 tested).

In the tested isolates, 37.3% of *E. coli* and 50.4% of *K. pneumoniae* produced extended-spectrum β -lactamase. The resistance of *E. coli* to ampicillin was 79.1%, to ceftriaxone 41.8%, and to imipenem 0.7%. The resistance of *K. pneumoniae* to ampicillin, ceftriaxone, and imipenem was 6.3%. Both *E. coli* and *K. pneumoniae* exhibited high resistance to third-generation cephalosporin (ceftriaxone)

and ampicillin but relatively low resistance to amikacin and imipenem (Table 3).

Discussion

For clinicians to consider optimal prevention and treatment strategies, it is important to monitor and understand the distribution of bacterial pathogens causing NS, as well as their antimicrobial resistance for following clinical management. The bacterial spectrum may vary geographically and temporally, and this variability can be affected by antibiotic use and implementation of preventive measures.¹ In addition, the attitude adopted toward CoNS can contribute to the

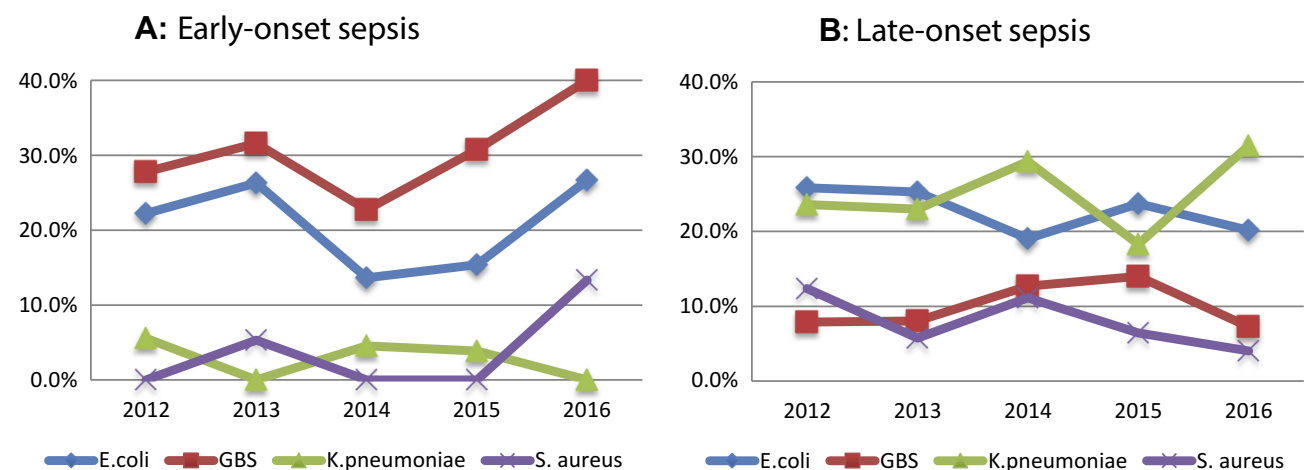


Figure 2 Annual trends of the four predominant pathogens (*Klebsiella pneumoniae*, *Escherichia coli*, Group B *Streptococcus* (GBS), and *Staphylococcus aureus*) in (A) early-onset sepsis (EOS) and (B) late-onset sepsis (LOS) during 2012–2016.

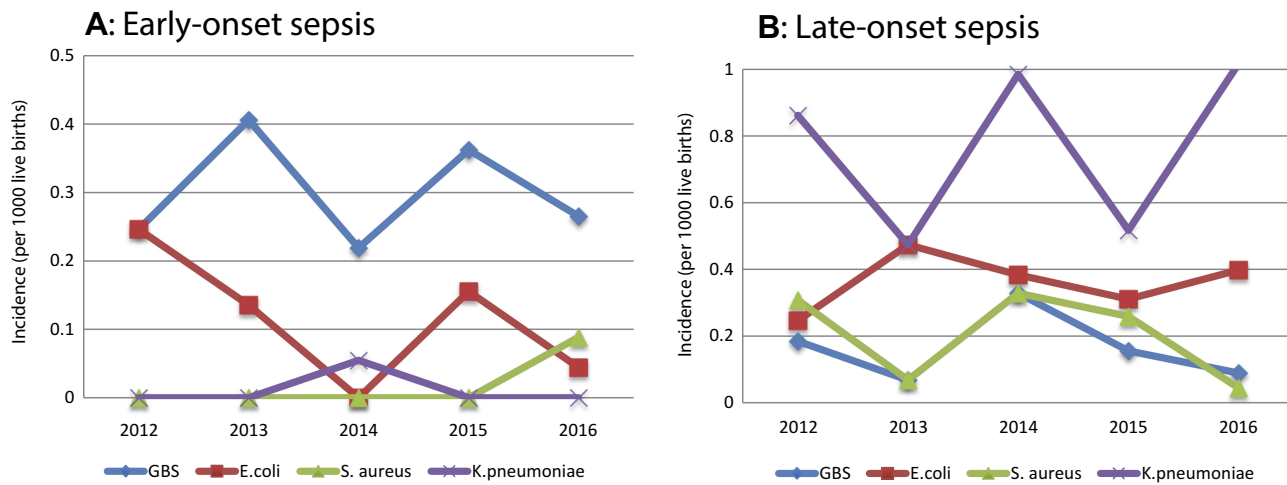


Figure 3 Incidence rate (per 1000 live births) of *Klebsiella pneumoniae*, *Escherichia coli*, Group B *Streptococcus* (GBS), and *Staphylococcus aureus* infections in (A) early-onset sepsis (EOS) and (B) late-onset sepsis (LOS).

differences in bacterial spectra that are pervasive in various studies. When CoNS are counted, Gram-positive bacteria are reported as the main cause of NS in most countries, which is similar to most other hospitals in China, reporting

the highest percentage of 84%.^{11–13} Of the Gram-positive bacteria, CoNS account for a large proportion. When CoNS are not counted or only the positive results in the second culture are counted, as in the present study, Gram-negative bacteria are the prominent pathogens.^{10,14,15} In these studies eliminating the uncertainty caused by CoNS, *E. coli* and *S. aureus* are always reported as the most common bacteria in NS by almost all relevant studies.

Table 2 Antibiotic Resistance Of Group B *Streptococci* (GBS) And *Staphylococcus aureus*

	GBS (n/N/%)			S. aureus (n/N/%)		
	n	N	%	n	N	%
Penicillin	0	80	0.0	37	42	88.1
Ampicillin	0	70	0.0	–	–	–
Erythromycin	61	78	70.9	14	42	33.3
Tetracycline	76	81	88.4	5	42	11.9
Clindamycin	55	81	64.0	14	42	33.3
Nitrofurantoin	0	69	0.0	1	42	2.4
Ciprofloxacin	10	71	11.6	0	42	0.0
Moxifloxacin	8	68	9.3	0	42	0.0
Levofloxacin	9	73	10.5	0	42	0.0
Vancomycin	0	80	0.0	0	42	0.0
Tigecycline	0	62	0.0	0	42	0.0
Quinapril/duphuddin	0	71	0.0	0	42	0.0
Linezolid	1	76	1.2	0	42	0.0
Oxacillin	–	–	–	8	42	19.0
Cefazolin	–	–	–	5	22	22.7
Cefaclor	–	–	–	5	22	22.7
Cefuroxime	–	–	–	5	22	22.7
Cefoperazone	–	–	–	5	22	22.7
Ceftriaxone	–	–	–	5	22	22.7
Ceftazidime	–	–	–	5	22	22.7
Rifampicin	–	–	–	0	42	0.0
Trimethoprim/sulfamethoxazole	–	–	–	2	42	4.8
Gentamycin	–	–	–	0	42	0.0

Notes: n, number of resistant isolates; N, number of tested.

Table 3 Antibiotic Resistance Of *Escherichia coli* And *Klebsiella pneumoniae*

	E. coli (n/N/%)			K. pneumoniae (n/N/%)		
	n	N	%	n	N	%
Ampicillin	106	134	79.1	126	127	99.2
Ampicillin/sulbactam	37	131	27.6	70	122	55.1
Piperacillin/tazobactam	2	130	1.5	7	124	5.5
Cefazolin	57	128	42.5	82	121	64.6
Ceftazidime	15	134	11.2	41	126	32.3
Ceftriaxone	56	134	41.8	75	127	59.1
Cefepime	6	130	4.5	17	126	13.4
Cefotetan	3	131	2.2	8	122	6.3
Imipenem	1	134	0.7	8	127	6.3
Ertapenem	5	134	3.7	8	120	6.3
Gentamycin	42	134	31.3	26	127	20.5
Amikacin	1	134	0.7	2	127	1.6
Tobramycin	4	131	3.0	5	122	3.9
Furadantin	14	131	10.4	24	122	18.9
Aztreonam	26	131	19.4	45	123	35.4
Ciprofloxacin	44	134	32.8	9	127	7.1
Levofloxacin	29	131	21.6	13	123	10.2
Trimethoprim/sulfamethoxazole	68	131	50.7	46	122	36.2

Notes: n, number of resistant isolates; N, number tested.

In a comparison with other pathogens, this study was the first in which GBS was identified as the main bacterial pathogen associated with early-onset NS in China, which has received attention for several decades in developed countries.^{4,6} Moreover, *K. pneumoniae* has been frequently isolated from infants with NS from Asian areas, including China.^{12,13} In this study, *K. pneumoniae* was primarily responsible for late-onset infection, especially in preterm infants with low birth weight, in contrast to the increased rates of *E. coli* infection among preterm infants reported in the USA.¹⁶ However, why the percentage of *K. pneumoniae* in the preterm infants, including those with VLBW and PLBW, was lower than that in the term infants, which is a different result from that of other studies,^{12,13} is currently unknown. This relation needs to be analyzed in conjunction with maternal information.

A strength of this study was that the study hospital is the largest maternity and children's hospital in South China and is one of the few medical institutions that provide continuous service for delivery and pediatric health care in mainland China. Therefore, the total number of live births during the study period could be used as the denominator to learn more precisely about the burden of NS. Of the 91,215 LBs from 2012 to 2016 in the GWCMC, the incidence of EOS (0.78 per 1000 LBs) was comparable to the incidence of 0.7 in the UK but a little lower than that of 0.98 reported in the USA in 2011, based on culture-proven results.^{10,16} Of the pathogens, *K. pneumoniae* had the highest incidence of 0.80 per 1000 LBs and was particularly associated with late-onset infection. Although the incidence was lower, GBS (0.30 per 1000 LBs) and *E. coli* (0.11 per 1000 LBs) were more commonly recorded in EOS, which is a result similar to that for these two pathogens in the USA.² The risk of death (16.2%) was significantly higher for infants with sepsis associated with *E. coli* infection than with *K. pneumoniae* (8.8%) or GBS (4.9%) infection. Owing to the incidence and associated fatalities, the important pathogens to combat and prevent NS in China are *K. pneumoniae* and *E. coli*. The epidemiological findings strongly demonstrated again the predominance of *E. coli* in NS in China and identified GBS and *K. pneumoniae* as the most common causative pathogens for EOS and LOS, respectively. The results hint that it is possible to decrease the occurrence of EOS to some extent by implementing preventive measures, according to the successful experience with GBS in developed countries.^{6,17}

GBS has emerged as a major pathogen responsible for NS and meningitis in developed countries since the 1970s.⁵ Prevention strategies based on intrapartum antibiotic prophylaxis in at-risk women resulted in a significant reduction in early-onset GBS disease.⁶ By contrast, the relevant data in developing countries, including China, are scarce, although according to limited data, GBS disease in some regions of China is low.^{18,19} However, recently, GBS cases have been reported more often, and a nationwide study is underway.²⁰ Nevertheless, the clinical profile of neonatal GBS sepsis is largely unexplored in China, similar to other eastern areas including Hong Kong, Malaysia, Thailand, and India.^{12,20–22} The percentage (13.2%) of GBS associated with NS in this study is very similar to the result (14.2%) from another hospital in South China.¹³ In two other hospitals in South China, GBS was the predominant pathogen associated with NS at 5.2–31.3%, which were higher values than those in middle China during the same period.^{7,9,23} Moreover, GBS (46.5%) was recently reported as the leading organism, followed by *E. coli* (23.3%) and *S. aureus* (7.0%), in infants <3 months old in a multicenter study on Chinese children diagnosed with bacterial meningitis between 28 days and 6 years of age, excluding neonates.²⁴ GBS was the most common pathogen in both early-onset and late-onset bacterial meningitis. GBS was also the most common pathogen in term infants in a multicenter retrospective epidemiological study from 2011 to 2016.²⁵ These findings indicate that geographical disparity might exist in the spectra of pathogens causing NS in China. Therefore, the status of neonatal GBS invasive infection in China needs to be surveyed, and preventive measures should be taken.

Sepsis ranks as the third most common cause of neonatal deaths in China, and Chinese clinicians are generally more active in the management of neonates with suspected infections.²³ Ampicillin/piperacillin and third-generation cephalosporin are the choices for the first-line empirical antibiotics to treat NS in China, whereas ampicillin combined with gentamicin is used in developed areas.²¹ *K. pneumoniae* and *E. coli* received much attention because of their high rates of multidrug resistance.²⁵ In this study, *E. coli* had the same resistance to antibiotics as that found in other reports from China and in children of different ages.²⁴ However, the high incidence rate of extended-spectrum β -lactamase producers and the high resistance to ampicillin and the third-generation cephalosporins continue to suggest that serious concern is warranted. Regardless of the high resistance reported consistently to erythromycin or clindamycin, penicillin or ampicillin is effective against GBS in

China.^{5,21,26} In general, empirical therapy should be guided by the antimicrobial resistance patterns of bacterial isolates commonly detected.

Several limitations occurred in this study. Because the positive rates of CSF or blood cultures can decrease significantly if antibiotics are used more than 24 h before sample collection, some infants that had NS but were culture-negative for infection would not have been identified. Although the study hospital is the largest children's medical organization in the local area, there remains a small portion of the infants born inside that will be admitted to their nearest hospital in the case of emergency. Both of the above-mentioned scenarios would underestimate the incidence of NS. Additionally, a single sample with CoNS was excluded from analysis in the study, which might have led to bias. Last, maternal histories were not collected and analyzed, even though they would provide important information about exposure to infectious disease and bacterial colonization, natural and acquired immunity, and obstetric risk factors.

In summary, *K. pneumoniae*, *E. coli*, GBS, and *S. aureus* were the predominant pathogens in culture-proven NS in South China. This study was the first to use epidemiological data of a population in China to reveal that *K. pneumoniae* was the most frequent pathogen. *Klebsiella pneumoniae* was primarily associated with late-onset sepsis in preterms, whereas GBS predominated the pathogens associated with early-onset sepsis. *Escherichia coli* was common in both EOS and LOS with the highest mortality. As optimal prevention and treatment strategies are considered, continued surveillance to monitor changes in pathogens, disease severity, and outcome is important. The results of this study will contribute to the management of neonatal sepsis by focusing on the pathogens that may have been overlooked in the past.

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Disclosure

The authors report no conflicts of interest in this work.

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