Group B *Streptococcus* causes severe sepsis in term neonates: 8 years experience of a major Chinese neonatal unit

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Original article

Background: **In contrast to industrialized countries, the clinical characteristics of neonatal sepsis caused by Group B *Streptococcus* (GBS) are largely unexplored in China.**

Methods: **A retrospective case series study was performed at a high-capacity neonatal unit in Shanghai, China from January 2008 to December 2015. Clinical characteristics of neonates with culture-proven GBS sepsis and antibiotic susceptibility of isolated strains were analyzed.**

Results: **Forty-three term neonates were included during the study period. The majority (74.4%) had early-onset sepsis with symptoms of respiratory distress. Meningitis was significantly more common in late-onset sepsis than in early-onset sepsis (81.5% *vs.* 18.8%, *P*<0.0001). Approximately one third of all patients (*n*=16) developed severe sepsis, defined as sepsis with organ dysfunctions, and respiratory dysfunction/failure was the most common (32.6%). The in-hospital mortality rate of GBS sepsis was 4.7%. Neonates who progressed to severe sepsis had significantly lower pH level at the onset of symptoms than those who did not (7.26±0.12 *vs.* 7.39±0.05, *P*=0.006). Treatment of severe GBS sepsis required lots of medical resources including extracorporeal membrane oxygenation. All tested GBS strains were susceptible to penicillin, but the rate of resistance to clindamycin (84.0%) and erythromycin (88.0%) was high.**

Conclusions: **GBS as a pathogen for neonatal sepsis has been receiving little attention in China. Our data demonstrated that GBS sepsis was likely to be fulminant. Early recognition followed by antibiotics and adequate supportive therapies was critical for successful treatment. Chinese clinicians should be aware of GBS infection when treating neonatal sepsis, especially in the absence of universal maternal GBS screening.**

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Introduction

Since 1970s, *Streptococcus agalactiae*, or Group B *Streptococcus* (GBS), has emerged as a common pathogen responsible for neonatal sepsis. In industrialized countries, the incidence of early-onset neonatal GBS infections has declined from approximately 1.7 to 0.3 per 1000 live births after the policy of intra-partum antibiotic prophylaxis while that of late-onset neonatal GBS infections remained around 0.5 per 1000 live births.[1-5] In contrast, relevant data were scarce in developing countries including China. Current literature demonstrated that the incidence of neonatal GBS infection varied from 0.11 to 3.06 per 1000 live births in Africa, Middle East, Asia/Pacific and India/Pakistan.[2,6-8]

GBS sepsis among Chinese newborns has been receiving little attention, probably because the proportion of GBS in causative pathogens of neonatal sepsis was very low (0 to 5.9%).[9-15] However, it should be noted that these data were not from multi-center or population-based studies, and the exact incidence of neonatal GBS sepsis in China still remains elusive. GBS was demonstrated to be able to cause very severe infections, and a treatment protocol of neonatal GBS sepsis has been established in industrialized countries based on a thorough understanding of the risk factors, clinical manifestations and outcomes. In contrast, the clinical profile of neonatal GBS sepsis is largely unexplored in China. Whether China should develop its own protocol of treating neonatal GBS sepsis depends on multiple factors involving clinical practice, public health as well as policy making, and first-hand clinical data on neonatal GBS infection hold key in the decision-making process.

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Our study is motivated by the current gap of knowledge on neonatal GBS sepsis in China. Because there is limited resource to conduct prospective multi-center surveys, we conceptualized a retrospective case series study in a representative high-capacity Chinese neonatal unit. The study objective was to explore the risk factors, clinical course, laboratory manifestations, antibiotic susceptibility of neonatal GBS sepsis. Results of this study will contribute to the management of neonatal sepsis by focusing on a pathogen which may have been overlooked in China.

Methods

Institute and ethics statement

We conducted a retrospective case series study at the neonatal unit of Children's Hospital of Fudan University in Shanghai. With a total capacity of 250 beds and approximately 6000 hospitalized neonates per year, this neonatal unit ranks as one of the largest and most well-equipped nurseries in China. Because there is no provision of maternal services, our unit also serves as a key transferal center for birth facilities in Shanghai, whose population is 24 million with 160 000 births per year. The catchment population of our unit, by estimation, is 30% of annual births in Shanghai. This study was approved by the ethics committee of Children's Hospital of Fudan University.

Data collection

We identified all neonates with culture-proven GBS sepsis in our unit between January 1, 2008 and December 31, 2015. By reviewing medical records, data on maternal history, delivery, neonatal demographic characteristics, signs and symptoms at presentation, as well as the subsequent clinical course including laboratory findings, treatment and outcome at discharge were collected. Neonates who died within 48 hours of admission were also included as long as the culture result was positive for GBS and the case data were relatively complete.

Standard of care

According to the policy of our department, a full sepsis work-up (blood culture, complete blood cell count, C-reactive protein level, lumbar puncture, chest and abdomen radiography) was performed for every case of suspected sepsis. The urine culture was performed for patients with suspected sepsis as well. Evaluation of sepsis likelihood is based on perinatal risk factors, clinical signs and the result from laboratory tests. The empirical antibiotic therapy for sepsis was ampicillin in combination with third-generation cephalosporin. Antibiotics were promptly discontinued if blood culture yielded negative results after 48-72 hours, and the infant had no subsequent clinical evidence or risk factors of neonatal infections. Cultures were consecutively performed until negative results were obtained, and antibiotics were administered for a minimum of 10-14 days from the first negative culture.

Definitions

GBS sepsis was defined for neonates in whom GBS was cultured from blood with clinical symptoms or signs including fever (anal body temperature >38.0°C), respiratory distress, apnea, cyanosis, poor feeding, jaundice, lethargy and seizure. Additionally, meningitis was diagnosed if cerebral spinal fluid (CSF) was cultured positive for GBS, or GBS negative but with a cellular reaction of >20 leukocytes/μL in CSF associated with GBS positive blood culture and consistent clinical manifestation. We defined sepsis with onset of symptoms between birth and 1 week of age as early-onset sepsis (EOS) and those afterwards as late-onset sepsis (LOS).[3] Information on maternal history, gestational age and birth weight was provided by maternal hospitals and registered in neonates' medical records. Thresholds for abnormal peripheral blood cell counts in this study were determined by referring to the textbook as well as recent investigations.[16,17] As there is no neonatal-specific consensus on sepsis, severe sepsis was defined according to the International Pediatric Sepsis Consensus Conference 2005 as sepsis with cardiovascular organ dysfunction or acute respiratory distress syndrome or two or more other organ dysfunctions.[18] Inconsistencies on organ dysfunction/failure were resolved by discussion among all authors.

Bacterial sample processing

GBS strains in blood samples were identified using the automated BacT/ALERT system (BioMérieux, Lyons, France). For CSF samples, blood agar culturing followed by Gram staining, catalase reaction assays, CAMP tests, and Lancefield grouping was used for strain confirmation. E-test and disk-diffusion method were applied for antimicrobial susceptibility test before 2013. Since then, VITEK 2 Compact System (BioMérieux) has been used. Molecular techniques for strain detection and strain serotyping were not performed in this study.

Statistical analysis

Continuous variables were expressed as mean±standard deviation or as median (range), analyzed by Student's *t* or Mann-Whitney *U* test. Categorical variables were presented as number (proportion), analyzed by Chi-square test. Statistical analyses were performed using

SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA). A *P* value of less than 0.05 was considered to be statistically significant.

Results

Baseline characteristics of the study population

A total of 43 term neonates were included during the study period. No maternal complications nor intrapartum fever were reported. None of the mothers had prenatal GBS screening. Table 1 shows the majority of EOS cases (*n*=23, 71.9%) presented clinical symptoms within 6 hours after birth, whereas the median age of symptoms onset for LOS cases was 20 days (range: 8 to 25 days) postnatally. Ten of the surviving neonates were discharged before full recovery to a community-based nursery at parents' request. The median length of hospitalization for surviving EOS and LOS neonates was 16 days (range: 5 to 52 days) and 28 days (range: 10 to 75 days), respectively.

Table 1. Demographic and clinical characteristics of neonates with Group B *Streptococcus* sepsis categorized by the onset of disease

Characteristics	All cases (*n*=43)	EOS (*n*=32)	LOS (*n*=11)	*P* value
Maternal age (y), mean±SD	27.4±3.8	27.1±4.0	28.5±3.5	0.322
Gestational age (wk), mean±SD	39.2±1.4	39.3±1.4	38.9±1.2	0.449
Birth weight (g), mean±SD	3358±368	3383±305	3284±521	0.561
Male, *n* (%)	22 (51.2)	15 (46.9)	7 (63.6)	0.488
Caesarean section, *n* (%)	14 (32.6)	9 (28.1)	5 (45.5)	0.457
PROM, *n* (%)	10 (23.3)	9 (28.1)	1 (9.1)	0.409
Death, *n* (%)	2 (4.7)	1 (3.1)	1 (9.1)	0.613
Age at presentation, *n* (%)				
<6 h	23 (53.5)	23 (71.9)	0	-
6-24 h	5 (11.6)	5 (15.6)	0	-
2-7 d	4 (0.09)	4 (12.5)	0	-
>7 d	11 (25.6)	0	11 (100)	-
Clinical signs at presentation, *n* (%)				
Respiratory signs*	30 (69.8)	26 (81.3)	4 (36.4)	0.009
Fever >38.0°C	25 (58.1)	15 (46.9)	10 (90.9)	0.014
Jaundice	23 (53.5)	23 (71.9)	0	<0.0001
Poor feeding	19 (44.2)	12 (37.5)	7 (63.6)	0.170
Lethargy	14 (32.6)	10 (31.3)	4 (36.4)	0.755
Poor perfusion	9 (20.9)	6 (18.8)	3 (27.3)	0.672
Seizure	5 (11.6)	3 (9.4)	2 (18.2)	0.589
Meningitis, *n* (%)	15 (34.9)	6 (18.8)	9 (81.8)	<0.0001
Organ dysfunction/failure, *n* (%)				
Respiratory	14 (32.6)	10 (31.3)	4 (36.4)	0.755
Cardiovascular	6 (14.0)	5 (15.6)	1 (9.1)	0.972
Hematological	3 (7.0)	2 (6.3)	1 (9.1)	0.750
Hepatic	1 (2.3)	1 (3.1)	0	0.256
Peripheral blood test within 24 h of presentation, *n* (%)				
Number of samples	37 (86.0)	28 (87.5)	9 (81.8)	-
WBC >20×10^3/μL	9 (24.3)	9 (32.1)	0	0.079
WBC <5×10^3/μL	11 (29.7)	8 (28.6)	3 (33.3)	0.786
Neutrophil <7.5×10^3/μL	21 (56.8)	15 (53.6)	6 (66.7)	0.702
Platelet count <100×10^3/μL	2 (5.4)	2 (7.1)	0	0.401
CRP >8 mg/L	17 (45.9)	10 (35.7)	7 (77.8)	0.025
Supportive therapy, *n* (%)				
Mechanical ventilation	12 (27.9)	10 (31.3)	2 (18.2)	0.698
Inhaled nitric oxide	4 (9.3)	4 (12.5)	0	0.558
Surfactant	2 (4.7)	2 (6.3)	0	0.985
IVIG	11 (25.6)	6 (18.8)	5 (45.5)	0.114
Vasoactive agents	6 (14.0)	5 (15.6)	1 (9.1)	0.970
Glucocorticosteroids	3 (7.0)	2 (6.3)	1 (9.1)	0.750

*: tachypnea, apnea, cyanosis, grunting, retraction. "-": no data; EOS: early-onset sepsis; LOS: late-onset sepsis; SD: standard deviation; PROM: premature rupture of membrane; WBC: white blood cell; CRP: C-reactive protein; IVIG: intravenous immunoglobulin.

Clinical presentation and laboratory parameters of neonatal GBS sepsis

Lumber puncture was performed with parental consent in 88.4% of all neonates, and intracranial images were obtained before discharge/death from 80% (*n*=12) of neonates with meningitis. Fig. 1 illustrates the distribution of different chest radiograph manifestations among EOS and LOS neonates. Severe sepsis occurred in approximately one third (*n*=16) of all neonates, and respiratory dysfunction/failure was the most common (Table 2). Patients who progressed to severe sepsis in clinical course had significantly lower pH level at presentation (*P*=0.006) (Table 2). For neonates with severe sepsis, white blood cell and neutrophil counts demonstrated a decreasing trend within 48 hours of presentation, while platelet count remained persistently lower (*P*>0.05) (Fig. 2). Nine out of 11 abnormal intracranial images, manifesting as malacia (*n*=3), intraventricular hemorrhage (*n*=4) or hydrocephalus (*n*=2), were observed in neonates with meningitis.

Treatment of neonatal GBS sepsis

Antibiotic susceptibility results were available for 58.1% (*n*=25) of all neonates (Table 3). Missing data were due to inaccessibility to medical records at an outside birth hospital (*n*=6), premature discharge (*n*=10)

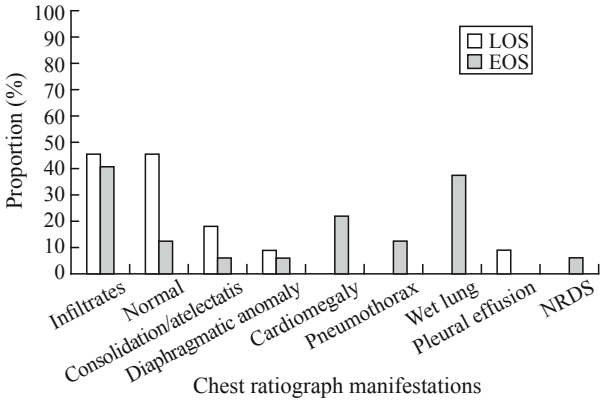

Fig. 1. Distribution of different chest radiograph manifestations among neonates with Group B *Streptococcus* sepsis categorized by the onset of disease. Diaphragmatic anomaly indicates elevation or depression of the diaphragm. EOS: early-onset sepsis; LOS: late-onset sepsis; NRDS: neonatal respiratory distress syndrome.

Table 2. Clinical characteristics of neonates with Group B *Streptococcus* sepsis categorized by the severity of illness

Characteristics	Severe sepsis (n=16)	Sepsis without organ dysfunction /failure (n=27)	P value
Male, n (%)	9 (56.3)	13 (48.1)	0.755
Caesarean section, n (%)	10 (62.5)	19 (70.4)	0.739
PROM	4 (25.0)	6 (22.2)	0.835
Maternal age (y), mean±SD	26.8±3.6	27.8±4.0	0.468
Gestational age (wk), mean±SD	39.3±1.4	39.2±1.4	0.819
Birth weight (g), mean±SD	3301.3±394.4	3391.6±354.8	0.443
EOS, n (%)	12 (75.0)	20 (74.1)	0.946
Death, n (%)	2 (12.5)	0	0.133
Clinical signs at presentation, n (%)			
Respiratory signs*	15 (93.8)	15 (55.6)	0.014
Fever >38.0°C	9 (56.3)	16 (59.3)	0.847
Jaundice	8 (50.0)	15 (55.6)	0.761
Poor feeding	10 (62.5)	9 (33.3)	0.111
Lethargy	5 (31.3)	9 (33.3)	0.888
Poor perfusion	8 (50.0)	1 (3.7)	0.001
Seizure	3 (18.8)	2 (7.4)	0.344
Blood gas within 24 h of onset of symptoms, n (%)			
Number of samples	13 (81.3)	12 (44.4)	-
pH, mean±SD	7.26±0.12	7.39±0.05	0.006
Lactate (mmol/L), median (range)	10.8 (4.6-21.0)	6.3 (1.5-10.4)	0.119
Peripheral blood test within 24 h of presentation, n (%)			
Number of samples	16 (100)	21 (77.8)	-
WBC >$20\times10^3/\mu$L	3 (18.8)	6 (28.6)	0.702
WBC <$5\times10^3/\mu$L	7 (43.8)	4 (19.0)	0.151
Neutrophil <$7.5\times10^3/\mu$L	10 (62.5)	11 (52.4)	0.739
Platelet count <$100\times10^3/\mu$L	1 (6.3)	1 (4.8)	0.843
CRP >8 mg/L	7 (43.8)	10 (47.6)	0.815
Supportive therapy, n (%)			
Mechanical ventilation	12 (75.0)	0	<0.0001
Inhaled nitric oxide	4 (25.0)	0	0.015
Surfactant	2 (12.5)	0	0.133
IVIG	5 (31.3)	6 (22.2)	0.719
Vasoactive agents	6 (37.5)	0	0.001
Glucocorticosteroids	3 (18.8)	0	0.045

*: tachypnea, apnea, cyanosis, grunting, retraction. "-": no data. PROM: premature rupture of membrane; SD: standard deviation; EOS: early-onset sepsis; WBC: white blood cell; CRP: C-reactive protein; IVIG: intravenous immunoglobulin.

and death (n=2). The median time to initiate antibiotics was 12.5 hours (range: 1 to 33 h) postnatally for EOS, and 4 hours within admission for LOS. Third-generation of cephalosporin was administered for more than 72 hours among 39.5% (n=17) of all neonates (median: 9.5 days, range: 3 to 31 days) despite negative culture results for Gram-negative bacteria in samples obtained from blood, CSF, sputum and endotracheal tube.

Approximately one third of the 43 neonates had mechanical ventilation during hospitalization, the modes included conventional mechanical ventilation (n=5), high frequency ventilation (n=4) and nasal continuous positive airway pressure (n=3). All ventilated neonates except one were EOS cases, and the median time of initiating ventilation was 7.5 hours postnatally (range: 2 to 29 hours). Intravenous immunoglobulin and vasoactive agents, most frequently dopamine (83.3%), were given to more than one third of neonates who developed severe sepsis. One neonate presenting apnea, cyanosis, fever and poor perfusion at 8 hours postnatally rapidly deteriorated within 20 hours, and was on veno-arterial extracorporeal membrane

Table 3. Antibiotic susceptibility test of Group B *Streptococcus* strains

Antibiotics	Non-susceptibility (n=25), n (%)
Penicillin	0
Cefazolin	0
Clindamycin	21 (84.0)
Erythromycin	22 (88.0)
Vancomycin	0
Levofloxacin	5 (20.0)
Ceftriaxone	1 (4.0)
Cefotaxime	1 (4.0)
Tetracycline	24 (96.0)
Meropenem	0
Tigecycline	0

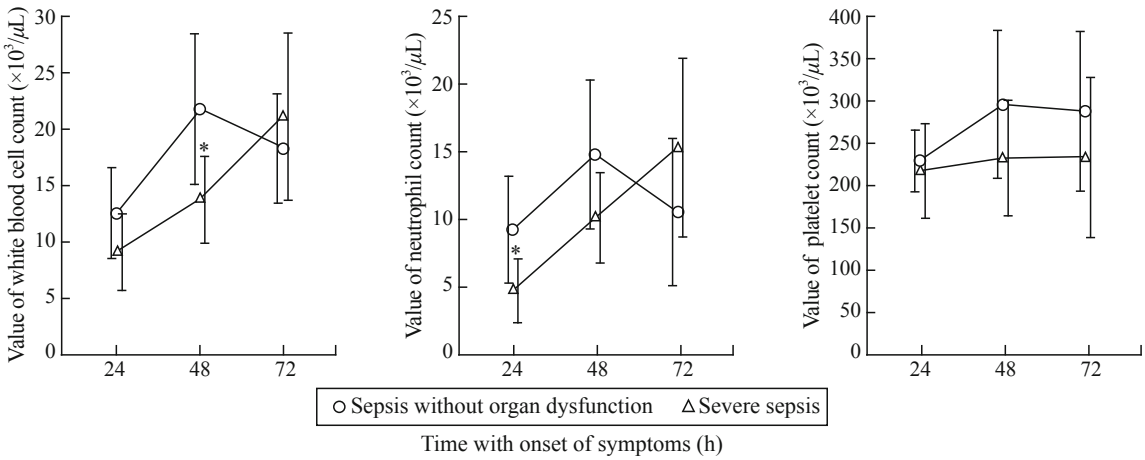

Fig. 2. The temporal trend of blood cell counts within 72 h of the onset of symptoms among neonates with Group B *Streptococcus* sepsis categorized by illness severity. Error bars indicate 95% confidence intervals of the mean values. *: P<0.05, between the two groups at the same time point.

oxygenation (VA-ECMO) for 275 hours combined with continuous renal replacement therapy (CRRT). She survived to discharge on day 35 without evidence of complications. Another LOS case admitted with diaphragmatic abscess above the liver at 20 days of age developed right-sided diaphragmatic hernia 3 weeks later, and was discharged uneventfully after surgical intervention.

Discussion

To the best of our knowledge, this study is the very first focusing on clinical characteristics of neonatal GBS sepsis in China, thus has several important aspects. First, Chinese neonates with GBS sepsis have similar clinical manifestations as their counterparts in other middle- and high-income countries. Second, GBS was likely to cause severe sepsis in term neonates, as evidenced by a high rate of organ dysfunction/failure in our study, although term neonates generally have a lower sepsis-specific mortality rate than preterm neonates.[1] The reason why GBS sepsis in our department during a prolonged period of 8 years was exclusively identified among term neonates is unclear. A possible explanation is that the intrapartum antibiotic treatment was generally more active pending preterm birth, thus the clinical course of GBS infection in preterm infants may be prevented or masked. Third, the mortality rate (2/43, 4.7%) for GBS sepsis in our department was comparable to that from developed countries (4%-6%).[4,8] This indicates that early awareness of severe sepsis followed by a rapid and active treatment strategy supported by advanced intensive care facilities is central in decreasing the mortality rate of severe GBS sepsis. We are also able to provide ECMO to treat critically ill patients with infections as the underlying pathology in our hospital.

Maternal GBS carriage in lower digestive and urogenital tracts is the primary risk factor for neonatal GBS sepsis.[3] The carriage rate ranged from 10%-30% in industrialized countries[1-5] and 12%-33.7% in developing regions,[6-8] respectively. In China, there is no standard policy to screen pregnant women for GBS carriage during antenatal checks, and the actual status of maternal GBS colonization is not clear. Limited data showed that maternal GBS colonization rate in some regions of China was low (6.5%-11.1%).[19-21] Genetic susceptibilities may be one factor to explain the difference between China and other countries, while underreporting can not be ruled out due to mothers' inadequate access to prenatal health care and suboptimal GBS detection techniques in China. Pilot studies in recent years have demonstrated that real-time polymerase chain reaction may allow a more rapid and reliable detection of GBS in the third trimester as compared to conventional culture method (8.2% *vs*. 2.9%).[8,10] Clarification on maternal GBS colonization status is of significant importance to assess the risk of neonatal GBS sepsis. Some neonatal deaths due to GBS sepsis might have been avoided if their mothers had undergone maternal GBS screening and received intrapartum antibiotic prophylaxis.

Consistent with data reported elsewhere,[3,4] our study demonstrated that neonates with EOS showed clinical signs overlapping with those of respiratory distress. In contrast, LOS cases had a less fulminant clinical course and predominantly manifested as meningitis.[3,4] However, the long-term outcome of LOS caused by GBS is a serious concern, and neurodevelopmental sequelae were reported in up to 50% of survivors.[22,23] So far, no method can satisfactorily diagnose GBS sepsis, or predict the severity of infection, with high specificity and sensitivity, a short laboratory turnaround time as well as a reasonable price. Our study added that routine blood examination in current practice such as white blood cell count, platelet count and C-reactive protein may not have a good ability to identify critically ill cases. Because misjudgement can have fatal outcomes, neonates suspected to have GBS sepsis should be monitored vigilantly.

We had the first case of neonatal sepsis successfully treated with ECMO in mainland China. As compared with similar cases, ours was more challenging as demonstrated by a prolonged treatment time, the need to frequently change ECMO membrane oxygenator as well as the combination of neonatal CRRT. The uncomplicated discharge of our patient highlighted the importance of organ function support in the treatment of severe sepsis. In this series, we also identified a case with late-onset GBS sepsis and right-sided diaphragmatic hernia. To our current knowledge, this is the first case reported in the mainland of China. The mechanisms underlying the association between GBS sepsis and diaphragmatic hernia have not been elucidated.[24] Possible explanation was the predisposition of neonates to GBS pneumonia due to congenital diaphragmatic defect, or postnatal necrosis/rupture of diaphragmatic tissues resulted from GBS sepsis.[24] Surgery in a timely manner is central in the treatment of this severe complication.

Globally, surveillance data demonstrated uniform susceptibility of GBS strains to penicillin/ampicillin and most β-lactams for more than 50 years.[3,5] However, emergence of strains with reduced susceptibility to penicillin have been very recently reported.[26] While there is no evidence of penicillin non-susceptible GBS strains in China,[9,14] our study and other similar studies

over the past two decades showed high resistance of GBS strains to erythromycin, clindamycin and tetracycline.[9,25] Notably, GBS isolates not susceptible to third-generation cephalosporin was identified in our study. Sepsis ranks as the third most common cause of neonatal deaths in China,[15] and Chinese clinicians are generally active, if not aggressive, in the management of neonates with suspected infections. This has been reflected in our department's policy of sepsis work-up as mentioned earlier. In industrialized countries, the first-line empirical antibiotics to treat neonatal sepsis are ampicillin combined with gentamicin, whereas in China and some developing countries the choice is often ampicillin/piperacillin and third-generation cephalosporin.[27] Diversities in antibiotic regimen were dependent on local pathogenic epidemiology, microbial resistance profile and drug availability. However, the increasing number of multi-resistant strains, especially in developing countries, is a serious matter of concern. An inappropriately prolonged duration of third-generation cephalosporins probably due to risk factors of nosocomial infections is alarming and may contribute to antibiotic resistance.

Limitations of this study included a small sample size on account of the single-center design. The retrospective nature of study design also prevented a complete retrieval of data on maternal complications, perinatal history and neonatal laboratory results during hospitalization, and GBS serotyping was not performed. Therefore, our statistical analysis may be underpowered to detect significant differences in clinical characteristics and laboratory parameters between neonates who progressed to severe sepsis and those who did not. Furthermore, specific consensus on the definition and severity grading of neonatal sepsis has not been achieved yet.[28] Although the currently applied paediatric consensus was intended to include term neonates,[21] inaccuracy was probable and may be another factor explaining the lack of between-group differences in our study. Last but not the least, future epidemiological studies are desperately needed to elucidate the incidence and risk factors of neonatal GBS sepsis, as well as maternal GBS carriage rate and neonatal post-discharge outcomes, in order to obtain a complete clinical picture of this disease and fully evaluate the burden of disease.

GBS as a causative pathogen for neonatal sepsis has been receiving little attention in China. Our data demonstrated that there is a lack of information on perinatal risk factors associated with neonatal GBS sepsis. GBS can cause severe sepsis in term neonates, and prompt recognition followed by early administration of antibiotics in combination with adequate supportive therapies were critical for successful treatment. Chinese clinicians should be aware of GBS infection when treating neonatal sepsis, for term and preterm neonates alike, especially in the absence of universal maternal GBS screening.

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Contributors: Dong Y analyzed data and drafted the manuscript. Jiang SY and Zhou Q contributed to acquisition and analysis of data. Cao Y was responsible for study concept and design, and manuscript revision. All authors contributed to the intellectual content and approved the final version.

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