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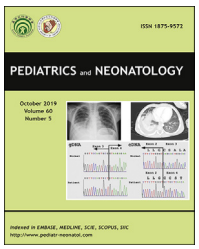

Review Article

Epidemiology of group B streptococcal infection in pregnant women and diseased infants in mainland China

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Group B *Streptococcus* (GBS) is a leading cause of neonatal sepsis and an important cause of maternal disease in many countries; however, no accurate population-based epidemiological data on GBS is yet available in mainland China. In this systematic literature review, we obtained published data regarding the maternal GBS colonization rate, incidence of invasive GBS disease in infants, clinical screening, and the associated GBS typing and clinical outcomes in China. The maternal GBS colonization rate in mainland China ranged from 3.7 to 14.52%, and the incidence of invasive GBS disease in infants was 0.55–1.79 per 1000 live births, with a case fatality risk ranging from 6.45 to 7.1%. Serotype III was the dominant serotype that was observed in GBS isolates. GBS detection and identification has become more commonplace, due to the availability of polymerase chain reaction and DNA microarray technologies. Immunizing pregnant women against GBS is an emerging approach through which newborns are protected from GBS. The available data suggest that five GBS serotypes (Ia, Ib, II, III, and V) account for the majority of the cases of GBS disease in mainland China. Furthermore, conjugate vaccines comprising some or all of these serotypes are of potential value in the prevention of GBS infection.

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1. Introduction

Group B *Streptococcus* (GBS) is a normal commensalistic microbe that inhabits the gastrointestinal and vaginal tracts. GBS is a predominant pathogen of perinatal infection in Western countries and can cause serious harm to maternal and child health. In pregnant women, the manifestations of GBS commonly include asymptomatic bacteriuria, urinary tract infections, bacteremia, chorioamnionitis, and placental abruption. These manifestations are responsible for adverse events such as premature birth and stillbirth. Neonatal GBS infection causes pneumonia, sepsis, and meningitis. Intrapartum antibiotic prophylaxis (IAP) has significantly reduced the incidence of early-onset GBS disease (GBS-EOD) in European countries and the US.[1,2] However, recommendations for the treatment of GBS are still up for debate due to controversies surrounding the challenges involved in the identification of the best candidates for IAP and the disadvantages of this treatment. There is a lack of epidemiological survey data regarding the incidence of neonatal GBS disease. Thus, the effectiveness of IAP cannot be adequately assessed. For instance, there are no established guidelines for the diagnosis or treatment of perinatal GBS in China and little attention has been paid to neonatal GBS infection. Here, we review the epidemiology, typing distribution, clinical screening and prevention of perinatal GBS in mainland China with reference to the international GBS prevention strategy.

2. Literature search and selection criteria

In this review, we included all of the studies that have reported GBS infection in mainland China, published in Chinese and English, up to August 2018. Searches were performed in the PubMed, Wanfang Data, VIP, and CNKI databases using the following key words: China, group B *streptococcus*, *Streptococcus agalactiae*, GBS, colonization, invasive GBS disease, GBS screening, GBS typing, antibiotic prophylaxis, newborns, antimicrobial resistance, and GBS vaccine. Two authors individually reviewed all of the titles and abstracts and extracted the related results. Conference abstracts and letters were excluded from inclusion in this review. Full-text articles were screened according to inclusion criteria. A total of 1220 papers (PubMed: 315; Wanfang Data: 340; VIP Database: 364; CNKI: 201) were identified; of these, 1179 were excluded due to duplication, irrelevance or ineligible population or research methods. The remaining 41 full-text articles were assessed for eligibility.

3. Epidemiology

GBS colonization during pregnancy can be transient, intermittent, or persistent,[1,2] leading to varying GBS test results in the same patient across different stages of pregnancy. It has been reported that the overall estimated mean prevalence of rectovaginal GBS colonization is 17.9%. Africa has the highest reported prevalence of GBS (22.4%), while Southeast Asia has the lowest (11.1%).[3] In Taiwan the prevalence of GBS is 23.7%.[4] Large-scale, multicenter epidemiological studies on maternal GBS colonization in mainland China remain rare. Regional differences in maternal GBS colonization have been noted. Data inputs regarding the rates of maternal GBS colonization in mainland China are illustrated in Fig. 1A, B.

The Centers for Disease Control and Prevention (CDC, U.S; 2010) estimated that approximately 20—30% of pregnant women have GBS; in this population, approximately 50% of babies acquire GBS, and 1—2% of these babies go on to develop the invasive disease.[1] A previous review analyzed the incidence risk (per 1000 live births) for infant GBS disease in 53 countries. The overall incidence risk was 0.49, with incidence risks of 1.12, 0.49, 0.46, and 0.30 in Africa, Latin America and the Caribbean, developed countries, and Asia, respectively. The incidence of GBS-EOD and late-onset GBS (GBS-LOD) worldwide is 0.41 and 0.26, respectively. The overall case fatality risk (CFR) is 8.4%, and the CFRs for GBS-EOD and GBS-LOD are 10.0% and 7.0%, respectively.[5] GBS remains the leading cause of neonatal sepsis and meningitis, and is associated with significant mortality and morbidity. After the introduction of IAP to at-risk women, striking declines have been noted in the incidence of GBS-EOD. An active population-based surveillance in the USA demonstrated a further 80% decrease in the incidence of GBS-EOD from 1993 to 2008 after the widespread implementation of IAP. The CFR associated with GBS-EOD dropped from $\geq$50% in the 1990s to 4—6% in 2010. The mortality rate is higher among preterm infants, with a CFR of approximately 20%, However, IAP did not affect the incidence of GBS-LOD, which remains unchanged, at 0.25—0.5 per 1000 live births.[1,2] Chinese studies, published between 2011 and 2016, have demonstrated that perinatal GBS infection can lead to severe adverse pregnancy outcomes and serious harm to infants.[6,7] Several studies have reported 0.55—1.79 cases of neonatal GBS per 1000 live births, with a CFR of 6.45—7.1%.[8,9] Therefore, physicians should pay great attention to GBS infection, relevant research should be actively performed, and appropriate guidelines for the diagnosis and treatment of GBS should be formulated to prevent or reduce the incidence of neonatal GBS infection and improve maternal and infant outcomes.

4. GBS typing

4.1. Serotyping

GBS isolates from humans express a capsular polysaccharide (CPS). GBS isolates can be divided into ten CPS serotypes (Ia, Ib, II, III, IV, V, VI, VII, VIII, and IX), each of which is antigenically and structurally unique.[2] In a systematic literature review and meta-analysis of 390 articles across 85 countries, serotypes Ia, Ib, II, III, and V were found to account for 98% of all of the GBS isolates that were obtained from pregnant women. Serotype III has a lower frequency in some South American and Asian countries; serotype V has a higher prevalence (observed together with lower serotype III prevalence) in Western Africa; and serotypes VI, VII, VIII, and IX are more common than other serotypes in Asia.[10] A study from Beijing, China, in the 1990s demonstrated that types II (33%), III (23%), Ia (16%), and V (6%) were the most prevalent observed GBS

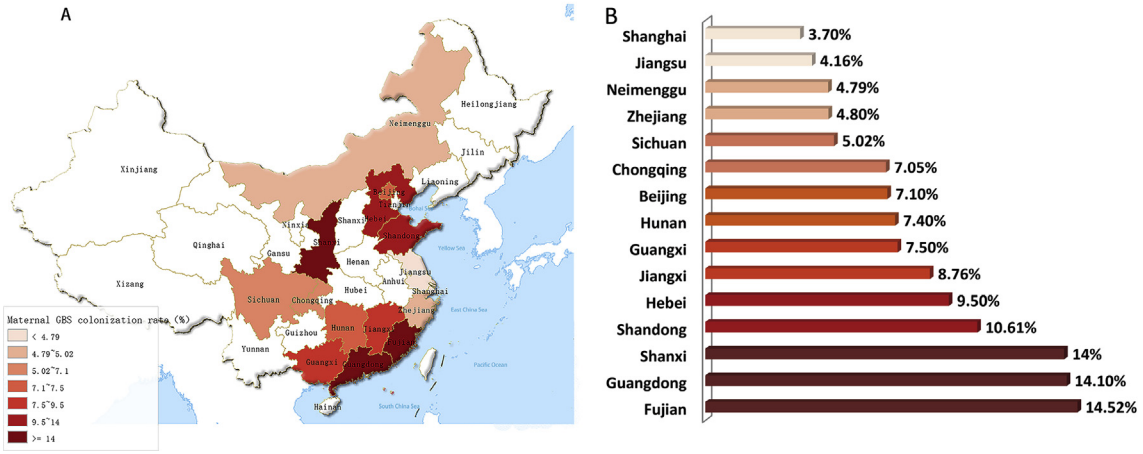

Figure 1 National distribution of data inputs. A. Map illustrating the maternal group B *streptococcus* colonization rate in mainland China. The rates are as follows: Northern China, including Hohhot and Inner Mongolia, 4.79%[49]; Qinhuangdao in Hebei Province, 9.5%[6]; Hanzhong in Shanxi Province, 14.0%[50]; Beijing, 7.1%[12]; Qingdao in Shandong Province, 10.61%[51]; Eastern China including Shanghai, 3.7%[52]; Nanjing, 4.16%[53]; Southern China including Chongqing, 7.05%[54]; Chengdu in Sichuan Province, 5.02%[55]; Taizhou in Zhejiang Province, 4.8%.[56] Changsha in Hunan Province, 7.4%[57]; Jiangxi Province, 8.76%[58]; Xiamen in Fujian Province, 14.52%[8]; Guilin in Guangxi Province, 7.50%[59]; Shenzhen and Dongyuan in Guangdong Province, 9.1—19.1%.[60] B. Bar chart showing the maternal GBS colonization rates in 15 provinces.

serotypes.[11] In a more recent study of pregnant women in Beijing, serotype III accounted for 41.8% of all cases of GBS, while the remainder of cases consisted mainly of serotypes Ia (21.4%), Ib (11.9%), and V (14.9%).[12] These two studies indicate that the prevalence of serotypes III and Ia have increased over time, while that of serotype II has significantly decreased in recent years. A multicenter study from Shanghai identified seven serotypes of GBS (Ia, Ib, II, III, V, VI, and VIII) with a prevalence of 0.9—35.9%. Of these, serotypes III (35.9%), Ia (22.5%), V (21.2%), and Ib (10.4%) were the most predominant.[13] In a study of pregnant women in Guangdong, the main GBS serotype was found to be Ib (36.7%), followed by types Ia (28.3%), III (18.3%), and IX (10%).[14] The distribution of GBS serotypes shows temporal and geographic variations. This variation may reflect the differences in serotype fitness, changes in herd immunity, or the spread of antibiotic-resistance clones.

In a review and meta-analysis of 135 studies worldwide, five serotypes (Ia, Ib, II, III, and V) were found to account for 97% of the invasive isolates in all regions.[5] This study reported that nearly half (47%) of the cases of GBS-EOD and 73.0% of the cases of GBS-LOD cases were caused by serotype III. Serotypes Ia, Ib, and V were frequently isolated in GBS-EOD and GBS-LOD. Several reports have investigated the serotype distribution of invasive GBS isolates in China. Forty GBS isolates were recovered from infected neonates below 3 months of age in Shenzhen and Beijing. Here, serotype III (85%) was the most prevalent isolate, followed by serotypes Ia (7.5%), Ib (5%), and V (2.5%). The proportion of neonates with serotype III isolates was significantly higher among GBS-LOD cases than among GBS-EOD cases. The other identified serotypes (Ia, Ib, and V) were more likely to cause GBS-EOD.[15] A total of 84 cases of neonatal GBS bloodstream infection were analyzed in Jinhua, Zhejiang between 2008 and 2016. The mainly serotype was III, which accounted for 60.7% of cases, followed by serotypes Ia (14.3%), Ib (11.9%), V (8.3%) and NT (4.8%).[16] Among the 26 GBS isolates that were recovered from neonates with invasive disease between 2013 and 2014 at Guangzhou and Changsha hospitals, serotype III was the most represented (57.6%), particularly among LOD strains (11 cases), followed by types Ib (19.2%), V (11.5%), Ia (7.6%), and II (3.8%).[17] Twenty-six GBS isolates were recovered from infected neonates in Shenzhen between 2008 and 2014. Here, serotype III (65.4%) was the most prevalent isolate, followed by serotypes Ia (11.5%), Ib (11.5%), V(3.8%), and NT (7.7%).[18] Between 2011 and 2014, Guan et al.[9] collected 68 GBS isolates from infants under 3-months of age with positive GBS cultures in South China. In this study, serotype III accounted for 77.9% of all isolates, followed by serotypes Ib (14.7%), V (4.4%), and Ia (2.9%). Serotype III was found in 68.2% of cases of GBS-EOD and 82.6% of cases of GBS-LOD. Based on the findings of all of these studies, serotype III is the most common serotype that is isolated from cases of neonatal invasive GBS infection in mainland China. Fig. 2A, B presents the prevalence of GBS serotypes in pregnant women and infants with invasive infections in mainland China, respectively.

4.2. Genotype

Multilocus sequence typing (MLST) for GBS involves the sequencing of short fragments of seven housekeeping genes (*adhP*, *pheS*, *atr*, *glnA*, *sdhA*, *glcK*, and *tkt*). This method is used to identify bacterial pathogenic genotypes. The most common GBS sequence types (STs) are ST1, ST17, ST19, and ST23. MLST for a global GBS collection identified ST1, ST19, and ST23 as predominant STs in colonized pregnant women while ST17 was significantly associated with invasive neonatal infections.[19,20] Some epidemiological studies have found that ST19 is predominant in colonized pregnant women and ST17 is

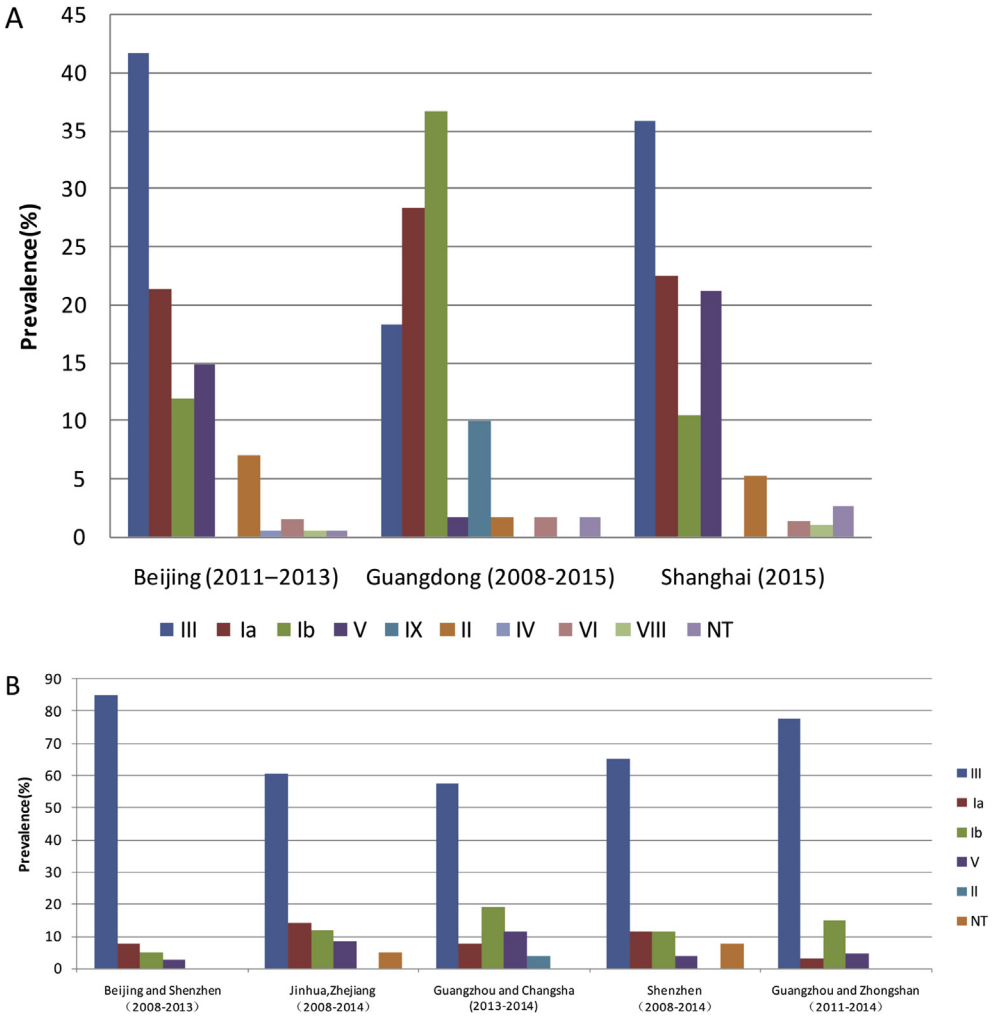

Figure 2 Distribution of group B *streptococcus* (GBS) serotypes. A. Prevalence of GBS serotypes in pregnant women presented as percentages. B. Prevalence of GBS serotypes in infants with invasive infections presented as percentages.

predominant in neonatal invasive infection in China.[9,15,21] Different genotypes cause GBS infections with different pathogenic characteristics. Takei et al.[22] reported late-onset serotype VIII and ST1 GBS infections in a neonate with congenital biliary atresia who presented with bacteremia and urinary tract infection. Li et al. analyzed 26 GBS strains in Shenzhen, China, and found that ST17 was most commonly associated with meningitis and septicemia, followed by ST12 and ST19.[18] Many studies have revealed that GBS colonization and infection are closely related to certain specific STs, which show different geographical distributions.

4.3. Relationship between serotypes and genotyping, virulence genes, resistance genes

The first studies employing the MLST scheme revealed that the capsular serotype usually contains several different STs, and GBS strains with the same ST may have different serotypes. For colonizing as well as invasive GBS strains, dominant serotype-MLST genotypes associations have been observed such as serotype III with ST-17, serotype V with ST-1, and serotype IV with ST-196.[20] In Shenzhen, China, 57 GBS isolates were recovered from 1277 pregnant women, and ST10 was the dominant ST in serotype Ib; ST19 and ST17 in serotype III; ST12 in serotype V; ST103, ST485, and ST624 in serotype Ia.[23] Among 56 strains taken from pregnant women in two hospitals in Beijing, China, ST19 and ST17 were the dominant STs in serotype III; ST23 and ST485 in serotype Ia; ST12 and ST10 in serotype Ib; and ST1 and ST19 in serotype V.[21] In Taiwan, MLST was performed in 83 GBS isolates that were derived from infants and children younger than 18 years old with invasive GBS infections, ST1 was detected in multiple serotypes (II, III, V, VI, VII), ST12 was specifically in serotype Ib, ST17/ST19 was in serotype III, and ST23/ST24 was in serotype Ia.[24] Among 40 GBS isolates recovered from infected neonates less than 3 months of age in Beijing and Shenzhen, serotype III isolates included ST17 (94.2%), ST19 (2.9%), and ST650 (2.9%).[15] The study of 8 GBS isolates of invasive disease in infants in Guangzhou and Changsha identified ST17 in serotype III, ST23 in serotype Ia, ST12 and ST10 in serotype Ib, and ST1 in serotype V.[25] These findings were consistent with those reported by Lu et al. in a study of 95 GBS isolates that were collected from eight cities in China.[26]

The pathogenicity of GBS depends on the virulence factors. In addition to its CPSs, its virulence genes include *bac, scpB, lmb, hylB, cylE*, and surface protein antigen genes (*bca, rib, epsilon, alp2, alp3*, and *alp4*), which encode Cβ, C5a peptidase, laminin-binding protein, hyaluronidase, β-cyle hemolysin, and surface-localized proteins (Alpha C, Rib, Epsilon/Alp1/Alp5, Alp2, Alp3, and Alp4), respectively. All of these virulence factors play an important role in escaping host immune defenses and invading host cells. Su et al.[14] analyzed 60 GBS strains in pregnant women in Shenzhen, China, and identified *hylB, lmb*, and *scpB* as the main virulence-associated genes. Chen et al.[27] analyzed the serotypes and virulence genes of GBS among 1277 pregnant women in Shenzhen and found that all GBS strains carried the *scpB* and *hylB* genes. The predominant surface-localized protein antigen genes were *rib* (49.1%), *epsilon* (28.1%), and *bca* (21.1%). Serotype III isolates were more likely to carry the *rib* gene, serotype Ia carried the *epsilon* gene, and serotype V carried the *bca* gene. Multiplex PCR-based reverse line blot assay revealed the relationships between molecular serotypes and protein antigen gene profiles, namely, serotype Ia and IV-*alp1*, serotype Ib-*bca* and *bac*, serotype II-various genes, serotype III-*rib*, and serotype V and VIII-*alp3*.[28] Specific virulence genes might affect the pathogenicity of the corresponding GBS serotype (See Table 1).

The GBS hypervirulent adhesin (HvgA) is a novel ST17-specific surface-anchored protein that was first described by Tazi et al., who demonstrated that HvgA contributed to the crossing of the blood-brain barrier by GBS and the subsequent onset of meningitis. Pilus structures in GBS have been shown to be primarily involved in epithelial cell colonization, biofilm formation, translocation, and invasion. Three pilus islands (PI), PI-1, PI-2a, and PI-2b encode three structural proteins: a backbone protein, two ancillary proteins and two pilus-specific class C sortase enzymes, respectively.[29] Genomic studies have revealed that all GBS strains carry at least one of these three pilus islands. PI-1 and PI-2a are associated with maternal colonization, while PI-1 and PI-2b are associated with neonatal invasive disease. Moreover, PI-2b has been shown to be conserved in the ST17 hypervirulent clone.[30] Campisi et al. collected 26 isolates from infants that were affected by sepsis and meningitis in the Guangzhou/Changsha area and showed that 14 strains of serotype III were HvgA positive, and thus associated with ST17, 13 isolates presenting PI-2b alone belonged to serotype III/ST17.[17] Li et al. conducted a prospective cohort study of 1815 GBS colonized mother–neonate pairs in Shenzhen, China, and demonstrated that the most common combination of PIs was PI-2b alone, followed by PI-1+PI-2a, PI-2a alone and PI-1+PI-2b. Furthermore, strong relationships were noted between ST17 and serotype III/rib/PI-2b, ST19 and serotype III/rib/PI-1+PI-2a, ST10 and serotype Ib/alphaC/PI-2a, and ST12 and serotype V/alphaC/PI-2a.[31] However the most prevalent pilus island of GBS colonized in pregnant women in Beijing was PI-2a alone. This indicates that there was a geographical variation in the distribution of the pilus island.[32] GBS strains contain macrolide resistance genes, including *ermA, ermB, ermC, ermTR, mefA/E, mefA*, and *linB*. Wang et al.[15] reported that, of 40 invasive GBS isolates identified in Shenzhen and Beijing, 37 (92.5%) were resistant to erythromycin, in which 27 harbored the *ermB* gene alone, 2 isolates harbored the *mefA* gene alone, and 8 isolates harbored both the *ermB* and *mefA* genes. In a cross-sectional GBS colonization study of 1814 neonates, only *scpB* and *hlyB* were found in 24 GBS isolates. ST19/III and ST17/III carrying *ermB* and *rib*, ST10/Ib and ST12/Ib carrying *ermB* and *alphaC*, ST485/Ia carrying *mefA/E* and *epsilon* were all resistant to erythromycin.[33] Therefore, identifying the GBS serotypes and genotype characteristics as well as the geographic distribution can aid in the prevention and treatment of GBS infection.

5. Diseases and sequelae caused by GBS

GBS plays an important role in severe materno-neonatal infections. For mothers, GBS cause intrauterine infection and puerperal sepsis, and for newborns, GBS is the most common cause of early-onset sepsis.[34] Furthermore, GBS remains the leading cause of neonatal meningitis, causing neonatal deaths and long-term neurological sequelae among survivors. A retrospective study of cases of fatal neonatal pneumonia suggested that GBS, especially GBS-EOD, is an important pathogen in fatal neonatal pneumonia in China.[35]

GBS-EOD occurs at ≤6 days of life, with the majority of cases occurring within the first 24 h following birth. Maternal carriage of GBS in the gastrointestinal and/or

Table 1 Relationships between serotype, sequence type, and virulence genes in group B *streptococcus* isolates.

Serotype	SEQUENCE TYPE	VIRULENCE GENES
Ia	ST23/ST24[21,24,25]	*scpB/hylB/lmb/epsilon*[14,27,28]
Ib	ST10/ST12/ST19/ST23[21,23–25]	*bac/scpB/hylB/lmb/bca*[14,27,28]
II	–	Various genes[28]
III	ST17/ST19[15,23–25]	*scpB/hylB/lmb/rib*[14,27,28]
IV	–	*scpB/hylB*/Epsilon[27,28]
V	ST1/ST12/ST19[21,23,25]	*scpB/hylB/bca/alp3*[14,27,28]
VI	ST19[14]	*bac/scpB/hylB/lmb//bca/epsilon*[14,27]
VII		*alp3*[28]
VIII		*alp3*[28]
IX	ST19/ST23[14]	*scpB/hylB/lmb*[14]

ST = sequence type.

genital tracts is a pre-requisite for EOD, and vertical transmission occurs during or just prior to birth. The most common clinical syndromes of GBS-EOD are sepsis, fulminant pneumonia or, less frequently, meningitis. Without prompt therapy, such cases may show rapid deterioration, with dyspnea, temperature instability, circulatory disorders, and fatigue. GBS-LOD occurs between 7 days and 3 months of age, and horizontal transmission during the perinatal period may occur from mother, hospital or community sources to infant. Infants present with bacteremia and one-quarter of all cases develop meningitis. Cellulitis and osteoarticular infections rarely occur. Among survivors of GBS meningitis, approximately 50% of children have some deficit, and up to 30% have severe neurological sequelae, including vision or hearing loss, hydrocephalus, and mental retardation.[36]

Between 2010 and 2017, data from 95 GBS isolates that were recovered from infected neonates and mothers in eight tertiary hospitals across China were analyzed.[26] Of these, 55 isolates were responsible for bacteremia and/or meningitis in mothers, and 28 and 22 isolates were responsible for EOD and LOD, respectively. Of the 28 cases of EOD, 11% (3/28) had pneumonia, 68% (19/28) had sepsis alone, 14% (4/28) had meningitis alone, and 7% (2/28) had both sepsis and meningitis. Of the 22 cases of LOD, 63% (14/22) had sepsis, 9% (2/22) had meningitis, 14% (3/22) had pneumonia and 14% (3/22) had sepsis/meningitis (for clinical manifestations of neonatal GBS infection, see Fig. 3). The incidence of invasive GBS infection in neonates <3 months of age in Guangzhou has been studied, and 0.51‰ of infants were found to have GBS infection. Furthermore, the incidence of GBS-EOD was 0.32‰ and GBS-LOD was 0.19‰. The incidence of GBS-EOD has increased annually, while the incidence of GBS-LOD has remained relatively stable.[37] Zhou et al.[38] reported using extracorporeal membrane oxygenation (ECMO) to rescue a newborn with refractory GBS sepsis who developed cardiopulmonary failure. Respiratory distress, hypotension, and persistent pulmonary hypertension developed in 20 h of life, and the clinical condition deteriorated rapidly. Following ECMO for 275 h, combined with intermittent continuous renal replacement therapy, the patient regained stable hemodynamics, good oxygenation and the infection was controlled. One case of neonatal early-onset GBS septicemia and bacterial meningitis that was complicated by a large area cerebral infarction was reported.[7] Another case of an infant with perinatal hemorrhagic stroke with culture-proven sepsis and meningitis caused by GBS was reported.[39]

6. Laboratory methods for GBS identification

Culture is the current gold standard for the diagnosis of invasive GBS disease. However, this technique has a long turnaround time (48—72 h) and is not 100% sensitive. Moreover, the results of culture are affected by the time of specimen collection, preservation conditions, and environmental factors.[1,2] In China, hospitals prefer to use standard microbiological culture to diagnose GBS. Due to overgrowth of other bacteria in the vagina and rectum, GBS growth is inhibited; therefore, the CDC recommend the use of an enrichment broth to improve detection. Lu et al.[40] placed samples in enrichment broth for 18—24 h, and inoculated the enriched samples in GBS screening medium or Colombia blood agar. These samples were compared with those that had been directly inoculated, and it was found that prior enrichment helped easily identify GBS and improved the positive detection rate. To overcome the disadvantage of bacterial culture, a variety of rapid detection methods, including latex agglutination, immunoassay, molecular biological tests, have been developed. Some of these methods have been applied in clinical practice. Wu et al.[41] explored the use of a novel colloidal gold immunochromatographic test strip for GBS detection. This test strip showed better sensitivity, shorter detection time (5—8 min), was easy to perform, and had high value in clinical application at primary medical institutions. PCR has relatively higher sensitivity and specificity and is a rapid method, which might determine the appropriate antibiotic for use in pregnant women at term with an unknown colonization status and no other risk factors.[2,8,42] Some researchers have found that placing swabs in enrichment broth for 15—16 h before PCR can increase the detection of GBS.[43] However, the utility of real-time PCR in the intrapartum setting remains limited, as there is no antimicrobial susceptibility testing for penicillin-allergic women and because it is expensive. The Xpert GBS LB assay is a new molecular diagnostic test that

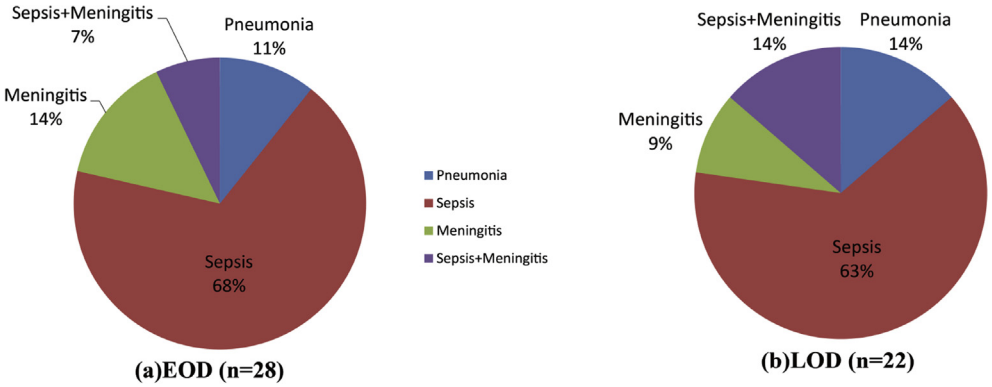

Figure 3 Clinical manifestations of neonatal GBS infection from 2010 to 2017 at 8 tertiary hospitals in mainland China in the early-onset GBS disease (EOD) group and the late-onset GBS disease (LOD) group.

is performed within a test cartridge. This assay is easy to handle and allows for minimal hands-on time, requiring <2 min per sample.[44] Zeng et al.[28] developed a 33-primer and 34-probe multiplex PCR-based reverse line blot (mPCR/RLB) assay to simultaneously identify GBS serotypes and surface protein antigen genes, which would provide a convenient and inexpensive tool for high-throughput epidemiological studies of GBS. Wen et al. developed a *cpsH* gene-based DNA microarray to identify the nine GBS serotypes.[45]

7. Prevention of perinatal GBS disease by IAP

The CDC recommends antenatal screening of women at 35—37 weeks of gestation and selective administration of IAP to GBS-positive women for a minimum of four hours.[1] The following are the indications for IAP to prevent GBS-EOD: having a previous infant with invasive GBS disease; GBS bacteriuria during any trimester of the current pregnancy; positive GBS vaginal-rectal screening culture in late gestation during current pregnancy; unknown GBS status at labor onset (culture not performed, incomplete, or results unknown and any of the following factors: delivery at <37 weeks gestation, amniotic membrane rupture ≥18 h, intrapartum temperature ≥100.4 °F (≥38.0 °C), or intrapartum nucleic acid amplification tests positive for GBS. IAP is not indicated in cases of GBS-negative culture, regardless of intrapartum risk factors; and delivery via cesarean section performed before labor onset with intact amniotic membranes regardless of GBS colonization status or gestational age.

Currently, there are no universal guidelines for GBS screening and prophylactic antibiotic use in expectant mothers in mainland China. Many hospitals have adopted IAP, but many medical personnel fail to grasp the indications of IAP, as a result of which the incidence of GBS disease varies widely across China. Widespread antibiotic use increases allergic responses in pregnant women, can lead to increased drug resistance, and even increase the risk of sepsis due to non-GBS pathogens. The incidence of early-onset sepsis was retrospectively studied at the Taipei Mackay Memorial Hospital in Taiwan. After screening and IAP treatment were implemented, it was found that the GBS-EOD incidence decreased and the percentage of early-onset sepsis induced by *Escherichia coli* increased, especially in extremely premature low-birth-weight neonates.[46]

GBS is susceptible to penicillin and to most β-lactam antibiotics. Other treatment options include ampicillin, cefazolin, clindamycin, erythromycin, or vancomycin for patients with penicillin allergies. However, increasing rates of clindamycin and erythromycin resistance have been detected in several regions of the world, including Europe, North America, and Asia.[2] In the United States, reports published between 2006 and 2009 revealed that the prevalence of the resistance of invasive GBS isolates to erythromycin and clindamycin ranged from 25 to 32% and 13—20%, respectively.[1] In mainland China, studies between 2008 and 2015 reported that these percentages range from 57.4 to 92.5% and 51.5—87.5%, respectively.[9,15] Therefore, antenatal GBS cultures from high-risk women with penicillin allergies should undergo antimicrobial susceptibility.

8. GBS vaccine

IAP dramatically decreased the incidence of GBS-EOD; however, IAP did not influence GBS-LOD. The burden of disease is substantial in these cases, and IAP may be more difficult to implement in low/middle income countries due to the unclear epidemiology of GBS, the higher number of babies being delivered at home, late presentation to healthcare facilities for delivery, inadequate culture methods, and prohibitive cost. Therefore, developing a GBS vaccine would be an ideal and promising approach towards the prevention of GBS infections in babies, given the potential adverse effects of IAP as well as the need for effective prevention of both adult and late perinatal disease.

Currently, an understanding of the GBS serotypes is crucial to the development of serotype-based vaccines against GBS disease. Serotypes III, Ia, Ib, and V are the predominant serotypes among pregnant women and infants in mainland China. Phase I and II clinical trials have demonstrated the safety and immunogenicity of monovalent CPS-conjugate vaccines among healthy women (only one trial was performed in pregnant women with a III tetanus toxoid conjugate). However, monovalent formulations with serotype-specific immune responses are not sufficient to provide protection against the different GBS serotypes found in invasive infections, and no licensed vaccines are currently available. Multivalent vaccines would provide broader vaccine coverage and overcome problems of serotype switching. A trivalent GBS vaccine (CRM_{197}-conjugated capsular polysaccharides of GBS serotypes Ia, Ib and III) has gone through phase I and II trials and appears to be well tolerated and immunogenic. However, there are no plans for these trivalent vaccine candidates to progress to phase III studies. Furthermore, preclinical studies of a pentavalent (Ia, Ib, II, III, V) CPS-CRM_{197} vaccine are currently in progress.[47]

A systematic review of global GBS disease in infants below 3 months of age revealed that serotypes Ia, Ib, and III, and serotypes Ia, Ib, II, III, and V account for 79.0% and 88.0% of all cases, respectively.[48] Results of the serotyping in mainland China indicate that a pentavalent conjugate vaccine covering serotypes Ia, Ib, II, III, and V could potentially prevent 80—90% cases of neonatal invasive GBS disease. Both temporal and geographical variations can be seen in the serotype distribution of GBS. Continuing surveillance of the GBS serotype distribution in China will aid in the future formulation of multivalent GBS vaccines. In recent years, there has been a welcome emergence of pilus proteins, surface proteins, and genomics, which present exciting new opportunities for an effective and globally relevant GBS vaccine.[31]

9. Conclusion

GBS is an important neonatal pathogen that is associated with high morbidity and mortality, especially in premature infants. Universal intrapartum screening and IAP are effective strategies proven to prevent GBS infection in neonates. Understanding the epidemiological distribution of GBS and identifying the prevalent serotypes and

genotypes in maternal and neonatal GBS infections in China are essential for the development of an effective GBS vaccine and for the prevention and treatment of GBS infection.

Conflicts of interest

The authors declare that there are no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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