Neonatal Group B *Streptococcus* Disease

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EDUCATION/PRACTICE GAPS

Group B *Streptococcus* (GBS) is a leading cause of invasive infection in neonates and young infants. Clinicians must be familiar with obstetric approaches to mitigating neonatal GBS disease, as well as the management of neonates at risk for GBS disease. Clinicians should understand how mechanisms of pathogen transmission, risk factors, and clinical presentation may differ between infants with early- and late-onset GBS disease.

OBJECTIVES *After completing this article, readers should be able to:*

1. Describe the epidemiology of neonatal early- and late-onset group B *Streptococcus* (GBS) disease.
2. Describe the pathogenesis of perinatal GBS disease.
3. Describe the obstetric guidelines for GBS screening and intrapartum antibiotic prophylaxis.
4. List the approaches to management of infants at risk for GBS disease, including postnatal risk stratification and management of confirmed infections.

ABSTRACT

Group B *Streptococcus* (GBS) is an important cause of neonatal sepsis in term and preterm infants. Because GBS colonizes human genitourinary and gastrointestinal tracts, a significant focus of neonatal GBS disease prevention is to interrupt vertical transmission of GBS from mother to infant during parturition. Routine antepartum GBS screening in pregnant women, as well as widespread use of intrapartum antibiotic prophylaxis, have aided in overall reductions in neonatal GBS disease during the past 3 decades. However, neonatal GBS disease persists and may cause mortality and significant short- and long-term morbidity among survivors. Herein, we highlight contemporary epidemiology, microbial pathogenesis, and the clinical presentation spectrum associated with neonatal GBS disease. We summarize obstetric recommendations for antenatal GBS screening, indications for intrapartum antibiotic prophylaxis, and considerations for antibiotic selection. Finally, we review national guidelines for risk assessment and management of infants at risk for GBS disease.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
ACOG	American College of Obstetricians and Gynecologists
CDC	Centers for Disease Control and Prevention
EOGBS	early-onset group B *Streptococcus*
EOS	early-onset sepsis
GBS	group B *Streptococcus*
HIV	human immunodeficiency virus
IAP	intrapartum antibiotic prophylaxis
LOGBS	late-onset group B *Streptococcus*
NDI	neurodevelopmental impairment
NRN	Neonatal Research Network

INTRODUCTION

Group B *Streptococcus* (GBS) emerged in the 1970s as a leading cause of neonatal sepsis in the United States, and it currently accounts for approximately 30% of neonatal early-onset sepsis (EOS) cases. (1) Maternal GBS colonization occurs in 10% to 35% of parturients in the United States, (2)(3)(4) and it is a major risk factor for neonatal early-onset GBS (EOGBS) disease acquired via vertical transmission during birth. The overall incidence of neonatal GBS disease has decreased during the past several decades, largely due to reductions in EOGBS disease in the era of protocolized screening for maternal GBS colonization and widespread use of GBS-targeted intrapartum antibiotic prophylaxis (IAP). However, there are no current strategies for neonatal late-onset GBS (LOGBS) disease prevention, and the national incidence of late-onset infection has not changed with use of IAP. This article summarizes the epidemiology of neonatal GBS disease, consensus recommendations for maternal screening and IAP, and management of neonates at risk for GBS disease.

EPIDEMIOLOGY

EOGBS Disease

EOGBS disease is defined as infection presenting between days 0 and 6 after birth. (5) The estimated US EOGBS disease incidence has steadily decreased during the past 3 decades (6)(7)(8): from 1.8 cases per 1,000 live births in 1992 (9) to 0.2 cases per 1,000 live births in 2020. (10) Globally, EOGBS disease incidence is 0.41 cases per 1,000 live births, with 2-fold higher incidence in low- and middle-income countries compared with high-income countries. (11) In 2020, 43% of all neonatal GBS disease cases in the United States occurred in the early-onset period. (10) A Neonatal Research Network (NRN) study of infants born in 2015 through 2017 with neonatal EOS identified that GBS caused 30% of all EOS cases occurring within 72 hours of birth. GBS was the second-most common pathogen overall in this cohort (after *Escherichia coli*, which was isolated in 35% of all cases). (1) However, EOGBS disease rates differ between infants born at term (≥37 weeks' gestation) versus preterm (<37 weeks' gestation); almost 75% of all EOGBS disease cases occur in term infants. (6) Among infants in the NRN with EOS, GBS accounted for 51% of EOS cases in term infants compared with 13% of EOS cases in preterm infants. Among very low birthweight infants (<1,500 g) admitted to Vermont Oxford Network center NICUs in 2018 and 2019, GBS accounted for 19% of EOS cases. (12)

LOGBS Disease

LOGBS disease is defined as invasive GBS disease presenting on days 7 to 89 after birth. LOGBS disease incidence has remained stable during the past 2 decades, with incidence estimated to be 0.3 to 0.4 cases per 1,000 live births in the United States and worldwide. (6)(8)(11) LOGBS disease is now the predominant form of neonatal GBS disease, accounting for 57% of all neonatal GBS cases in 2020. (10) Preterm infants account for 10% to 11% of all US births, (13) but Centers for Disease Control and Prevention (CDC) surveillance reports indicate that 48% of LOGBS disease cases occur in preterm infants. (6) Population-level estimates suggest that preterm infants are at 6 times higher risk for LOGBS disease compared with term infants. (6) Accordingly, a substantial proportion of LOGBS disease occurs in chronically hospitalized infants, accounting for 19% of all LOGBS disease cases in a large Japanese surveillance study. (14)

PATHOGENESIS

Microbiology

GBS is a β-hemolytic encapsulated Gram-positive bacterium that colonizes the human genitourinary and gastrointestinal tracts. Colonization is mediated by GBS surface proteins, which allow effective adherence to the extracellular matrix on the epithelial surface. (15) The molecular pathogenesis of GBS is complex (15) and involves invasion of epithelial barriers (including placental membranes and pulmonary epithelium) via endocytosis. GBS produces numerous toxins (eg, β-hemolysin/cytolysin and CAMP [Christie-Atkins-Munch-Peterson] factor) that proceed to cause direct cytotoxic tissue injury. GBS evades the host immune response via its polysaccharide surface capsule, which mimics human surface antigens and evades complement deposition, thus interfering with host opsonization and phagocytosis. Among bacteria undergoing phagocytosis, GBS is uniquely able to resist oxidative burst killing via expression of superoxide dismutase and production of carotenoid pigments that neutralize host oxidative stressors.

GBS' capsular polysaccharides are major virulence factors and the primary microbial element distinguishing GBS serotypes. (16) Ten GBS serotypes have been identified (types Ia, Ib, and II-IX), with types Ia, Ib, II, III, and V occurring most commonly and accounting for 98% of serotypes causing maternal colonization and neonatal GBS disease. (6)(11)(16)(17) Serotype distribution differs by timing of GBS onset; CDC US surveillance during 2006 through 2015 identified that EOGBS disease was most commonly associated with serotypes Ia (27%), III (27%), and II (16%) and that LOGBS disease was most commonly associated with serotypes III (56%) and Ia (20%). (6)

GBS is a common cause of neonatal meningitis and effectively invades and causes direct injury to the central nervous system. GBS penetrates the epithelial blood-brain barrier via transcytosis, aided by β-hemolysin/cytolysin's direct cytotoxic activity. Preclinical studies in mice suggest that invasion of GBS through the blood-brain barrier then triggers a robust inflammatory response leading to diffuse neutrophil recruitment, cytokine release, vascular damage, and neuronal death. (15)

Transmission

Vaginal-rectal GBS colonization rates range from 10% to 35% among parturients in the United States. (2)(3)(4)(18) Maternal GBS colonization can produce an adaptive immune response in the form of serotype-specific IgG production, detectable in 50% of colonized mothers at delivery. (2) Among colonized women, young maternal age is associated with negative GBS serostatus. Neonates colonized at birth almost universally share the same GBS serotype colonizing their mothers antenatally. (19)(20)(21) Among colonized mothers not receiving IAP, neonatal GBS colonization rates at birth are reported to be 43% to 60%, (22)(23) decreasing to as low as 0% to 9% in the setting of intrapartum ampicillin treatment. (23)(24)(25) Maternal receipt of IAP is also associated with lower rates of heavy neonatal GBS colonization burden (decreasing from 35% to 12% in 1 prospective cohort study of mother-infant dyads). (21)

Among all infants of GBS-colonized women, EOGBS disease rates are approximately 1% to 2% in the absence of IAP, decreasing to 0.3% in settings with routine IAP use. (26) Neonatal EOGBS disease results from vertical transmission of GBS from mother to fetus via ascending infection through ruptured membranes, translocation through intact membranes, or aspiration during parturition. (25) Higher maternal colonization density is associated with increased likelihood of neonatal colonization at birth. (24)(27) In addition to GBS colonization, risk factors for development of EOGBS disease include preterm birth, prolonged duration of membrane rupture, presence of intra-amniotic infection, GBS bacteriuria during pregnancy, and history of a previous neonate with GBS disease. (28) Transplacental transfer of maternal serotype-specific GBS antibodies seems to protect neonates from invasive GBS disease. Presence of serotype-specific maternal antibody is associated with an estimated 70% to 90% risk reduction of neonatal EOGBS disease, (29) and negative maternal GBS serostatus is associated with invasive neonatal GBS disease. (30) In the era of universal screening and GBS IAP, EOGBS disease now most commonly occurs in the setting of negative maternal GBS screening results (reported 50%–80%) (1)(31)(32), potentially attributable to false-negative antenatal screening results or to maternal GBS colonization occurring after screening but before delivery.

GBS acquisition in LOGBS disease is likely multifactorial. Only 10% to 50% of infants with LOGBS disease are born in the setting of positive antenatal maternal GBS screening. (33)(34)(35) Nonetheless, vertical transmission is implicated in LOGBS disease, with up to 50% of infants colonized at birth. (18) Delayed vertical transmission from GBS-colonized mothers to their infants after hospital discharge also occurs. (21) IAP reduces maternal GBS colonization burden and decreases immediate transmission during birth; delayed transmission can occur when maternal GBS colonization burden rises after IAP-induced suppression wanes. Mothers with negative antenatal GBS screens may become colonized after delivery, resulting in delayed neonatal GBS colonization and disease onset. Among 53 Italian neonates with LOGBS disease, only 33% were born in the setting of positive maternal GBS screening; by the time LOGBS disease was diagnosed, 63% of these infants' mothers were GBS-colonized. (33) A longitudinal cohort study of infants of GBS-colonized mothers identified that 1) delayed neonatal colonization does occur, as early as 15 days after delivery, and 2) GBS strains identified in delayed neonatal colonization were identical to maternal strains present at birth. (21) Associations of LOGBS disease with exposure to GBS from human milk are reported, but the importance of human milk as a source of neonatal colonization is controversial. One prospective study of LOGBS found that 6 of 83 mothers GBS-colonized postpartum had GBS in human milk. (21) It remains unclear whether the colonized or infected mammary gland is a source of neonatal colonization or vice versa. (33)(36)(37)(38) Finally, horizontal transmission is implicated, from community nonmaternal sources and from nosocomial origins (including hospital-based outbreaks with presumed transmission via nursery staff). (33)(39)

CLINICAL PRESENTATION

GBS is primarily a perinatal pathogen, and in addition to neonatal disease it causes bacteremia, chorioamnionitis, and endometritis in parturient women. (40) Rising rates of invasive GBS disease are also noted in nonpregnant adults, particularly the elderly, largely manifested as bacteremia, pneumonia, and skin/soft tissue infections. (41)(42)

Fetal

GBS infection is associated with adverse fetal outcomes, particularly stillbirth. A systematic review indicated that 0% to 12% of stillbirths are associated with isolation of GBS from an otherwise sterile compartment, (43) an estimated annual 57,000 GBS-associated stillbirths worldwide. (44) Maternal GBS colonization has also been associated with preterm birth, although this relationship is confounded by accompanying perinatal factors (eg, preterm labor, preterm premature rupture of membranes) that may themselves increase the risk of GBS infection. Maternal GBS bacteriuria is associated with preterm labor and premature rupture of membranes, but an association with preterm birth has not been consistently identified. (45)(46)

EOGBS Disease

Although EOGBS disease is defined as GBS disease presenting during days 0 to 6 after birth, 95% of contemporary EOGBS disease cases present during the birth hospitalization, within the first 48 hours after birth. (6) Clinical risk factors for EOGBS infection overlap with general neonatal EOS risk factors and include preterm birth, maternal intrapartum fever, clinical concern for intra-amniotic infection, prolonged duration of membrane rupture, and inadequate exposure to IAP (if indicated). (31)(47) Isolated bacteremia is the most common manifestation of EOGBS disease (80%–90%); meningitis with cerebrospinal fluid culture-confirmed infection is less commonly reported (1%–10%). (1)(6)(7) EOGBS meningitis incidence may be underestimated given low rates of lumbar punctures performed before antibiotic initiation. (1) Clinical signs at EOGBS disease presentation are nonspecific and commonly include respiratory distress, tachycardia, apnea, and/or lethargy. Infants with early-onset meningitis often present with seizures. (48) Rarer but severe manifestations of EOGBS disease may include shock, perinatal encephalopathy, and pneumonia with or without pulmonary hypertension. (49) GBS pneumonia may appear radiographically indistinguishable from the respiratory distress syndrome of the newborn, (50)(51) mandating a high index of suspicion for early-onset infection among infants with respiratory failure at birth.

LOGBS Disease

Reported median age at LOGBS disease presentation ranges from 27 to 41 days, with term infants presenting earlier than preterm infants. (6)(14)(33)(35) Clinical factors associated with LOGBS disease include preterm birth, maternal GBS colonization, and multiple gestation. (33)(52) Globally, human immunodeficiency virus (HIV)–exposed but uninfected infants seem to have 4-fold higher rates of LOGBS disease compared with HIV-unexposed infants; reduced transplacental transfer of GBS-specific antibodies to HIV-exposed infants is 1 proposed explanation for this finding. (53) Clinical manifestations of LOGBS disease are more heterogeneous compared with EOGBS disease. Isolated bacteremia occurs most frequently (61%), although meningitis is also common (31%). (6) Less common presentations include pneumonia, urinary tract infection, septic arthritis/osteomyelitis, skin and soft tissue infections, and adenitis. (6)(33)(35) Importantly, up to 8% of infants with any LOGBS disease (and up to 30% of infants with cerebrospinal fluid culture-confirmed meningitis) have negative blood cultures, (6)(54) highlighting the utility of inclusion of urine, cerebrospinal fluid, and focal site cultures (as applicable) in routine evaluations of infants with suspected late-onset neonatal sepsis. Clinical signs reported in LOGBS disease include fever, poor feeding, respiratory distress with tachypnea, emesis, changes in mental status (irritability, lethargy), and seizures (particularly among infants with LOGBS meningitis). (35)(48)(49) LOGBS disease may progress to fulminant disease with septic shock (variably reported with rates of 3%–10%), (6)(33)(35) and up to 30% of all infants with LOGBS disease presenting to emergency departments require ICU admission. (35) Table 1 summarizes characteristics of EOGBS and LOGBS disease.

Recurrent GBS disease is uncommon and poorly described, although it seems to occur among 2% to 3% of infants with any invasive GBS disease. This phenomenon most frequently manifests as LOGBS disease in both the initial and the recurrent episodes, and it most commonly affects preterm infants. (14)(33)(55) Recurrent GBS disease may occur in the setting of recrudescence of the original GBS serotype in a colonized infant; most studies of recurrent disease find identical GBS strains in each episode of disease. (55)(56) In a study of 21 infected infants and their 20 mothers, oropharyngeal and gastrointestinal GBS colonization was present in half of the infants at the completion of appropriate intravenous antibiotic therapy. Rifampin was administered to infants with persistent colonization and to their mothers, but this treatment did not eradicate colonization in most of the dyads. (57) The association of GBS-positive human milk with recurrent GBS disease is controversial. In a case series of 48 LOGBS disease cases associated with GBS-positive human milk, 35% of cases were recurrent. (38) However, human milk is also an important source of protection from neonatal GBS disease (via maternal serotype-specific GBS antibodies, if present), and it is unclear whether GBS-

Table 1. Comparison of Early- and Late-Onset GBS Disease

VARIABLE	EARLY-ONSET GBS DISEASE	LATE-ONSET GBS DISEASE
Timing	0–6 d of age	7–89 d of age
Epidemiology	US incidence decreasing, currently ~0.2 cases/1,000 live births ~75% occurs in term infants (≥37 weeks' gestation) Prevalence in preterm infants with early-onset sepsis is 13%–19%	Stable US incidence (~0.3 cases/1,000 live births) ~50% occurs in term infants Most common form of neonatal GBS disease (57% of all neonatal GBS cases)
Transmission	Vertical transmission from a colonized mother	Multifactorial: vertical transmission; horizontal transmission via nonmaternal community and/or nosocomial sources
Risk factors	Maternal GBS colonization Preterm labor Prolonged membrane rupture Concern for intra-amniotic infection at delivery	Maternal GBS colonization Preterm birth
Clinical presentation	Usually presents within first 48 h after birth Isolated bacteremia in 80%–90%, meningitis in up to 10% Nonspecific presenting signs, less frequent severe presentations (pneumonia, pulmonary hypertension, shock)	Median age at presentation 27–41 d Isolated bacteremia in 60%, meningitis in 30%–35% Less commonly presents as pneumonia, urinary tract infection, bone/joint infection, skin/soft tissue infection Nonspecific presenting signs; occasionally proceeds to shock
Management	Perform lumbar puncture if not already done Antibiotic of choice is parenteral penicillin G (ampicillin is an alternative agent) Antibiotic treatment duration 10 d for isolated bacteremia, 14 d for meningitis; longer courses required for osteomyelitis, ventriculitis Hearing screening in all infants with meningitis; consider cranial imaging also	

GBS=group B *Streptococcus*.

positive human milk causes LOGBS disease or whether it merely reflects a site of maternal colonization. (49) Horizontal transmission may account for episodes of recurrent disease with discordant GBS serotypes. (14)(55) Immature adaptive immune responses that reduce neonatal GBS antibody production may also compound susceptibility to recurrent infection.

Very-Late-Onset GBS Disease

Very-late-onset GBS disease in infancy presents on or after day 90 of age. It accounts for 10% to 25% of all GBS cases presenting after 7 days of age. (34)(54)(58) Median ages at presentation have been reported to be 115 days (range, 91–226 days) (54) and 118 days (interquartile range, 98–790 days). (34) Similar to LOGBS disease, bacteremia and meningitis are the primary clinical disease manifestations. Preterm birth is a consistent risk factor. (14)(54)(58)(59)(60) A national surveillance study of 242 LOGBS meningitis cases in France identified a significantly higher prevalence of infants born before 32 weeks' gestation among infants with very-late-onset disease (32%) compared with late-onset disease (7%). (54) The vulnerability of very preterm infants may be related to reduced exposure to protective, transplacentally acquired GBS-specific antibodies as well as to prolonged immature innate immune responses. Innate or acquired immunodeficiency is also reported in the setting of very-late-onset GBS disease, including hypogammaglobulinemia, symptomatic HIV infection, and immunosuppression after organ transplant. (14)(34)(59)

OBSTETRIC SCREENING AND INTRAPARTUM MANAGEMENT

In 2020, the American College of Obstetricians and Gynecologists (ACOG) published updated consensus guidance for obstetric approaches to neonatal GBS disease prevention. (61) This guidance is detailed in the following subsections and summarized in Table 2.

Antepartum Screening

The ACOG recommends universal GBS screening of all pregnant women between 36 0/7 and 37 6/7 weeks' gestation, maximizing the likelihood that GBS screening results will reflect colonization status at delivery. Rectovaginal cultures are the current gold standard screening test, although nucleic acid amplification testing demonstrates similar-to-improved rates of GBS isolation. Limitations of nucleic acid amplification testing for routine screening include an inability to perform antibiotic susceptibility testing on positive GBS screens and an up to 10% false-negative rate when used as a rapid point-of-care test.

Indications for IAP

IAP is administered with the intent of suppressing colonizing GBS bacterial burden at delivery to reduce neonatal colonization and EOGBS disease. IAP is indicated for all parturients with positive GBS screening results obtained after 36 0/7 weeks' gestation. Additional indications for IAP, including in the setting of unknown GBS status, are listed in Table 2. According to contemporary CDC surveillance, approximately 50% of EOGBS disease cases occur in settings in which perinatal IAP was not indicated, largely due to negative antenatal GBS screening results. (6) In 20% of EOGBS disease cases, IAP was indicated but not administered. Less than 10% of cases occurred in the setting of receipt of IAP for more than 4 hours before delivery as recommended by ACOG guidance, and in these cases it was unclear whether alternate medications, such as clindamycin, were given appropriately.

Antibiotic Selection and Timing of Administration

Intravenous penicillin is the preferred agent for GBS-targeted IAP given its narrow spectrum of activity with exceedingly low GBS resistance rates; ampicillin is an acceptable alternative (Table 2). These agents should be dosed every 4 hours until delivery; the effectiveness of penicillin or ampicillin to prevent neonatal EOGBS disease is highest when prophylaxis is received at least 4 hours before delivery. (62) IAP exposure as soon as 1 to 2 hours before delivery does reduce neonatal GBS colonization rates, although the effect on EOGBS disease reduction is more difficult to ascertain. (63)

Approximately 10% of US parturients report a penicillin allergy (32); clindamycin susceptibility testing should be performed on GBS isolates from penicillin-allergic parturients. In the setting of high-risk maternal penicillin allergy (eg, presumed IgE-mediated hypersensitivity reaction), IAP should consist of clindamycin if the GBS isolate is clindamycin-sensitive. If the isolate is clindamycin-resistant, IAP should consist of vancomycin. Among women with low-risk penicillin allergy (history not consistent with acute hypersensitivity reaction), the ACOG recommends cefazolin as GBS IAP.

Fetal-Neonatal Exposure to Intrapartum Antibiotics

Transplacental fetal-neonatal exposure to maternally administered antibiotics depends on multiple factors, including maternal drug dosing, duration of exposure before delivery, and conditions affecting placental blood flow and efficiency of drug transfer (eg, preeclampsia, diabetes). (64) β-Lactam antibiotics (penicillin, ampicillin, and cefazolin) exhibit rapid placental transfer; GBS bactericidal concentrations

Table 2. American College of Obstetricians and Gynecologists Guidance for Group B *Streptococcus* Screening and IAP (61)

VARIABLE	GUIDANCE
Screening	
Eligibility and timing	• All parturients between 36 0/7 and 37 6/7 weeks' gestation
Method	• Vaginal-rectal cultures are the gold standard • NAAT may be used as an alternative but does not report antibiotic susceptibilities
IAP	
Indications for IAP	• Positive GBS culture on or after 36 0/7 weeks' gestation (unless cesarean delivery without labor or rupture of membranes) • Positive GBS culture obtained <36 0/7 weeks' gestation, if delivery occurs within 5 wk of screening • GBS bacteriuria during the current pregnancy • Previous neonate with invasive GBS disease • Unknown GBS status and preterm prelabor rupture of membranes at <37 0/7 wk • Unknown GBS status at labor onset and ≥1 of: Gestation <37 0/7 wk (preterm labor) Duration of membrane rupture >18 h Intrapartum temperature >100.4°F (>38°C) GBS positive in a previous pregnancy Intrapartum NAAT positive Preterm premature rupture of membranes
Antibiotic selection	
No history of penicillin allergy	• Penicillin G (IV) is agent of choice, start at labor onset and continue through delivery (5 million unit load, then 2.5–3 million units every 4 h until delivery) • Ampicillin IV is acceptable alternative (2-g load, then 1 g every 4 h until delivery)
History of penicillin allergy	• If history of anaphylaxis/IgE-mediated hypersensitivity reaction, send clindamycin susceptibility testing on GBS isolate If clindamycin-susceptible: clindamycin IV recommended (900 mg every 8 h until delivery) If clindamycin-resistant: vancomycin IV recommended (20 mg/kg every 8 h, with maximum single dose of 2 g) • If allergy history is not consistent with IgE-mediated hypersensitivity reaction, cefazolin IV recommended (2-g load, then 1 g every 8 h until delivery)

GBS=group B *Streptococcus*, IAP=intrapartum antibiotic prophylaxis, IV=intravenous, NAAT=nucleic acid amplification testing.

are achieved in the fetal compartment within several minutes of administration and can persist for several hours. (64)(65) Although available data suggest that transplacental vancomycin and clindamycin transfer occurs, the magnitude of fetal exposure and its effectiveness against EOGBS is unclear. Vancomycin undergoes renal elimination (which is physiologically accelerated during pregnancy), and transplacental transfer is slow owing to its large molecular weight. (64) Ex vivo placental models suggested limited placental transfer of vancomycin at standard dosing (1 g every 12 hours). (66)(67) Weight-based vancomycin dosing (20 mg/kg every 8 hours) more frequently produced therapeutic vancomycin levels in the umbilical cord blood compared with standard dosing (77%–83% vs 9%, respectively). (68)(69) Based on these data, obstetric GBS IAP guidelines were revised in 2019 to recommend weight-based vancomycin dosing. (61) Clindamycin is highly protein-bound, and transplacental transfer is 3 times slower than β-lactam antibiotics. (64) Studies of transplacental transfer of clindamycin provide conflicting results; 1 pharmacokinetic study of 7 dyads identified that maternal clindamycin concentrations may be subtherapeutic, with neonatal clindamycin exposure even lower. (70) However, another study among 23 term infants identified that 96% achieved therapeutic clindamycin concentrations in cord blood after intrapartum exposure. (71) Further pharmacokinetic data are needed to optimize IAP antibiotic dosing, particularly among preterm infants for whom these data are most lacking.

GBS antibiotic resistance patterns have evolved since its emergence in the 1970s. Prevalence of erythromycin resistance among maternal GBS isolates is 33% to 45%, (6)(72)(73) and erythromycin is no longer recommended as a part of GBS IAP as of 2010. (74) Among currently used alternative IAP agents, clindamycin resistance rates in maternal GBS isolates are 18% to 33%, and vancomycin resistance is rare. (6)(72)(73) Rising resistance is similarly seen in invasive neonatal GBS disease, with clindamycin resistance in 50% and erythromycin resistance in 60% of infecting neonatal GBS isolates in 2021. (75) GBS remains highly susceptible to first-line IAP agents, and resistance to penicillin or ampicillin is rare.

MANAGEMENT OF NEONATES AT RISK FOR EOGBS DISEASE

Risk Assessment

All newborn infants require a clinical assessment of their EOS risk at birth. The American Academy of Pediatrics (AAP) endorses multiple approaches to assess EOS risk (inclusive of EOGBS disease risk) among infants born at 35 weeks' gestation or later (Fig 1). (49)(76) The first approach is a categorical risk assessment that identifies infants at higher EOS risk based on clinical status, presence of maternal intrapartum fever, and exposure to appropriate GBS IAP (if indicated). The Neonatal Early-Onset Sepsis Calculator (https://neonatalsepsiscalculator.kaiserpermanente.org) is a web–based multivariate approach to risk assessment that calculates a posterior probability (updated probability of an event occurring after accounting for new information) of EOS based on gestational age, highest maternal intrapartum temperature, duration of membrane rupture, maternal GBS colonization status, maternal receipt of IAP (if indicated) and duration of fetal exposure before delivery, and infant clinical status. A third approach is to leverage serial clinical observations to identify infants who may be at higher risk for EOS. An individual center's choice of which EOS risk assessment approach to use may be influenced by numerous factors, including local EOS incidence, preferences balancing risk acceptance with empirical antibiotic utilization, and availability and training of personnel to check vital signs and perform serial clinical assessments in the nursery.

For the purposes of neonatal risk stratification, AAP guidance defines "adequate" IAP as maternal administration of penicillin, ampicillin, or cefazolin, given these agents' favorable pharmacokinetic parameters, efficiency of transplacental transfer, and low GBS resistance rates. (49) Maternal receipt of clindamycin or vancomycin is considered inadequate IAP, given lack of clarity surrounding transplacental exposures and subsequent efficacy in reducing neonatal EOGBS disease.

These risk stratification approaches do not apply to preterm infants born at 34 weeks or before who are at statistically significantly highest risk of EOS and for EOS-related mortality. The maternal GBS status is often unknown in these infants because antenatal GBS screening is not routinely performed until 36 0/7 weeks' gestation. Accordingly, most (80%–90%) very preterm infants in the United States receive empirical antibiotics at birth owing to EOS risk. (77) The AAP currently endorses identification of a narrow cohort of preterm infants at very low EOS risk based on delivery characteristics and for whom empirical antibiotic therapy may be deferred in the appropriate clinical scenario. (78)

Management of Infants with Suspected or Confirmed EOGBS Disease

Risk assessment strategies are intended to support the management of infants with varying levels of EOS risk at birth. Options for clinical management among infants with higher EOS risk range from enhanced clinical observation to administration of empirical antibiotics after collection of a blood culture sample. (49)(76) Recommended empirical antibiotic regimens for infants aged 0 to 7 days at risk for EOGBS disease include ampicillin and an aminoglycoside.

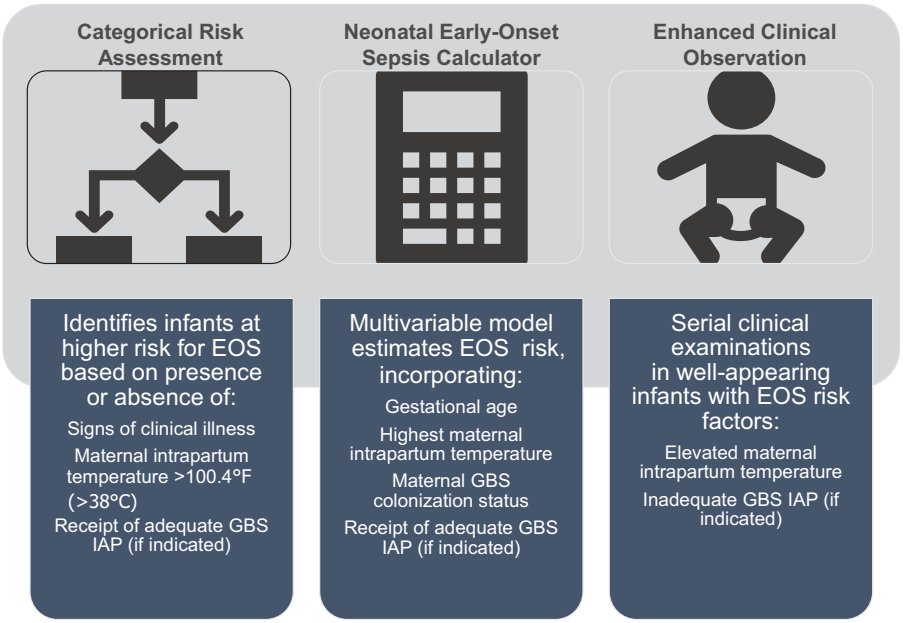

Figure. Comparison of American Academy of Pediatrics–endorsed approaches for early-onset sepsis (EOS) risk assessment in term infants. GBS=group B *Streptococcus*, IAP=intrapartum antibiotic prophylaxis.

Among healthy infants 8 days of age or older, empirical antibiotic therapy should include ampicillin and a cephalosporin (ceftazidime if aged 8–28 days, ceftriaxone if aged 29–90 days). Vancomycin may be added if there is high clinical concern for meningitis. Empirical antibiotic regimens for infants at risk for invasive GBS disease who remain hospitalized beyond 72 hours of age may vary by institution and depend on local antibiograms and patient-level factors (eg, presence of indwelling central lines).

Among infants with blood culture–confirmed GBS disease, a lumbar puncture should be performed if not already performed. Antibiotic therapy should be narrowed based on antibiotic susceptibilities; most isolates are susceptible to parenteral penicillin G, which is the preferred agent for GBS monotherapy (ampicillin is an acceptable alternative) (Table 3). The recommended total antibiotic duration for treatment of isolated GBS bacteremia is 10 days. If meningitis is present, the recommended antibiotic duration is 14 days, and clinicians should consider adjunctive brain imaging (eg, magnetic resonance imaging) to assess for associated abscesses or ventriculitis. Longer antibiotic durations are required for GBS osteomyelitis (≥3 weeks) and ventriculitis (≥4 weeks); clinicians should consider consultation with a pediatric infectious disease specialist in these cases.

PROGNOSIS

EOGBS disease case-fatality rates are estimated to be 5% to 7%, (1)(6)(8) with preterm infants at much higher risk for death than term infants (19% vs 2% mortality rates, respectively). (6) LOGBS disease case-fatality rates are estimated to be 3% to 5%, with higher mortality rates among preterm (8%) compared with term (3%) infants. (6)(8)(33) Infants surviving invasive GBS infection are at increased risk for neurodevelopmental impairment (NDI), which may include intellectual, motor, visual, and/or hearing impairments. In a systematic review, the prevalence of any NDI among survivors of neonatal GBS meningitis was 32% at 18 months' follow-up, with moderate-severe NDI in 18% of survivors. (79) Clinical factors associated with death or NDI in GBS meningitis include higher illness severity at presentation, failed hearing screening at hospital discharge, abnormal neurologic examination findings at discharge, and abnormal brain imaging after completion of antibiotic therapy. (80) Extremely preterm infants, who are already at significant baseline risk for death or NDI may be especially vulnerable to poor outcomes from invasive GBS disease. Among infants born at 22 to 28 weeks' gestation with invasive GBS disease in the NRN, 79% died or survived with NDI: the risk of death or NDI was 1.2-fold higher compared with extremely preterm infants with non-GBS infections, and 1.44-fold higher compared with uninfected infants. (81)

FUTURE DIRECTIONS

Neonatal GBS disease is not eradicated with universal GBS screening and IAP utilization, and LOGBS disease rates remain stable. This has spurred efforts to develop a maternal GBS vaccine that aims to 1) reduce maternal GBS colonization

Table 3. Antibiotic Regimens for Neonatal Early- and Late-Onset GBS Disease

	ANTIBIOTIC ROUTE	EARLY-ONSET GBS DISEASE (≤7 DAYS OF AGE)		LATE-ONSET GBS DISEASE (8–28 DAYS OF AGE)	
		GA ≤34 wk	GA ≥35 wk	GA ≤34 wk	GA ≥35 wk
Bacteremia					
Penicillin G aqueous	IV, IM	50,000 U/kg every 12 h	50,000 U/kg every 12 h	50,000 U/kg every 8 h	50,000 U/kg every 8 h
Ampicillin	IV, IM	50 mg/kg every 12 h	50 mg/kg every 8 h	75 mg/kg every 12 h	50 mg/kg every 8 h
Meningitis					
Penicillin G aqueous	IV, IM	150,000 U/kg every 8 h	150,000 U/kg every 8 h	125,000 U/kg every 6 h	125,000 U/kg every 6 h
Ampicillin	IV, IM	100 mg/kg every 8 h	100 mg/kg every 8 h	75 mg/kg every 6 h	75 mg/kg every 6 h

GA=gestational age, GBS=group B *Streptococcus,* IAP=intrapartum antibiotic prophylaxis, IM=intramuscular, IV=intravenous.
(Adapted from American Academy of Pediatrics. Table 4.2, Antibacterial Drugs for Neonates (≤28 Postnatal Days of Age). In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. *Red Book: 2021–2024 Report of the Committee on Infectious Diseases*. 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:877.)

and 2) reduce the incidence of neonatal GBS disease through maternal antibody transfer via the placenta and/or human milk. One candidate is a type III capsular polysaccharide–tetanus toxoid conjugate vaccine; in a phase 2 randomized controlled trial, this vaccine induced significantly higher GBS type III–specific IgG and significantly delayed maternal GBS colonization with GBS type III compared with control tetanus toxoid only. (82) Another candidate is a hexavalent GBS conjugate vaccine targeting the most frequent disease-causing GBS serotypes: Ia, Ib, II, III, IV, and V. In phase 1/2 trials, this vaccine induced robust immunoglobin responses that persisted for at least 6 months. (83) Other candidate vaccines target protein subunits, specifically alpha-like proteins associated with the GBS capsular surface. (84)(85) These candidate GBS vaccines require significant additional scrutiny, particularly regarding reduction of maternal colonization rates and neonatal GBS disease. Randomized controlled trials may require use of surrogate clinical end points for neonatal disease given that the relatively low incidence of EOGBS disease would require very large trial enrollment to demonstrate vaccine efficacy. These surrogate end points may include correlates of protection present in maternal and neonatal sera. (86)

Summary

- Invasive neonatal group B *Streptococcus* (GBS) disease now most frequently occurs as a late-onset process (on or after day 7 of age); the incidence of early-onset GBS (EOGBS) disease (occurring during days 0–6 of age) has declined in the setting of contemporary intrapartum antibiotic prophylaxis utilization. (Based on evidence from research)
- EOGBS disease is caused by vertical trans-mission of GBS from colonized mothers to their infants; late-onset GBS disease may be acquired via vertical transmission or via horizontal transmission from no-socomial and/or nonmaternal community sources. (Based on strong evidence from research and expert consensus)
- Maternal receipt of GBS-specific intrapartum antibiotic prophylaxis reduces maternal GBS colonization burden and neonatal EOGBS disease. (Based on strong evidence from research and consensus guidelines)
- For the purposes of stratification of neonatal GBS risk at birth, exposure to intrapartum penicillin, ampicillin, or cefazolin constitutes "adequate" GBS prophylaxis. Intrapartum exposure to vancomycin or clindamycin is considered inadequate prophylaxis against neonatal GBS disease. (Based on some evidence from research and consensus guidelines)
- At birth, all newborns require an individualized clinical assessment of their EOGBS disease risk. Multiple acceptable risk assessment strategies are available to neonatal clinicians. (Based on strong evidence from research and consensus guidelines)
- Infants surviving neonatal GBS disease, particularly those with GBS meningitis, are at significant risk for neurodevelopmental sequelae and should receive close developmental follow-up. (Based on evidence from research)

Take the quiz! Scan this QR code to take the quiz, access the references and teaching slides, and view and save images and tables (available on February 1, 2024).

PIR QUIZ

1. A second-year pediatric resident is collecting data on her institution's cases of neonatal late-onset group B *Streptococcus* (LOGBS) disease for a scholarly activity project. Which one of the following is most accurate concerning the epidemiology of LOGBS disease?

   A. LOGBS disease is now the predominant form of neonatal GBS disease.
   B. Preterm infants are not at greater risk for LOGBS disease compared with term infants.
   C. Term infants account for 78% of LOGBS disease.
   D. The incidence of LOGBS disease decreased by 25% during the past 2 decades.
   E. The incidence of LOGBS disease increased by 35% during the past 2 decades.

2. A 28-day-old girl is brought to the emergency department by her parents with a temperature of 101.8°F (38.8°C). She was noted to be fussy the past 2 days and not breastfeeding as well. She had 2 episodes of emesis. She was born at term, without any complications of the pregnancy, labor, and delivery. Her mother's prenatal screening for GBS colonization was negative. On physical examination, her temperature is 102.1°F (39°C) and her oxygen saturation is 97%. She is ill-appearing. A lumbar puncture is performed, and the cerebrospinal fluid (CSF) is noted to have a neutrophilic pleocytosis with decreased glucose and increased protein levels. A CSF multiplex polymerase chain reaction assay was positive for *Streptococcus agalactiae*. Which one of the following virulence factors is most strongly associated with aiding GBS penetration of the blood-brain barrier resulting in meningitis?

   A. β-Hemolysin/cytolysin.
   B. Outer membrane protein lipopolysaccharide complex (endotoxin).
   C. Pneumolysin.
   D. Streptokinase.
   E. Streptolysin S.

3. A 25-year-old gravida 1 woman presents to her obstetrician's office for routine follow-up at 36 weeks' gestation. A vaginal-rectal swab is obtained and is positive for GBS colonization. She believes she is penicillin allergic because she was told by her mother that she had a rash with penicillin that she took for pharyngitis when she was 6 years old. She has no history of anaphylaxis and has taken cefdinir for sinusitis without problem since that time. Which one of the following antimicrobial agents is recommended by the American College of Obstetricians and Gynecologists for GBS-targeted intrapartum antimicrobial prophylaxis when she goes into labor?

   A. Aztreonam.
   B. Cefazolin.
   C. Clindamycin.
   D. Penicillin.
   E. Vancomycin.

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4. A first-year pediatric resident on the newborn service asks about neonatal early-onset sepsis risk stratification strategies and how the choice of antibiotic for GBS intrapartum antimicrobial prophylaxis affects risk stratification. For the purposes of neonatal risk stratification, which one of the following antibiotics is considered inadequate based on American Academy of Pediatrics guidance?

    A. Ampicillin.
    B. Cefazolin.
    C. Clindamycin and vancomycin.
    D. Only clindamycin.
    E. Only vancomycin.

5. A previously healthy 16-day-old boy presents to the emergency department with a history of fever at home that day (temperature of 100.9°F [38.3°C]). He is breastfeeding normally. At the emergency department, a rectal temperature is 100.6°F (38.1°C). He is alert and not toxic-appearing. There are no focal abnormalities on his physical examination. A catheterized urine sample is obtained, and the urinalysis is normal. His C-reactive protein level is 2.20 mg/dL (22 mg/L). A lumbar puncture is performed, and the CSF is normal, with a negative CSF multiplex polymerase chain reaction panel. Blood, urine, and CSF cultures are pending. Which one of the following is the most appropriate empirical antibacterial therapy?

    A. Ampicillin and ceftazidime.
    B. Ampicillin and vancomycin.
    C. Ceftriaxone and gentamicin.
    D. Ceftriaxone and vancomycin.
    E. Vancomycin and gentamicin.