Updated Guidance: Prevention and Management of Perinatal Group B *Streptococcus* Infection

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Practice Gaps

New data have emerged to inform the microbiology, epidemiology, and clinical management of perinatal group B *Streptococcus* (GBS) infection. In 2019–2020, the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists released separate but aligned guidance for prevention and management strategies for pregnant women and newborns at risk of developing GBS disease. Together, these documents replace the 2010 guidance from the Centers for Disease Control and Prevention.

Abstract

Group B *Streptococcus* (GBS) remains the most common cause of neonatal early-onset sepsis among term infants and a major cause of late-onset sepsis among both term and preterm infants. The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists published separate but aligned guidelines in 2019 and 2020 for the prevention and management of perinatal GBS disease. Together, these replace prior consensus guidelines provided by the Centers for Disease Control and Prevention. Maternal intrapartum antibiotic prophylaxis based on antenatal screening for GBS colonization remains the primary recommended approach to prevent perinatal GBS disease, though the optimal window for screening is changed to 36 0/7 to 37 6/7 weeks of gestation rather than beginning at 35 0/7 weeks' gestation. Penicillin, ampicillin, or cefazolin are recommended for prophylaxis, with clindamycin and vancomycin reserved for cases of significant maternal penicillin allergy. Pregnant women with a history of penicillin allergy are now recommended to undergo skin testing, because confirmation of or delabeling from a penicillin allergy can provide both short- and long-term health benefits. Aligned with the American Academy of Pediatrics recommendations for evaluating newborns for all causes of early-onset sepsis, separate consideration should be given to infants born at less than 35 weeks' and more than or equal to 35 weeks' gestation when performing GBS risk assessment. Empiric antibiotics are recommended for infants at high risk for GBS early-onset disease. Although intrapartum

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ABBREVIATIONS

AAP	American Academy of Pediatrics
ACOG	American College of Obstetricians and Gynecologists
CDC	Centers for Disease Control and Prevention
EOD	early-onset disease
EOS	early-onset sepsis
GBS	group B *Streptococcus*
IAP	intrapartum antibiotic prophylaxis
LOD	late-onset disease
NAAT	nucleic acid amplification test
ROM	rupture of membranes

antibiotic prophylaxis is effective in preventing GBS early-onset disease, currently there is no approach for the prevention of GBS late-onset disease.

Objectives After reading this article, readers should be able to:

1. Explain the current microbiology and epidemiology of neonatal disease caused by group B *Streptococcus* (GBS)
2. Describe obstetric interventions for the prevention of neonatal early-onset GBS disease
3. Describe recommendations for the identification and treatment of newborns at risk for early-onset GBS disease
4. List key changes in the current approach to obstetric and neonatal prevention and management of GBS disease in comparison to the Centers for Disease Control and Prevention 2010 guidance

INTRODUCTION

Streptococcus agalactiae, or group B *Streptococcus* (GBS), is a facultative gram-positive organism commonly found in the adult gastrointestinal and genitourinary microbiome. (1) In the United States, between 10% and 30% of all pregnant women are colonized with GBS, with vaginal-rectal colonization rates varying by age, race, and geographic location. (2) GBS continues to be identified as the most common cause of neonatal early-onset sepsis (EOS; blood or cerebrospinal fluid culture-confirmed infection occurring from birth to 6 days of age) among infants born at term (≥37 weeks') gestation, accounting for approximately 45% to 50% of all culture-confirmed EOS cases. GBS is also isolated in approximately 15% to 25% of all culture-confirmed EOS cases in preterm infants. (3)(4)(5) Approximately 50% of all newborns of women colonized with GBS will themselves become colonized during birth in the absence of preventive measures, and of those, 1% to 2% will develop invasive disease. (2) The incidence of GBS early-onset disease (EOD) has declined with the use of intrapartum antibiotic prophylaxis (IAP), from 1.8 cases per 1,000 live births in 1990 to 0.25 cases per 1,000 live births in 2018. (6)(7) Neonatal GBS late-onset disease (LOD; infection occurring from 7–89 days of age) has not been affected by IAP, with mean national incidence of 0.31 cases per 1,000 live births in 2006-2015 national surveillance. (7)

The Centers for Disease Control and Prevention (CDC) first published consensus guidelines for the prevention of perinatal GBS disease in 1996, recommending either 1) universal screening of pregnant women for GBS colonization between 35 and 37 weeks' gestation and administration of IAP to women with positive GBS screening results, or 2) the use of clinical risk factors for perinatal GBS disease to determine indication for IAP. (6) The CDC revised these guidelines in 2002 based on active surveillance demonstrating that the antenatal screening approach was more effective in preventing GBS EOD compared to the risk factor–based approach. The superiority of antenatal screening–based IAP was reaffirmed in the CDC's revised 2010 guidelines. (8)(9)(10) In 2017, CDC officials indicated a desire to transition further leadership in perinatal GBS prevention to the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP). These professional organizations collaborated and released updated guidelines in June and July 2019, with additional ACOG revisions in April 2020, reflecting changing practice standards based on evolving epidemiology and newly published evidence. (2)(3) This review provides updated epidemiologic data on neonatal GBS disease and summarizes the revised recommendations, highlighting updates with important practice implications for obstetric and neonatal clinicians.

NEONATAL GBS DISEASE

GBS Early-onset Disease

GBS EOD is defined as isolation of GBS from blood, cerebrospinal fluid, or other normally sterile sites in a newborn infant from birth to 6 days of age. (3) Among term infants, the most common pathogenesis of GBS EOD is vertical transmission from a colonized pregnant woman,

primarily during labor or after rupture of membranes (ROM). (2) Vertical transmission occurs via ascending colonization of the uterine compartment, and subsequent colonization and infection of the fetus and/or fetal aspiration of infected amniotic fluid. (11) The pathogenesis of GBS EOD and timing of transmission is less certain among preterm infants; although vertical transmission can occur in a similar fashion, maternal GBS colonization and intraamniotic infection may contribute to the pathogenesis of preterm delivery. (12) Most GBS EOD presents clinically as bacteremia without a focus, with the organism isolated from blood in 99% of cases. Clinical meningitis is identified in approximately 10% of cases, with bacteria isolated from the cerebrospinal fluid in approximately 4% of affected newborns. (7) Studies of human protective immunity to GBS infection have focused on the role of serotype-specific antibody directed to capsular polysaccharide; the risk of neonatal infection is decreased in the presence of maternally derived, transplacentally acquired, type-specific antibody. (13)(14) Ten antigenically distinct capsular polysaccharides have been identified, but types Ia, Ib, and II-V together currently account for 99.3% of neonatal EOD in the United States, with type Ia and type III each accounting for approximately 25% of cases. (7)

GBS Late-onset Disease

GBS LOD is defined as isolation of group B *Streptococcus* from a normally sterile site 7 to 89 days after birth. (3) The pathogenesis of GBS LOD is debated, but generally thought to be the invasion of normally sterile sites preceded by infant pharyngeal or gastrointestinal colonization. Neonatal colonization may result from maternal vertical and horizontal transmission as well as from horizontal transmission from nonmaternal sources. It remains unclear whether breast milk is a potential source of horizontal transmission to the infant or simply a marker for high levels of neonatal nasopharyngeal GBS colonization. (15)(16) GBS is isolated from blood cultures in 93% of LOD cases but additional organ involvement is more frequently observed in LOD compared with EOD cases. Meningitis is diagnosed in ~30% of cases, with GBS isolated from cerebrospinal fluid in 20% of LOD cases. (7) In addition, GBS LOD may involve bone, joint, or soft tissue infection. (7)(12) Serotypes Ia, Ib, and II-V account for 99.7% of GBS LOD in the United States, whereas serotype III alone accounts for 56% of cases. (7)

Disparities in Neonatal GBS Disease

Both GBS EOD and LOD disproportionately affect prematurely born infants and infants born to black women in the United States. Among cases identified in CDC surveillance studies from 2006-2015, a quarter of GBS EOD cases and 40% of GBS LOD cases occurred in infants born at less than 37 weeks' gestation. The absolute incidence per 1,000 live births for EOD is roughly 3 times higher among preterm versus term infants, and the incidence of LOD is 6 times higher among preterm versus term infants. (7) Mortality is also disproportionately greater among those born preterm: EOD case-fatality was 2.1% among term infants and 19.2% among preterm infants whereas LOD case-fatality was 3.4% and 7.8% among term and preterm infants, respectively. (7) Studies in the United States also identify persistent racial disparities in GBS EOD, with rates being 1.5 to 3 times higher among black versus nonblack infants, among both term and preterm infants born before 37 weeks of gestation. (7)(17)(18) These differences have not been explained by variations in antenatal screening or administration of IAP. (19) GBS LOD rates were also roughly 3 times higher among black versus nonblack infants in 2006-2015 surveillance, but this finding was not adjusted for gestational age at birth.

UPDATED OBSTETRIC GUIDANCE

Background

The administration of antibiotics to laboring women can decrease the occurrence of GBS EOD. IAP is hypothesized to prevent GBS EOD by 3 mechanisms: 1) by temporarily decreasing the burden of maternal GBS colonization, 2) by preventing fetal or newborn colonization of surfaces and mucus membranes, and 3) by reaching blood levels above minimum inhibitory concentration for GBS in newborns. (20)(21) The pharmacokinetics and pharmacodynamics of this observation have been addressed in a number of studies using ampicillin and penicillin. Fewer studies have addressed the actions of cefazolin, clindamycin, and vancomycin, but in total, such studies suggest multiple modes of action for neonatal disease prevention. IAP with all 5 of these antibiotics can rapidly decrease maternal vaginal GBS colony counts. Ampicillin, penicillin, and cefazolin can quickly cross the placenta, and are subsequently excreted by the fetal kidney, resulting in antibiotic levels in amniotic fluid, cord blood, and neonatal blood above the minimal inhibitory concentration needed to kill GBS within 1 to 2 hours after maternal administration. (2)(3) IAP is thus hypothesized to derive from a combination of decreased exposure to GBS during labor and delivery and decreased colonization of the fetus and newborn, as well as some potential efficacy in clearing low-level fetal bacteremia. Studies addressing the impact on neonatal surface colonization with GBS after birth, as well as epidemiologic analyses of efficacy, suggest that optimal benefit is achieved

when penicillin, ampicillin, or cefazolin are administered at least 4 hours before delivery.

Only 10% to 30% of US women are colonized with GBS during pregnancy, (22) and targeting IAP to these women should provide the optimal balance to the risk-benefit of intrapartum antibiotic exposure. IAP is conceptualized as prophylaxis—interrupting the pathogenesis of GBS EOD—and should be differentiated from the administration of intrapartum antibiotics as maternal and fetal treatment when intra-amniotic infection is suspected or confirmed. Studies comparing the efficacy of administering GBS IAP based on antenatal culture results versus the administration of IAP only when risk factors for infection develop during labor, have established that antenatal screening–based IAP is the more effective strategy. (9) The prophylactic administration of IAP based on antenatal GBS vaginal-rectal culture results has formed the core of perinatal GBS prevention guidance since the CDC 2002 guidelines were published. This core recommendation is unchanged in the ACOG 2020 guidance. (2) Table 1 summarizes the current key elements of the ACOG 2020 perinatal prevention guidance. Table 2 highlights differences between the 2020 guidance and prior CDC 2010 guidance. In the following sections, we expand on some of the key ACOG updates.

TABLE 1. **Summary of ACOG 2020 Recommendations**

Pregnant women should be screened for GBS colonization by vaginal-rectal culture
• Between 36 0/7 and 37 6/7 weeks of gestation
• With onset of labor <37 0/7 weeks' gestation with or without preterm ROM
• With occurrence of preterm, prelabor ROM
• If they remain pregnant >5 weeks after a prior negative GBS culture
Pregnant women should be administered IAP in labor
• If colonized with GBS as identified on antenatal culture
• With GBS bacteriuria during current pregnancy
• With history of a previous infant with GBS disease
• With positive intrapartum NAAT result
• At ≥37 0/7 weeks' gestation with unknown GBS status; or with negative GBS status obtained >5 weeks prior; or with negative intrapartum NAAT result ***if*** maternal temperature ≥100.4°F (≥38°C) ***or*** ROM ≥18 hours occurs during labor
• At ≥37 0/7 weeks' gestation with unknown GBS status, IAP may be considered if woman is known to have been GBS positive in prior pregnancy
• At <37 0/7 weeks' gestation with unknown GBS status
Notes: Standard obstetric antibiotic regimens for preterm, prelabor ROM should include coverage for GBS IAP if GBS status is unknown or positive. Women undergoing planned cesarean delivery before the onset of ROM or labor do not require GBS IAP regardless of GBS status
IAP Regimens
• Penicillin G: Preferred
• Ampicillin: Acceptable alternative to penicillin G
• Cefazolin: Women with low-risk penicillin allergy[a]
• Clindamycin: Women with high-risk penicillin allergy[a] if colonizing isolate is susceptible to clindamycin
• Vancomycin: Women with high-risk penicillin allergy[a] if colonizing isolate is resistant to clindamycin ***or*** susceptibility is unknown

ACOG=American College of Obstetricians and Gynecologists; GBS=group B Streptococcus*; IAP=intrapartum antibiotic prophylaxis; NAAT=nucleic acid amplification test; ROM=rupture of membranes.*
[a]*Allergy testing is safe during pregnancy and may be beneficial for all women reporting penicillin allergy.*

Timing of Antenatal Culture

GBS colonization of the maternal gastrointestinal and genitourinary flora is transient and changeable. The correlation between antenatal GBS vaginal-rectal culture results and colonization status at the time of presentation for delivery is better the closer the antenatal culture is performed relative to delivery. Further, regardless of the timing of antenatal culture, the correlation decreases with passing time such that negative culture results are considered unreliable if performed more than 5 weeks before delivery. These issues are counterbalanced by uncertainty around delivery timing as a woman approaches her estimated due date. Because GBS IAP is recommended for all women with onset of preterm labor (before 37 0/7 weeks' gestation), the new ACOG recommendation is that routine antenatal screening is optimally timed between 36 0/7 and 37 6/7 weeks of gestation rather than beginning at 35 0/7 weeks' gestation. This new time frame provides a 5-week window for valid culture results that includes births occurring up to 41 0/7 weeks' gestation. This change addresses the epidemiologic observation that in an era of good compliance with antenatal screening and administration of IAP, most cases of persistent GBS EOD are seen among term infants born to women with negative antenatal screening culture results. (19)(23)

Nucleic acid amplification tests (NAAT) are currently available to detect GBS, and their performance is validated in numerous published studies. (24) The performance of NAAT is equivalent to culture-based screening for GBS

TABLE 2. **Comparison of CDC 2010 and ACOG 2020/AAP 2019 GBS Prevention Guidance**

CDC 2010	ACOG 2020
Differences	
Recommended timing for antenatal GBS screening culture at 35 0/7–37 6/7 weeks' gestation	Recommended timing for antenatal GBS screening culture changed to 36 0/7–37 6/7 weeks' gestation
No recommendation regarding confirmation of reported penicillin allergy	Pregnant women with any history of allergy to penicillin may undergo skin testing to confirm or refute penicillin allergy
For pregnant women with history of penicillin allergy: Request antibiotic susceptibility testing on laboratory requisitions for antenatal GBS screening cultures	For pregnant women with history of penicillin allergy: Clearly state the penicillin allergy on laboratory requisitions for antenatal GBS screening cultures to ensure antibiotic susceptibility testing
If a pregnant woman presents in labor at ≥37 0/7 weeks' gestation with unknown GBS status, IAP should be administered if intrapartum risk factors are present	If a pregnant woman presents in labor at ≥37 0/7 weeks' gestation with unknown GBS status, IAP should be administered if intrapartum risk factors are present; IAP may also be considered if the woman was GBS positive in a prior pregnancy
When indicated, 1 g of vancomycin should be administered intravenously every 12 hours	When indicated, vancomycin should be administered over 1–2 hours, based on weight and baseline renal function (20 mg/kg intravenously every 8 hours; maximum of 2 g per single dose)
CDC 2010	**ACOG 2019**
Differences	
Full newborn diagnostic evaluation includes (a) blood culture; (b) CBC with WBC differential and platelets at birth, and/or at 6–12 hours of age; (c) lumbar puncture; and (d) chest radiograph (if indicated) *Limited* newborn diagnostic evaluation includes (a) blood culture and (b) CBC with WBC differential and platelets at birth, and/or at 6–12 hours of age	CBC with WBC differential and platelets are no longer routinely recommended as part of the newborn diagnostic evaluation for GBS EOD, because of poor sensitivity and modest likelihood ratios for predicting early-onset infection
Full or limited newborn diagnostic evaluation for GBS disease should be performed and newborn empiric antibiotics administered if: (a) newborn has signs of sepsis (full) (b) maternal chorioamnionitis is present (limited) (c) inadequate GBS IAP was given and infant is born <37 0/7 weeks' gestation (limited) *or* ROM ≥18 hours (limited)	Separate risk stratification strategies should be used for infants based on gestational age: • *Infants born ≥35 weeks' gestation*: 1 of 3 possible approaches are recommended—categorical risk assessment, multivariate risk assessment, or risk assessment based on enhanced observation • *Infants born <35 weeks' gestation*: Management should be based on circumstances of preterm delivery
Maternal chorioamnionitis diagnosis is made based on obstetric clinical judgment	Among infants born ≥35 weeks' gestation, the obstetric clinical diagnosis of maternal chorioamnionitis is replaced by consideration of highest maternal intrapartum temperature
No detailed discussion of GBS late-onset disease epidemiology, risk assessment, or empiric therapy	Includes discussion of GBS late-onset disease epidemiology and risk assessment

Continued

TABLE 2. (Continued)

CDC 2010	AAP 2019
No recommendations for definitive therapy for GBS disease	Provides a table with dosing guidelines for treatment of GBS bacteremia and meningitis with ampicillin and penicillin G, based on gestational age at birth and postnatal age during treatment.
Recommendations Common to CDC 2010, AAP 2019, and ACOG 2020	
• Optimal management is based on antenatal GBS vaginal-rectal culture results	
• Antenatal GBS vaginal-rectal culture is not necessary for women diagnosed with GBS bacteriuria during pregnancy or for women with a prior infant with GBS disease; these women should be administered GBS IAP	
• Women undergoing planned cesarean delivery before the onset of membrane rupture or labor do not require GBS IAP regardless of GBS status	
• Centers able to perform rapid, point-of-care nucleic acid amplification tests for GBS may use this technology for the care of pregnant women who present in labor with unknown GBS status and no additional risk factors	
• Risk factors used to administer GBS IAP to pregnant women with unknown GBS status include preterm gestation (<37 0/7 weeks) with prelabor ROM and/or preterm labor; intrapartum maternal temperature ≥100.4°F (≥38°C); or ROM ≥18 hours	
• Penicillin, ampicillin, or cefazolin given >4 hours before delivery is considered adequate IAP; clindamycin and vancomycin given for any duration should not be considered as adequate IAP for the purpose of newborn risk assessment	
• Penicillin G is the recommended antibiotic for definitive treatment of confirmed GBS disease; ampicillin is acceptable alternative	

AAP=American Academy of Pediatrics; ACOG=American College of Obstetricians and Gynecologists; CBC=complete blood cell count; CDC=Centers for Disease Control and Prevention; GBS=group B Streptococcus; IAP=intrapartum antibiotic prophylaxis; ROM=rupture of membranes; WBC=white blood cell.

detection if the specimen has been incubated in an enrichment broth for 18 to 24 hours. The sensitivity of NAAT without an enrichment broth step is suboptimal. Aligned with the CDC 2010 recommendations, ACOG 2020 continues to endorse the use of NAAT on specimens that first undergo incubation in enrichment broth, to maximize detection as well as to allow for subsequent antibiotic susceptibility testing for penicillin-allergic women. When available, ACOG 2020 endorses the use of rapid, point-of-care NAAT for the care of women who present in labor with unknown GBS status.

Indications for IAP

ACOG 2020 endorses the same basic indications for GBS IAP (Table 2) with 1 addition. Although GBS colonization is transient, a 2016 systematic review and meta-analysis demonstrated that women with GBS colonization during pregnancy have an estimated 50% risk of colonization in a subsequent pregnancy. (25) Based on this, ACOG 2020 recommends that IAP be considered for a woman who presents in labor with current unknown GBS status if she is known to have had GBS colonization in a previous pregnancy, before the development of intrapartum risk factors for infection.

Penicillin Allergy Testing

Up to 10% of pregnant women report an unconfirmed history of penicillin allergy, but true, IgE-mediated hypersensitivity can be ruled out in more than 90% of such persons if formal allergy skin testing is performed. (26) The opportunity to "delabel" a pregnant woman with an unconfirmed history of penicillin allergy provides long-term health care management advantages beyond the opportunity to administer β-lactam–based IAP. ACOG 2020 confirms the safety of skin testing during pregnancy and endorses its use for all pregnant women with an unconfirmed allergy history. ACOG 2020 also provides new guidance for the history-based clinical determination of low- and high-risk for penicillin anaphylaxis as well as for identification of histories that suggest severe but rare non–IgE-mediated reactions (such as Stevens-Johnson syndrome).

Vancomycin Administration

Vancomycin is the antibiotic of last resort for women with confirmed or unconfirmed high-risk penicillin allergy if the woman is colonized with clindamycin-resistant GBS. Vancomycin is also recommended if the susceptibilities are unknown, because up to 47% of GBS cases in the United States are resistant to clindamycin. However, as summarized in ACOG 2020, the transplacental pharmacokinetics and pharmacodynamics of vancomycin have been informed by conflicting data. ACOG 2020 recommends changes to vancomycin administration to pregnant women, including the use of weight-based doses given at shorter intervals to optimize transplacental drug transfer.

GBS and Obstetric Procedures

ACOG 2020 directly addresses GBS colonization and obstetric interventions such as membrane sweeping or mechanical cervical ripening to initiate labor; artificial ROM to augment labor progression; vaginal examinations and intrauterine monitoring to assess labor progression; and water immersion during labor. ACOG 2020 notes that overall, specific data to inform the relative risks of these procedures in GBS-positive (vs GBS-negative) women are limited, and counsels that they each be undertaken as otherwise clinically indicated, with administration of appropriate IAP.

UPDATED NEONATAL GUIDANCE

Background

Over 60 years have passed since the first clinical and pathologic descriptions of neonatal early-onset bacterial infection focused on the identification of factors that signal risk of this potentially fatal complication of birth. (27)(28) Such risk factors derive from an understanding of the pathogenesis of EOS as primarily resulting from ascending colonization of the uterine compartment and fetus with maternal genitourinary and gastrointestinal flora, with colonization and pathologic infection of the fetus and newborn. A multitude of publications address the factors that can be used to identify newborns at high enough risk of GBS-specific (and all-bacterial cause) early infection to warrant laboratory investigation and empiric antibiotic treatment. Maternal age, maternal race, obstetric interventions during labor, indications of intrauterine infection (including the obstetric diagnosis of chorioamnionitis, "foul-smelling" amniotic fluid, intrapartum maternal fever, and maternal and fetal tachycardia), duration of ROM, presence of meconium-stained fluid, GBS colonization, gestational age at birth, twin gestation, and neonatal instability at birth have all been associated with increased risk, though many of these factors are not *independent* predictors of neonatal infection. (29) Recommendations for newborn evaluation contained in the CDC 1996, 2002, and 2010 GBS prevention documents focused on the categorical use of single specific risk factors and did not distinguish between term and preterm newborns. Although motivated by the aim of preventing sepsis-associated morbidity and mortality, these approaches have been associated with high rates of laboratory testing and empiric antibiotic administration to term infants compared with the current incidence of confirmed disease and antibiotic administration to the majority of preterm newborns. (30)(31)(32)(33) The AAP 2019 GBS guidance addresses infants born at 34 6/7 weeks or less and 35 0/7 weeks or greater gestation separately, aligned with guidance issued by the AAP in 2018 regarding all bacterial causes of EOS. Table 3 summarizes the current key elements of the AAP 2019 neonatal guidance. Table 2 highlights differences between the AAP 2019 guidance and prior CDC 2010 guidance. In the following sections, we expand on some of the key AAP updates.

Chorioamnionitis as a Risk Factor for GBS EOD

Infants born to women diagnosed with chorioamnionitis are at elevated risk for EOS. However, the subjective nature of this diagnosis has presented difficulties for obstetric and neonatal clinicians, particularly among women laboring at term gestation. ACOG recently opted to transition away from use of the term chorioamnionitis to "intra-amniotic infection." (34) Further, ACOG highlights the uncertainty in this diagnosis and now provides classifications for definitive and suspected intra-amniotic infection. A definitive diagnosis of intra-amniotic infection is made with amniotic fluid analysis and/or culture, or with placental histopathologic examination. Intra-amniotic infection is suspected on the basis of a single maternal intrapartum temperature greater than 102.2°F (39.0°C), or in cases of maternal temperature of 100.4°F to 102.0°F (38.0°C–38.9°C) occurring in combination with maternal leukocytosis, purulent cervical discharge, or fetal tachycardia. Isolated maternal fever is defined as maternal temperature of 100.4°F to 102.0°F (38.0°C–38.9°C) without associated signs and can also signal evolving intra-amniotic infection. ACOG recommends the administration of intrapartum antibiotics when there is concern for suspected or confirmed intra-amniotic infection or isolated maternal fever. AAP 2019 uses the highest maternal intrapartum temperature in recommended risk assessment algorithms among infants born at 35 0/7 weeks' or greater gestation, rather than the more subjective

TABLE 3. **Summary of AAP 2019 Recommendations**

Management of Infants Born at ≥35 Weeks' Gestation
Centers should adopt 1 of 3 approaches for infants born at ≥35 weeks' gestation
Categorical Risk Assessment
• Thresholds for risk factors are used to identify infants at increased risk
• Risk factors include
o Signs of newborn clinical illness (no guidance provided; determine details locally)
o Maternal intrapartum temperature ≥100.4°F (≥38.0°C)
o Inadequate IAP in a GBS-colonized mother
• Blood culture and empiric antibiotics recommended for infants with signs of clinical illness or maternal intrapartum temperature ≥100.4°F
• Clinical observation for 36–48 hours after birth recommended for infants born in the setting of inadequate IAP in the absence of other risk factors
Multivariate Risk Assessment (Neonatal Early-Onset Sepsis Calculator)
• Available at https://neonatalsepsiscalculator.kaiserpermanente.org
• Calculator combines factors known at birth with newborn clinical condition to provide estimated risk of early-onset infection
• Factors considered:
o Gestational age at birth
o Highest maternal intrapartum temperature
o Duration of ROM
o Maternal GBS status
o Type and duration of IAP (clindamycin and vancomycin given for any duration should not be considered adequate IAP)
o Newborn clinical condition (detailed guidance is provided)
• Website provides recommended clinical actions (enhanced observation, blood cultures, empiric antibiotics) at different levels of estimated risk
o Evolving clinical condition can be used to update the risk estimates over the first 6-12 hours after birth
o Centers may use these recommendations or locally determine actions at specific levels of risk
Risk Assessment Based on Enhanced Observation
• Risk factors include
o Signs of newborn clinical illness (no guidance provided; determine details locally)
o Maternal intrapartum temperature ≥100.4°F (≥38.0°C)
o Inadequate IAP in a GBS-colonized mother
• If infant has signs of clinical illness, empiric antibiotics are administered
• In all other cases, regardless of the risk factors and circumstance of birth and IAP, infants are followed by close, serial clinical assessment and administered empiric antibiotics if signs of illness develop
Management of Infants Born at <35 Weeks' Gestation
Infants are considered at high risk of GBS disease and other causes of early-onset infection, if delivered in the setting of:
• Preterm labor
• Prelabor, preterm ROM
• Concern for intra-amniotic infection
• Cervical insufficiency

Continued

TABLE 3. (Continued)

Management of Infants Born at <35 Weeks' Gestation
• Unexplained, acute non-reassuring fetal status
Infants are considered at low risk of GBS disease and other causes of early-onset infection, if delivered with all of the following:
• For maternal/fetal non–infection-related indications *and*
• By cesarean section *and*
• No labor or attempts to induce labor *and*
• ROM at the time of delivery
Infants are considered at high risk of GBS disease and other causes of early-onset infection if:
• Delivered vaginally or by cesarean delivery, with induction of labor or ROM before delivery for maternal/fetal non–infection-related indications *and*
• Indicated, adequate GBS IAP was not given *or*
• Infant has respiratory or cardiovascular instability after birth
In preterm infants at high risk, blood cultures should be performed and empiric antibiotics administered. Preterm infants at lower risk may be cared for without blood cultures or empiric antibiotics, at the discretion of the care team
Definitive Treatment for Invasive Neonatal GBS Disease
• Penicillin G is the preferred antibiotic for definitive treatment of early-onset and late-onset neonatal GBS disease; ampicillin is an acceptable alternative
• Duration of therapy is based on site of GBS isolation (bacteremia vs meningitis vs organ-specific infection)
• Dosing is based on gestational age at birth and postnatal age at treatment; see Table 1 in the AAP 2019 document for details

AAP=American Academy of Pediatrics; ACOG=American College of Obstetricians and Gynecologists; GBS=group B Streptococcus*; IAP=intrapartum antibiotic prophylaxis; ROM=rupture of membranes.*

obstetric clinical diagnosis. Among those born at less than or equal to 34 6/7 weeks' gestation, AAP 2019 uses the term "any concern for intra-amniotic infection" because the signs and symptoms may be subtle and complex among women at risk for preterm delivery.

Strategies for GBS EOD Risk Assessment Among Infants Born at ≥35 Weeks' Gestation

CDC 2010 provided a single strategy for GBS EOD risk assessment, based on the categorical presence or absence of specific single risk factors as well as the adequacy of indicated GBS IAP. Studies addressing the clinical use of CDC 2010 guidance demonstrate that approximately 5% to 10% of infants born at 35 to 36 weeks' gestation received empiric antibiotics using this approach. AAP 2019 follows the AAP 2018 revised guidance on the care of infants at risk for all-bacterial cause EOS and offers 3 possible approaches. (35)(36) As detailed in AAP 2019, each approach has its advantages and disadvantages, and centers are counseled to adopt 1 of the approaches tailored to local structures of care and risk acceptance.

Categorical Risk Assessment. Modeled on the CDC 2010 guidelines, the revised algorithm removes reliance on the obstetric diagnosis of "chorioamnionitis" and uses a cutoff value for maternal intrapartum temperature aligned with the ACOG 2017 recommendations on intra-amniotic infection. (34) Risk factors included in the algorithm are provided in Table 3. Blood culture and empiric antibiotic therapy are recommended for infants who are clinically ill and for infants born to mothers with an elevated intrapartum temperature. Clinical observation for 36 to 48 hours after birth is recommended for infants born with inadequate maternal IAP; this timing was shortened from a full 48 hours to allow for local discretion in discharge timing. An advantage of this approach is that it is familiar to most neonatal clinicians and has been studied extensively. It is limited by poor discrimination and wider use of empiric antibiotics compared with other approaches.

Multivariate Risk Assessment. The neonatal early-onset sepsis calculator is available as a web-based online tool (https://neonatalsepsiscalculator.kaiserpermanente.org). The "calculator" is a combination of 2 multivariate prediction models developed for estimating risk of all bacterial causes of EOS, not only GBS EOD, with clinical recommendations for observation, blood culture, and empiric antibiotics provided at specific levels of estimated risk. The calculator provides individualized estimates for the baseline probability of infection using variables known at birth (Table 3). (37) The newborn's clinical status for the first 6 to 12 hours after birth can be used to obtain updated risk estimates; clinical criteria for illness are provided on the calculator website. (38)(39) The calculator models have been prospectively validated in large newborn cohorts. (40)(41)(42) Advantages of this approach are that it provides more individualized management and overall lower use of empiric antibiotics. A limitation is that it requires that centers develop workflows for risk calculation and newborn observation.

Risk Assessment Based on Enhanced Observation. With this risk assessment approach, infants are categorized as at-risk or not at-risk for GBS EOD (Table 3), but are evaluated and administered empiric antibiotics *only* if they are ill-appearing at birth or develop signs of illness after birth. This approach requires serial, structured clinical assessments from birth through 36 to 48 hours of age. Small cohort studies demonstrate that this approach will expose fewer infants to empiric antibiotic treatment compared with a categorical or multivariate risk assessment approach. (43)(44)(45) An advantage of this risk assessment is the potentially low rate of empiric antibiotic administration. Disadvantages of this approach include the need for centers to define what constitutes "ill-appearing" and to develop care and documentation structures for close serial reassessments. If using this approach, centers must dispense with the concept of "missing cases" of GBS EOD and accept that the identification of illness in a previously well-appearing infant is an anticipated outcome.

Risk Assessment for Infants born at <35 Weeks' Gestation

The CDC 2010 guidelines recommended evaluation and empiric antibiotic administration for all newborns with "signs of neonatal sepsis." Because of the overlap between the physiologic instability characteristic of preterm infants and signs of neonatal sepsis, large proportions of preterm infants (particularly those born with extremely low birthweight) are administered empiric antibiotics at birth for risk of GBS EOD and all causes of bacterial EOS. (44)(45) AAP 2019 recommends categorizing risk among preterm infants using delivery characteristics. Infants delivered in the setting of preterm labor, prolonged ROM, intra-amniotic infection, cervical insufficiency, or otherwise unexplained in utero fetal distress should be considered at higher risk for GBS EOD and should be given empiric antibiotics (Table 3). Infants delivered preterm solely because of maternal indications, such as preeclampsia or intrauterine growth restriction, and delivered via cesarean section before the onset of labor, with ROM at the time of delivery, can be considered to be at low risk for GBS EOD regardless of IAP administration. The rationale for this recommendation is that these infants are neither delivered because of concern for intra-amniotic infection nor subject to the risk from ascending colonization and infection provided by labor and vaginal delivery. The low risk among such infants has been demonstrated in single and multicenter studies and prospective implementation of this approach was recently validated in a multiyear single-center study. (46)(47)(48) AAP 2019 recommends that such infants can be treated without initiating empiric antibiotics (Table 3). Infants delivered preterm vaginally or via cesarean section for maternal or fetal indications, but after induction of labor and/or ROM before delivery, present a challenge for GBS EOD risk assessment. Although not delivered because of maternal infection, they are subject to the risks of labor and vaginal delivery. AAP 2019 recommends that such preterm infants be considered at high risk for GBS EOD if GBS IAP is inadequate (when indicated), or if obstetric concern for intra-amniotic infection arises during the course of induced labor and delivery, or if the infant has significant respiratory or cardiovascular instability after birth.

Empiric and Definitive Antibiotic Therapy

Unchanged from CDC 2010, AAP 2019 endorses the use of ampicillin and an aminoglycoside as empiric antibiotic treatment for suspected GBS EOD, because GBS almost universally remains susceptible to β-lactam antibiotics. The revised guidance acknowledges, however, that broader-spectrum empiric therapy should be considered when there is strong clinical concern for ampicillin-resistant infection, especially among very preterm and/or critically ill newborns. The evaluation and empiric treatment for GBS LOD falls into the general guidance for evaluation of the febrile young infant among otherwise healthy infants in the community. Although the approach to such infants may have local variations, AAP 2019 guidance endorses the use of ampicillin and ceftazidime among infants of age 8 to 28 days, and ceftriaxone for those 29 to 90 days of age. In both instances, empiric vancomycin should be added if there is concern for meningitis. Among those continuously hospitalized in the NICU, empiric antibiotic choice for infants

beyond 72 hours of age is informed by local microbiology and individual infant technicalities of care but should include agents active against GBS. A table is provided in the AAP 2019 document containing dosing guidelines for the use of penicillin G or ampicillin to treat confirmed GBS infection, based on the presence or absence of meningitis, gestational age at birth, and postnatal age at treatment.

SUMMARY

Together, the ACOG 2020 and AAP 2019 publications on prevention and management of neonatal GBS disease represent a collaborative effort on the part of these professional organizations to update guidance previously published in collaboration with the CDC. These guidelines continue to endorse the general approach of using antenatal maternal screening for GBS colonization and administration of appropriate intrapartum antibiotics to prevent neonatal GBS EOD. This strategy has no impact on the risk of late-onset GBS disease. The updated guidance leverages existing data on GBS epidemiology, microbiology, risk assessment strategies, and empiric and definitive treatment to guide the obstetric and neonatal clinician in caring for pregnant women and newborns affected by GBS colonization and infection. Unless effective multivalent vaccines become clinically available to replace or augment IAP, the ACOG and AAP guidance represents the most effective means of preventing neonatal GBS infection.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the rationale for, and approaches to, screening for maternal Group B *Streptococcal* colonization during pregnancy. (1.B.1.b.)
- Know the epidemiology, prevention, and pathogenesis of perinatal/neonatal Group B *Streptococcal* infections. (10.B.1.c.1.)
- Know the clinical manifestations and diagnostic criteria of Group B streptococcal infections. (10.B.1.c.2.)
- Know the treatment and complications of Group B *Streptococcal* infections. (10.B.1.c.3)

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