CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Management of Infants at Risk for Group B Streptococcal Disease

Karen M. Puopolo, MD, PhD, FAAP,[a,b] Ruth Lynfield, MD, FAAP,[c] James J. Cummings, MD, MS, FAAP,[d] COMMITTEE ON FETUS AND NEWBORN, COMMITTEE ON INFECTIOUS DISEASES

Group B streptococcal (GBS) infection remains the most common cause of neonatal early-onset sepsis and a significant cause of late-onset sepsis among young infants. Administration of intrapartum antibiotic prophylaxis is the only currently available effective strategy for the prevention of perinatal GBS early-onset disease, and there is no effective approach for the prevention of late-onset disease. The American Academy of Pediatrics joins with the American College of Obstetricians and Gynecologists to reaffirm the use of universal antenatal microbiologic-based testing for the detection of maternal GBS colonization to facilitate appropriate administration of intrapartum antibiotic prophylaxis. The purpose of this clinical report is to provide neonatal clinicians with updated information regarding the epidemiology of GBS disease as well current recommendations for the evaluation of newborn infants at risk for GBS disease and for treatment of those with confirmed GBS infection. This clinical report is endorsed by the American College of Obstetricians and Gynecologists (ACOG), July 2019, and should be construed as ACOG clinical guidance.

The Centers for Disease Control and Prevention (CDC) first published consensus guidelines on the prevention of perinatal group B streptococcal (GBS) disease in 1996. These guidelines were developed in collaboration with the American Academy of Pediatrics (AAP), the American College of Obstetricians and Gynecologists (ACOG), the American College of Nurse-Midwives, the American Academy of Family Physicians, and other stakeholder organizations[1] on the basis of available evidence as well as expert opinion. The 1996 consensus guidelines recommended either an antenatal culture–based or risk factor–based approach for the administration of intrapartum antibiotic prophylaxis (IAP) to prevent invasive neonatal GBS early-onset disease (EOD).[1] The guidelines were updated in 2002 primarily on the basis of new data from a CDC multistate retrospective cohort study in which authors found universal screening for group B streptococci (*Streptococcus agalactiae*) was >50% more effective at preventing the disease compared to a risk-based approach.[2,3] In 2010,

abstract

[a]*Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania;* [b]*Children's Hospital of Philadelphia, Philadelphia, Pennsylvania;* [c]*Minnesota Department of Health, St Paul, Minnesota; and* [d]*Departments of Pediatrics and Bioethics, Alden March Bioethics Institute, Albany Medical College, Albany, New York*

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Address correspondence to Karen M. Puopolo, MD, PhD. E-mail: puopolok@email.chop.edu

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the CDC once again revised the GBS perinatal prevention guidelines and continued to endorse the universal antenatal culture–based approach to identify women who would receive IAP to prevent GBS EOD.[4] Notable changes in the 2010 revision addressed the use of IAP for women in preterm labor and those with preterm prelabor rupture of membranes (PROM), the choice of specific antibiotics for IAP, and the use of nucleic acid amplification tests (NAATs) to identify maternal GBS colonization. The 2010 revision included a neonatal management algorithm for secondary prevention of GBS EOD that was widely adopted by neonatal physicians as a means of managing risk of all bacterial causes of early-onset sepsis (EOS).[5] With implementation of universal maternal antenatal screening and IAP, the national incidence of GBS EOD has declined from 1.8 cases per 1000 live births in 1990 to 0.23 cases per 1000 live births in 2015.[6]

Evolving epidemiology, newly published data, and changing practice standards inform periodic review of practice guidelines. In 2017, representatives from the CDC, AAP, ACOG, and other stakeholder organizations agreed to review and revise the 2010 GBS guidelines. A consensus was reached that the AAP would revise neonatal care recommendations and ACOG would revise obstetric care guidelines. These separate but aligned publications replace the CDC 2010 GBS perinatal guidance.

This clinical report addresses the epidemiology, microbiology, disease pathogenesis, and management strategies for neonatal early- and late-onset GBS infection. Maternal management is addressed in ACOG Committee Opinion No. 782, "Prevention of Group B Streptococcal Early-Onset Disease in Newborns."[7] This clinical report is endorsed by the American College of Obstetricians and Gynecologists (ACOG), July 2019, and should be construed as ACOG clinical guidance.

CURRENT EPIDEMIOLOGY OF NEONATAL GBS INFECTION

Early-Onset GBS Infection

GBS EOD is defined as isolation of group B *Streptococcus* organisms from blood, cerebrospinal fluid (CSF), or another normally sterile site from birth through 6 days of age.[8] Active Bacterial Core surveillance (ABCs), performed in collaboration with the CDC in 10 states from 2006 to 2015, found that the overall incidence of GBS EOD declined from 0.37 cases per 1000 live births in 2006 to 0.23 cases per 1000 live births in 2015.[6] Meningitis was diagnosed in 9.5% of infants with GBS EOD. CSF culture-positive GBS EOD occurred in the absence of bacteremia in 9.1% of early-onset meningitis cases (incidence: approximately 2.5 cases per 1 million live births).[6] Infants born at <37 weeks' gestation account for 28% of all GBS cases; approximately 15% of cases occur among preterm infants with very low birth weight (<1500 g).[6,9] Overall, GBS infection accounts for approximately 45% of all cases of culture-confirmed EOS among term infants and approximately 25% of all EOS cases that occur among infants with very low birth weight.[9,10] Death attributable to GBS EOD occurs primarily among preterm infants: the current case fatality ratio is 2.1% among term infants and 19.2% among those born at <37 weeks' gestation.[6]

GBS EOD primarily presents clinically at or shortly after birth. The majority of infants become symptomatic by 12 to 24 hours of age[11–13]; during the 2006–2015 period of ABCs, 94.7% of GBS EOD cases were diagnosed ≤48 hours after birth.[6] The incidence of newborn infants discharged from a birth hospital and readmitted to a hospital with GBS EOD within 6 days of age was approximately 0.3 cases per 100 000 live births in the ABCs. Although potentially an underestimate, this finding was consistent with data from the Northern California Kaiser Permanente health care system, which found the incidence of newborn infants readmitted to the hospital within the first week after hospital discharge with culture-confirmed infection attributable to any bacteria to be approximately 5 cases per 100 000 live births.[14] Globally, outside the United States, an estimated 200 000 cases of GBS EOD occurred in 2015. Stillbirth, GBS EOD, and late-onset GBS cases combined contribute to an estimated 150 000 fetal and neonatal deaths throughout the world, with the largest concentration of GBS perinatal deaths occurring in Africa.[15]

Late-Onset GBS Disease

GBS late-onset disease (LOD) is defined as isolation of GBS from a normally sterile site from 7 to 89 days of age.[8] Rarely, very–late-onset GBS disease may occur after 3 months of age, primarily among infants born very preterm or infants with immunodeficiency syndromes.[16,17] GBS LOD rates have not changed with widespread use of IAP. GBS LOD incidence was stable over the 2006–2015 ABCs study period, with an average incidence of 0.31 cases per 1000 live births.[6] The median age at presentation with GBS LOD was 34 days (interquartile range: 20–49 days). Bacteremia was identified in approximately 93% of GBS LOD, and bacteremia without focus was the most common form of disease. Group B streptococci were isolated from CSF in 20.7% of cases, and meningitis was diagnosed in 31.4% of cases. Cultures of bone and joint and peritoneal fluid yielded group B streptococci in 1.8% of cases. CSF culture-positive GBS LOD occurred in the absence of bacteremia in approximately 20% of late-onset meningitis cases (incidence: 1.9 cases per 100 000 live births). Infants born at <37 weeks'

gestation account for approximately 42% of all GBS LOD cases, and death attributable to GBS LOD occurs in preterm infants at roughly twice the rate of term infants (7.8% vs 3.4%, respectively).[6] GBS LOD complicated by meningitis has a higher patient fatality rate than those with other syndromes.

PATHOGENESIS OF AND RISK FACTORS FOR GBS INFECTION

EOD

Group B *Streptococcus* emerged as the primary bacterial cause of EOS in the 1970s, and subsequent studies identified maternal GBS colonization as the primary risk factor for GBS-specific EOS.[18–20] The most common pathogenesis of GBS EOD is that of ascending colonization of the uterine compartment with group B streptococci that are present in the maternal gastrointestinal and genitourinary flora. Infection occurs with subsequent colonization and invasive infection of the fetus and/or fetal aspiration of infected amniotic fluid. This pathogenesis primarily occurs during labor for term infants, but the timing is less certain among preterm infants for whom intraamniotic infection may be the cause of PROM and/or preterm labor.[21] Rarely, GBS EOD may develop at or near term before the onset of labor, potentially because of group B streptococci traversing exposed but intact membranes. GBS EOD also is associated with stillbirth.[22,23]

Maternal colonization is a prerequisite for GBS EOD. Authors of a recent meta-analysis estimated that globally, GBS colonization was detected at vaginal and/or rectal sites in 18% of pregnant women, with regional variation of 11% to 35%.[24] Authors of most clinical studies in the United States have found colonization rates of 20% to 30% among pregnant women,[14,25–28] with variation by maternal age and race. Colonization can be ongoing or intermittent among pregnant and nonpregnant women.[28,29] Transmission of group B streptococci from mother to infant usually occurs shortly before or during delivery. In the absence of IAP, approximately 50% of newborn infants born to mothers positive for GBS become colonized with group B streptococci, and of those, 1% to 2% will develop GBS EOD.[30–33]

Multiple clinical characteristics associated with greater risk of maternal GBS colonization and with the pathogenesis of GBS EOD are predictive of neonatal disease.[20,21,34–43] Lower gestational age is associated with less effective opsonic, neutrophil-mediated defenses in the infant as well as lower levels of protective maternally derived antibody.[44–46] Increased duration of rupture of membranes (ROM) promotes the process of ascending colonization and infection of the uterine compartment and fetus. Maternal intrapartum fever may reflect the maternal inflammatory response to evolving intraamniotic bacterial infection and is an important predictor of neonatal early-onset infection. African American race and, less consistently, a maternal age <20 years have been associated with a higher risk of GBS EOD.[10,34,37,39] The independent contribution of these factors remains unclear because maternal age and race are also associated with higher rates of GBS colonization, preterm birth, and socioeconomic disadvantage, and African American race has been associated with a greater likelihood of missed antenatal screening.[37,41] The delivery of a previous infant with GBS EOD is associated with increased risk in a subsequent delivery,[3] a factor that may be related to poor maternal antibody responses to colonizing strains or other immune- or strain-specific factors.[42] GBS bacteriuria is associated with a high level of maternal colonization and increased risk of neonatal colonization and disease.[41,47] Finally, obstetric practices that may promote ascending bacterial infection, such as the frequency of intrapartum vaginal examinations, invasive fetal monitoring, and membrane sweeping, have been associated with GBS EOD in some observational studies.[39,44] Such studies are difficult to interpret because of confounding; available data are not sufficient to determine if these procedures are associated with an increased risk for GBS EOD. Current ACOG guidance addresses the appropriate use of these procedures among GBS-colonized women.[7] Administration of IAP in women with GBS colonization minimizes the impact of intrapartum obstetric procedures on the risk of neonatal GBS EOD.

LOD

A positive GBS screen result in the mother at the time of birth and at the time of LOD diagnosis is significantly associated with LOD.[48,49] Maternal colonization is not universally present in LOD cases, however, suggesting that horizontal acquisition of group B streptococci from nonmaternal caregivers may also be part of the pathogenesis of GBS LOD. GBS LOD is strongly associated with preterm birth.[6,48–53] In studies from Washington in 1992 to 2011 and Houston in 1995 to 2000, it was found that the risk for LOD increased for each week of decreasing gestation and 40% to 50% of all LOD occurs among infants born <37 weeks' gestation.[48,50] Maternal age <20 years and African American race are variably associated with neonatal GBS LOD in United States studies.[10,48,50,51] Other clinical intrapartum factors predictive of GBS EOD (maternal intrapartum fever, duration of ROM) are not predictive of LOD. Authors of a population-based study in Italy found that group B streptococci could be cultured from a mother's milk in approximately 25% of cases that occurred in breastfed infants,[49] and authors of case reports associate colonized human milk with GBS LOD.[54] However, human milk–associated GBS antibody is protective against GBS LOD,[55] and it remains unclear whether human milk is simply a marker of heavy maternal

and infant colonization or a source of infection.

GBS Virulence

Bacterial factors promote invasive GBS infection. Group B streptococci are characterized by immunologically distinct surface polysaccharide capsules that define 10 serotypes (types I, Ia, and II–IX). Worldwide, serotypes I–V account for 98% of carriage and 97% of infant invasive strains; serotype III accounts for approximately 25% of colonizing strains and approximately 62% of invasive infant strains, with regional variation.[24,56] Surveillance data in the United States for invasive strains from 2006 to 2015 revealed that 93.1% of GBS EOD cases were attributable to serotypes Ia (27.3%), III (27.3%), II (15.6%), V (14.2%), and Ib (8.8%); the proportion attributable to the emerging serotype IV ranged from 3.4% to 11.3% over the study period.[6] Serotype III accounted for approximately 56.2% of 1387 GBS LOD cases during 2006–2015, with serotypes Ia (20%), V (8.3%), IV (6.2%), and Ib (6.1%) making up most of the remaining serotypes. The capsular polysaccharide of all GBS serotypes resists complement deposition and inhibits opsonophagocytosis. Maternally derived, serotype-specific antibody to maternal colonizing GBS isolates is protective against newborn infection.[44,45] Group B streptococci express multiple additional virulence factors, including surface proteins such as the α and β C-proteins that promote adherence and immune evasion, pore-forming toxins such as β-hemolysin and CAMP factor, and secreted proteases such as the C5a peptidase that cleaves complement.[57] Strains vary in their expression of virulence factors, many of which are highly regulated by 2-component regulatory systems.[58–62] The hypervirulent serotype III multilocus sequence type 17 (ST17), for example, is commonly found in cases of GBS meningitis.[6,23]

IAP FOR THE PREVENTION OF EARLY-ONSET GBS INFECTION

Prevention of Perinatal GBS Infection

Multiple observational studies and 1 randomized controlled trial have revealed that the administration of intrapartum antibiotics before delivery interrupts vertical transmission of group B streptococci and decreases the incidence of invasive GBS EOD.[30–32,63] IAP is hypothesized to prevent neonatal GBS disease in 3 ways: (1) by temporarily decreasing maternal vaginal GBS colonization burden; (2) by preventing surface and mucus membrane colonization of the fetus or newborn; and (3) by reaching levels in newborn bloodstream above the minimum inhibitory concentration (MIC) of the antibiotic for killing group B streptococci.[30,31] Current clinical practices are focused on the identification of women at highest risk of GBS colonization and/or of transmission of group B streptococci to the newborn infant to facilitate targeted administration of IAP.

The ACOG currently recommends universal antenatal testing of pregnant women for GBS colonization by using vaginal-rectal cultures obtained at 36 0/7 to 37 6/7 weeks' gestation.[7] GBS testing is also recommended for pregnant women who present in preterm labor and/or with PROM before 37 0/7 weeks' gestation. If maternal GBS colonization is identified by antenatal urine culture, it does not need to be reconfirmed by vaginal-rectal culture. GBS vaginal-rectal culture is optimally performed by using a broth enrichment step, followed by GBS identification by using traditional microbiologic methods or by NAAT-based methods. At some centers, NAATs may be used to perform real-time, point-of-care screening of women who present in labor with unknown GBS status. Point-of care NAAT-based screening is not the primary recommended approach to determine maternal colonization status, both because of variable reported sensitivity of the point-of-care NAAT as compared to traditional culture and because most NAAT-based testing cannot be used to determine the antibiotic susceptibility of colonizing GBS isolates among women with a penicillin allergy.

Updated ACOG recommendations address the indications for IAP.[7] IAP at the time of presentation for delivery is indicated for all women with GBS colonization identified by antenatal vaginal-rectal culture, for women with GBS bacteriuria identified at any point during pregnancy, for women with a history of a previous infant with GBS disease, and for women who present in preterm labor and/or with PROM at <37 0/7 weeks' gestation. Women who present in labor at ≥37 0/7 weeks' gestation with unknown GBS status should receive IAP if risk factors develop during labor (maternal intrapartum temperature ≥100.4°F [38°C] or duration of ROM ≥18 hours) or if the result of an available point-of-care NAAT is positive for group B streptococci. If a woman with unknown status has a negative point-of-care NAAT test result but develops intrapartum risk factors, IAP should be administered because the sensitivity of the NAAT may be decreased without an enrichment incubation step. Women with GBS colonization in one pregnancy have an estimated 50% risk of colonization in a subsequent pregnancy.[64] Therefore, current ACOG recommendations state that if a woman with unknown GBS status presents in labor and is known to have had GBS colonization in a previous pregnancy, IAP may be considered.

Recommended Antibiotics for GBS IAP to Prevent Neonatal GBS EOD

Group B streptococci remain susceptible to β-lactam antibiotics, and penicillin G and ampicillin are the antibiotics best studied for prevention of neonatal infection.

Penicillin G administered to the mother readily crosses the placenta, reaching peak cord blood concentrations by 1 hour and rapidly declining by 4 hours, reflecting elimination of the antibiotic by the fetal kidney into amniotic fluid.[65] Ampicillin has been detected in cord blood within 30 minutes and in amniotic fluid within 45 minutes of administration to the mother.[30] Ampicillin concentrations measured in 115 newborn infants at 4 hours of age were found to be greater than the GBS MIC if maternal IAP dosing occurred at least 15 minutes before delivery.[66] Ampicillin IAP decreases maternal vaginal colonization and prevents neonatal surface colonization in 97% of cases if IAP is administered at least 2 hours before delivery.[30,32] Penicillin G has a narrower antimicrobial spectrum compared to ampicillin and therefore remains the preferred agent, but ampicillin is acceptable.

Alternative Antibiotics for GBS IAP

Cefazolin is recommended for GBS IAP for women with a penicillin allergy who are at low risk for anaphylaxis[7] and has similar pharmacokinetics and mechanisms of action as ampicillin. Cefazolin rapidly crosses the placenta and is detected in cord blood and amniotic fluid at levels above the GBS MIC within 20 minutes after maternal administration.[67–70]

Clindamycin is recommended for GBS IAP for women with a penicillin allergy who are at high risk for anaphylaxis and who are colonized with GBS known to be susceptible to clindamycin.[7] Group B streptococci are increasingly resistant to clindamycin as well as to macrolide antibiotics such as erythromycin. In reports from the ABCs from 2016, authors found that 42% of GBS isolates were resistant to clindamycin and 54% were resistant to erythromycin.[71] Because of both poor placental kinetics and high levels of resistance, erythromycin is no longer recommended for GBS IAP.[7] Antibiotic susceptibility data for the maternal colonizing GBS isolate should be available to support the use of clindamycin for IAP in women who report a penicillin allergy. Several studies inform the potential efficacy of clindamycin prophylaxis.[72–75] Authors of 1 study of 21 women colonized with clindamycin-susceptible GBS isolates found vaginal GBS colony counts declined with administration of clindamycin IAP.[72] Clindamycin administered intravenously to 23 women for high-risk penicillin allergy resulted in cord blood concentrations that were 37% to 160% of maternal concentrations and within therapeutic ranges in 22 of the 23.[75] However, clindamycin undergoes hepatic metabolism and is poorly excreted in fetal urine and, therefore, does not reach significant concentrations in amniotic fluid until multiple doses are administered.[73,74] The clinical effectiveness of clindamycin as IAP administered a median of 6 hours before delivery was only 22% compared to no IAP in an ABCs study that included women treated with clindamycin during the time periods of 1998–1999 and 2003–2004.[76]

Vancomycin is recommended for use as GBS IAP for women with a penicillin allergy who are at high risk for anaphylaxis if colonized with clindamycin-resistant GBS isolates. Although authors of older studies using ex vivo perfusion models with placental lobules suggested that vancomycin crosses the placental poorly, authors of a subsequent study of 13 women undergoing elective cesarean delivery found cord blood concentrations of vancomycin greater than the GBS MIC within 30 minutes of maternal drug administration.[77,78] Authors of recent studies compared cord blood vancomycin concentrations after vancomycin was administered to pregnant women using standard dosing and maternal weight-based dosing.[79,80] Therapeutic maternal and cord blood vancomycin concentrations were achieved in most cases with weight-based dosing. The ACOG currently recommends weight-based dosing for vancomycin when this agent is indicated for IAP.

Current data support the use of clindamycin and vancomycin as alternative medications for GBS IAP when maternal allergy precludes the use of β-lactam antibiotics. These medications are likely to provide some protection against GBS infection for both mother and newborn infant when antimicrobial susceptibility testing supports the use of these second-line agents. In addition, new ACOG recommendations encouraging the use of penicillin allergy testing in pregnant women with uncertain or undocumented histories of penicillin reactions are intended to increase the number of pregnant women who can safely receive β-lactam–based regimens for GBS IAP.[7]

IAP and GBS EOD

The pharmacokinetics and pharmacodynamics of ampicillin, penicillin, and cefazolin suggest that effective GBS EOD prophylaxis may be achieved within 2 to 4 hours of maternal administration. The clinical effectiveness of different durations of GBS IAP was evaluated by using a data set including 7691 births collected as part of the ABCs system from 2003 to 2004. In this study, the administration of different durations of penicillin or ampicillin (≥4; 2–<4; or <2 hours before delivery) were compared to no administration to evaluate the effectiveness of each in preventing GBS EOD. Although all regimens were effective compared to no IAP, administration of IAP at ≥4 hours before delivery was most effective in preventing GBS EOD.[76] This study was limited by the fact that 85% of the cases occurred among infants born to women who screened negative for GBS or whose GBS status was unknown, meaning that in most cases, GBS IAP was administered in

response to risk factors and not as prophylaxis for known maternal GBS colonization. Despite this limitation, this study, combined with the time-dependent bactericidal mechanism of action of β-lactam antibiotics, supports the effectiveness of ampicillin and penicillin administered at least 4 hours before delivery. No data specifically inform the clinical effectiveness of cefazolin IAP, but the pharmacokinetics and mechanism of bacterial killing action for cefazolin are similar enough to those of penicillin and ampicillin that the administration of cefazolin can be considered to provide adequate prophylaxis against GBS EOD. Although data regarding the pharmacokinetics of clindamycin and vancomycin have been published, evidence regarding their clinical efficacy is more limited. Therefore, for the purpose of newborn GBS EOD risk assessment, when non–β-lactam antibiotics of any duration are administered for GBS IAP, such treatment should be considered as not fully adequate in neonatal risk calculation.

IAP and GBS LOD

There is no epidemiological evidence to suggest a protective effect of GBS IAP for the prevention of GBS LOD. This observation is likely attributable to the dynamic nature of GBS colonization. Early studies of IAP demonstrated initial maternal vaginal and/or rectal GBS clearance with IAP, followed by recolonization with group B streptococci within 24 to 48 hours after birth.[30] Authors of a study in Italy found that approximately 25% of infants born to mothers with GBS colonization who received GBS IAP were colonized by 1 month of age. Molecular analysis revealed the infant colonization was attributable to the same strain colonizing the mother antepartum.[81] Similarly, authors of a longitudinal cohort study conducted in Japan from 2014 to 2015 observed that among neonates born to mothers with GBS colonization who received IAP, approximately 20% were colonized with group B streptococci at 1 week and/or 1 month of age.[82] The authors also observed that 6.5% of infants born to mothers who screened negative for GBS were colonized at 1 week and/or 1 month of age, likely as a result of horizontal transmission from newly colonized mothers as well as from other contacts.

RISK ASSESSMENT FOR EARLY-ONSET GBS INFECTION

Because the pathogenesis of GBS EOD begins with vertical transmission of group B streptococci from mother to fetus and newborn infant, the strongest predictor of GBS EOD is maternal GBS colonization. Other factors that are important to the pathogenesis of GBS EOD, such as the virulence of the maternal colonizing isolate and the presence of maternal serotype-specific protective antibody, cannot be known to the physician at the time of neonatal risk assessment. The remaining clinical risk factors for GBS EOD are the same as those for EOS caused by other common bacterial causes of EOS, including gestational age at birth, intraamniotic infection, and duration of ROM. The administration of GBS IAP and the administration of intrapartum antibiotics in response to obstetric concern for intraamniotic infection both decrease this risk. The newborn infant's condition at birth and evolving condition over the first 12 to 24 hours after birth are strong predictors of early-onset infection attributable to any pathogen.[12,13]

Previous guidance on GBS EOD risk assessment presented challenges to physicians because of practical difficulties in establishing the obstetric diagnosis of maternal chorioamnionitis or intraamniotic infection, absence of guidance on what defines abnormal laboratory test results in the newborn infant, and a lack of clear definitions for newborn clinical illness. Each of these concerns are addressed in detail in the current AAP clinical reports on management of neonates with suspected or proven early-onset bacterial sepsis.[83,84] In summary, at this time, evidence supports the following:

- The ACOG provides guidance regarding intraamniotic infection[85]; neonatal risk assessment can be informed by this guidance. The definitive diagnosis of intraamniotic infection is that made by amniotic fluid Gram-stain and/or culture or by placental histopathologic testing. Such clear diagnostic information will rarely be available at the time of delivery for infants born at or near term. Suspected intraamniotic infection is defined as a single maternal intrapartum temperature ≥39.0°C or maternal temperature of 38.0°C to 38.9°C in combination with 1 or more of maternal leukocytosis, purulent cervical drainage, or fetal tachycardia. Recognizing the uncertainties surrounding the diagnosis of intraamniotic infection, the ACOG recommends that intrapartum antibiotic therapy be administered whenever intra-amniotic infection is diagnosed or suspected and should be considered when otherwise unexplained isolated maternal temperature 38.0°C to 38.9°C is present.[85]
- The routine measurement of complete blood cell counts or inflammatory markers such as C-reactive protein alone in newborn infants to determine risk of GBS EOD is not justified given the poor test performance of these in predicting what is currently a low-incidence disease.[86–89]
- Newborn clinical illness consisting of abnormal vital signs (eg, tachycardia, tachypnea, and/or temperature instability), supplemental oxygen requirement and/or need for continuous positive airway pressure, mechanical ventilation, or blood pressure support can be used to predict early-onset infection.[13] There is no evidence that hypoglycemia occurring in isolation

in otherwise well-appearing infants is a risk factor for GBS EOD or EOS. A newborn's clinical condition often evolves in the hours after birth, and physicians must exercise judgment to distinguish transitional instability from signs of clinical illness.

Clinicians should recognize that GBS EOD can occur among term infants born to mothers who have screened negative for GBS. Authors of 1 single-center study with policies mandating universal screening-based GBS IAP found that over an 8-year period, 17 GBS EOD cases occurred among term infants and 14 of 17 (82.4%) of the mothers had screened negative for GBS.[90] Multistate ABCs data in 2003–2004 identified 189 cases of GBS EOD among term infants and determined that 116 of 189 (61.4%) occurred among infants born to women who screened negative for GBS.[37] GBS EOD may occur in infants of mothers who screened negative for GBS because of changes in maternal colonization status during the interval from screening to presentation for delivery or because of an incorrect technique in obtaining vaginal and rectal screening cultures or in laboratory processing. Studies comparing antepartum culture to intrapartum culture or intrapartum molecular identification techniques reveal that approximately 7% to 8% of women who screen negative for GBS will be identified as positive for GBS at the time of delivery.[27,91] In some proportion of these cases, additional risk factors for EOS were present, but GBS EOD can develop in newborn infants without additional risk, and these will only be identified when they develop signs of illness.

Nonetheless, most infants who develop GBS EOD will do so in the setting of specific risk factors. In the current era of widespread use of GBS IAP, the clinical approach to risk of GBS EOD should be the same as that for all bacterial causes of early-onset infection. As addressed in the AAP clinical reports on management of neonates with suspected or proven early-onset bacterial sepsis,[83,84] risk of early-onset infection should be considered separately for infants born at or near term (≥35 weeks' gestation) and those preterm (≤34 6/7 weeks' gestation). A summary of the management strategies provided in the previous AAP reports are provided here.

There Are 3 Current Approaches to Risk Assessment Among Infants Born at ≥35 Weeks' Gestation

- Categorical risk assessment: Categorical risk factor assessment uses risk factor threshold values to identify infants at increased risk for

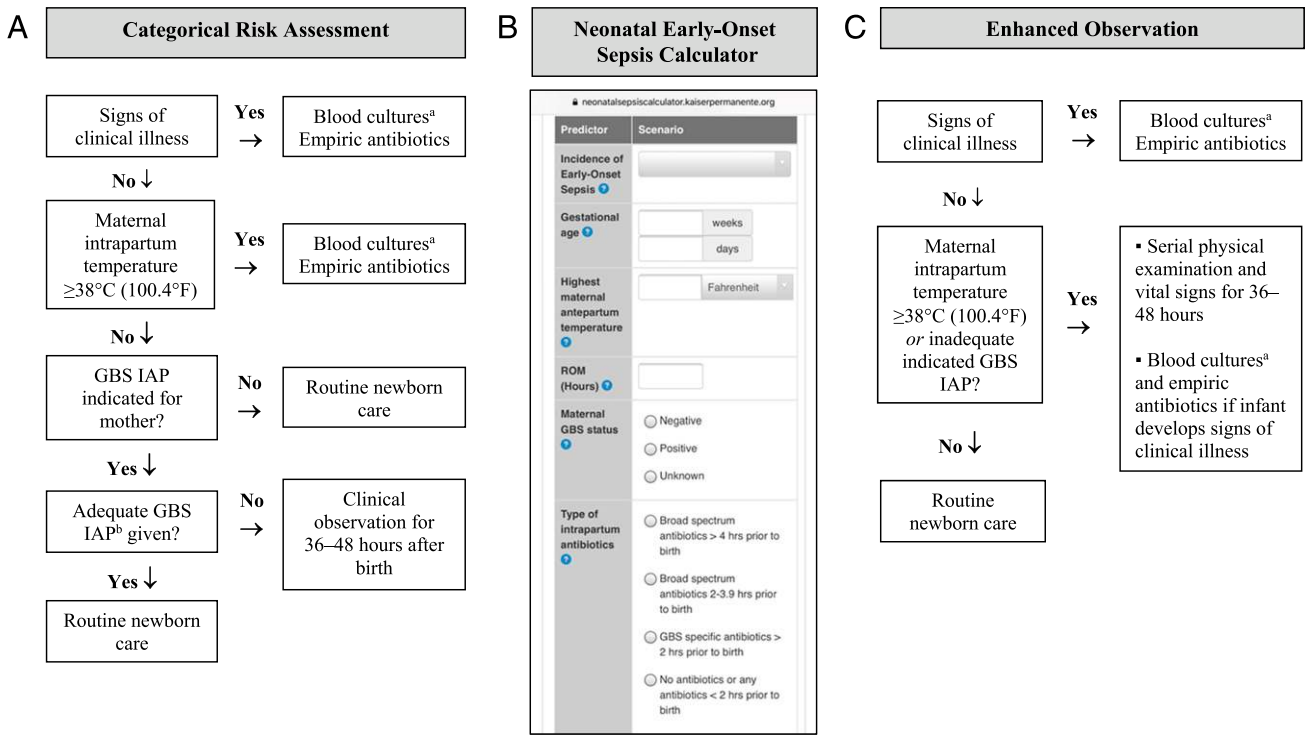

FIGURE 1

Options for EOS risk assessment among infants born ≥35 weeks' gestation. A, Categorical risk assessment. B, Neonatal Early-Onset Sepsis Calculator. The screenshot of the Neonatal Early-Onset Sepsis Calculator (https://neonatalsepsiscalculator.kaiserpermanente.org/) was used with permission from Kaiser-Permanente Division of Research. C, Enhanced observation. [a] Consider lumbar puncture and CSF culture before initiation of empiric antibiotics for infants who are at the highest risk of infection, especially those with critical illness. Lumbar puncture should not be performed if the infant's clinical condition would be compromised, and antibiotics should be administered promptly and not deferred because of procedure delays. [b] Adequate GBS IAP is defined as the administration of penicillin G, ampicillin, or cefazolin ≥4 hours before delivery.

GBS EOD (Fig 1A). Different versions of this approach have been published since 1996 and are based on infection epidemiology and expert opinion. For the purpose of categorical risk assessment, maternal intrapartum temperature ≥38.0°C is used as a surrogate for intraamniotic infection. The administration of penicillin G, ampicillin, or cefazolin ≥4 hours before delivery is considered adequate GBS IAP; other antibiotics or other durations of treatment <4 hours are considered inadequate when using this approach. Substantial data have been reported on the impact of using categorical risk factors to manage the risk of GBS EOD.[3,14,36,40] However, the risk is highly variable among the newborn infants recommended to receive empirical treatment in this approach, ranging from slightly lower than the baseline population risk to significantly higher, depending on the gestational age, duration of ROM, and timing and content of administered intrapartum antibiotics. Consequently, a limitation of this approach is that categorical management will result in empirical treatment of many relatively low-risk newborn infants.

- Multivariate risk assessment (the Neonatal Early-Onset Sepsis Calculator): Multivariate risk assessment integrates the individual infant's combination of risk factors and the newborn infant's clinical condition to estimate an individual infant's risk of EOS, including GBS EOD. Predictive models based on gestational age at birth, highest maternal intrapartum temperature, maternal GBS colonization status, duration of ROM, and type and duration of intrapartum antibiotic therapies have been developed and validated.[13,38] These models are available as a Web-based Neonatal Early-Onset Sepsis Calculator (Fig 1B) (https://neonatalsepsiscalculator.kaiserpermanente.org) that includes recommended clinical actions to be taken at specific levels of predicted risk. The models begin with the previous probability of infection, and because they predict all bacterial causes of EOS and not only GBS EOD, physicians in the United States should enter a previous probability of 0.5/1000, unless local incidence of EOS is known to differ from the national incidence of EOS among term infants. The models do account for the content and timing of GBS-specific IAP. When using these models, only penicillin, ampicillin, or cefazolin should be considered as "GBS-specific antibiotics." The administration of clindamycin or vancomycin alone for IAP for any duration is currently recommended to be entered as "no antibiotics." Because the models were developed to predict risk of all bacterial causes of EOS (and not just GBS EOD), and because these models account for other antibiotic types and indications for intrapartum antibiotic administration, "GBS specific antibiotics >2 hours prior to birth" is 1 of the calculator variables. The 2-hour timing is used because multiple factors in addition to GBS IAP are considered when using the multivariate models in the Neonatal Early-Onset Sepsis Calculator. Used in this manner, threshold risk estimates prompting enhanced clinical observation or blood culture and empirical antibiotic therapy have been prospectively validated in large newborn cohorts.[14,92] Centers that opt for this approach to risk assessment should develop methods to calculate the risk estimate for all newborn infants born at ≥35 weeks' gestation and will need to develop a structured approach to close clinical observation of infants at specific levels of estimated risk.
- Risk assessment based on newborn clinical condition: A final approach to GBS EOD risk assessment is to rely on clinical signs of illness to identify infants who may be at increased risk of infection. Among term infants, good clinical condition at birth is associated with an approximately 60% to 70% reduction in risk for early-onset infection.[13] Under this approach, infants who appear ill at birth and those who develop signs of illness over the first 48 hours after birth are treated empirically with antibiotics.[93–95] One center reported the use of clinical observation for initially well-appearing infants born at ≥34 to 35 weeks' gestation to mothers with the obstetric diagnosis of chorioamnionitis. Whether observed in a setting with continuous monitoring or with serial examinations during maternal-infant couplet care, this center ultimately administered empirical antibiotics to 5% to 12% of such infants.[94,95] Centers that adopt this approach will need to establish processes to ensure serial, structured, documented physical assessments and develop clear criteria for additional evaluation and empirical antibiotic administration. Physicians and families must understand that the identification of initially well-appearing infants who develop clinical illness is not a failure of care, but rather an anticipated outcome of this approach to GBS EOD risk management.

For Infants Born at ≤34 Weeks' Gestation, the Optimal Approach to Risk Assessment for All EOS Should Be Applied to Risk of GBS EOD

The circumstances of preterm birth may provide the best current approach to GBS EOD management for preterm infants (Fig 2). Clinicians may adopt one of the following strategies to develop institutional approaches best suited to their local resources and structure of care (Fig 1).

- Preterm infants at highest risk for EOS: Infants born preterm because of cervical insufficiency, preterm

labor, PROM, intraamniotic infection, and/or acute and otherwise unexplained onset of nonreassuring fetal status are at the highest risk of EOS and GBS EOD. The administration of GBS IAP may decrease the risk of infection among these infants, but the most reasonable approach to these infants is to obtain a blood culture and start empirical antibiotic treatment. A lumbar puncture for culture and analysis of CSF should be considered in clinically ill infants when there is a high suspicion for GBS EOD, unless the procedure will compromise the neonate's clinical condition.

- Preterm infants at lower risk for EOS: Preterm infants at lowest risk for all EOS and for GBS EOD are those born under circumstances that include all of these criteria[96, 97]: (1) maternal and/or fetal indications for preterm birth (such as maternal preeclampsia or other noninfectious medical illness, placental insufficiency, or fetal growth restriction), (2) birth by cesarean delivery, and (3) absence of labor, attempts to induce labor, or any ROM before delivery. Acceptable initial approaches to these infants include (1) no laboratory evaluation and no empirical antibiotic therapy or (2) blood culture and clinical monitoring. For infants who do not improve after initial stabilization and/or those who have severe systemic instability, the administration of empirical antibiotics may be reasonable but is not mandatory.
- Infants delivered for maternal and/or fetal indications but who are ultimately born by vaginal or cesarean delivery after efforts to induce labor and/or with ROM before delivery are subject to factors associated with the pathogenesis of GBS EOD. If the mother has an indication for GBS IAP and adequate IAP (penicillin, ampicillin, or cefazolin ≥4 hours before delivery) is not given or if any other concern for infection arises during the process of delivery, the infant should be managed as recommended above for preterm infants at higher risk for GBS EOD. Otherwise, an acceptable approach to these infants is close observation for those infants who are well appearing at birth and to obtain a blood culture and to initiate antibiotic therapy for infants with respiratory and/or cardiovascular instability after birth.

CLINICAL PRESENTATION AND TREATMENT OF GBS INFECTION

Newborn infants with GBS EOD may present with signs of illness ranging from tachycardia, tachypnea, or lethargy to severe cardiorespiratory failure, persistent pulmonary hypertension of the newborn, and perinatal encephalopathy. GBS LOD most commonly occurs as bacteremia without a focus and is often characterized by fever (≥38°C) as well as lethargy, poor feeding,

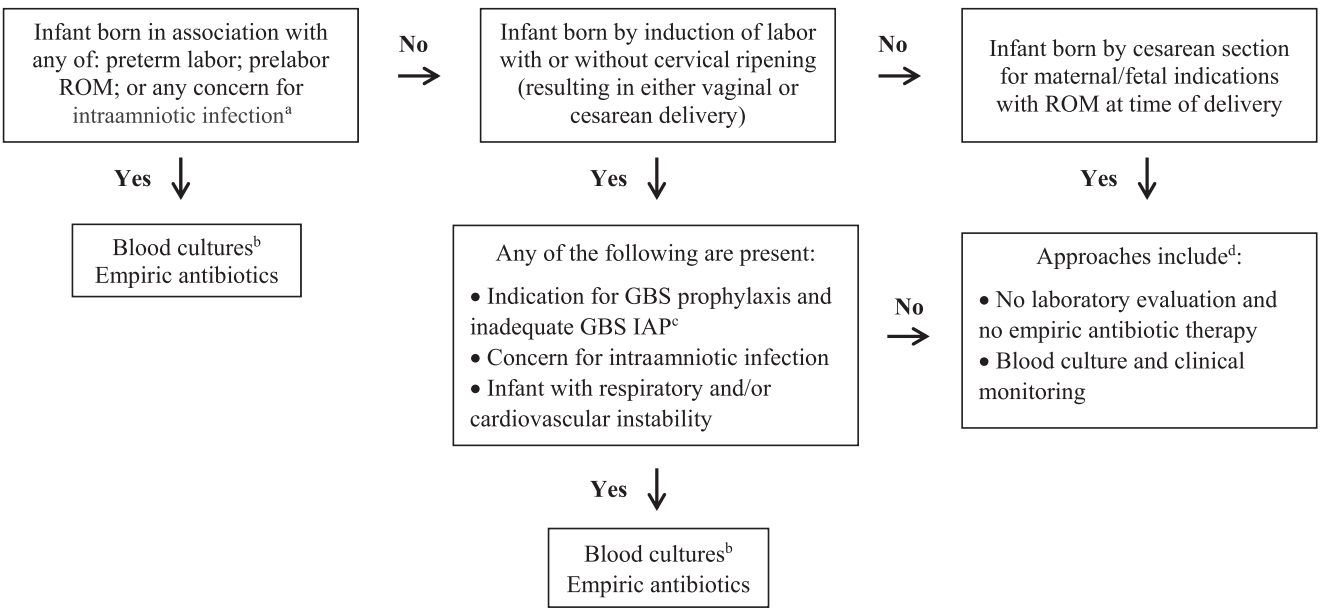

FIGURE 2

EOS risk assessment among infants born ≤34 weeks' gestation. [a] Intraamniotic infection should be considered when a pregnant woman presents with unexplained decreased fetal movement and/or there is sudden and unexplained poor fetal testing. [b] Lumbar puncture and CSF culture should be performed before initiation of empiric antibiotics for infants who are at the highest risk of infection unless the procedure would compromise the infant's clinical condition. Antibiotics should be administered promptly and not deferred because of procedural delays. [c] Adequate GBS IAP is defined as the administration of penicillin G, ampicillin, or cefazolin ≥4 hours before delivery. [d] For infants who do not improve after initial stabilization and/or those who have severe systemic instability, the administration of empiric antibiotics may be reasonable but is not mandatory.

irritability, tachypnea, grunting, or apnea. Infants with LOD meningitis can also have nonspecific signs such as irritability, poor feeding, vomiting, and temperature instability as well as signs suggestive of central nervous systems involvement such as bulging fontanelle or seizures. Focal syndromes such as pneumonia, bone or joint infection, cellulitis, or adenitis often have findings that point to the site of infection. Osteomyelitis frequently is insidious and may not be associated with fever. Complications are common for meningitis and can include neurodevelopment impairment, hearing loss, persistent seizure disorders, or cerebrovascular disease.[98]

Evaluation for GBS disease is the same as that for all forms of sepsis in the newborn and young infant.[83,84] Blood culture, lumbar puncture for culture and analysis of CSF, and markers of inflammation are discussed in detail in the AAP clinical reports on management of neonates with suspected or proven early-onset bacterial sepsis. The evaluation for GBS LOD should also include urine culture. If bone or joint infection is suspected, additional studies can include radiographs, MRI, and bone or joint fluid culture. When meningitis is diagnosed, cranial imaging is often useful to assess for complications such as ventriculitis or brain abscess. Cultures should include testing for antibiotic susceptibility.

Empirical and Definitive Treatment

Antibiotics initiated because of concern for GBS EOD are the same as those for all bacterial causes of EOS until the results of cultures are available. GBS neonatal disease isolates remain susceptible to β-lactam antibiotics, although ABCs has identified rare isolates of group B streptococci with mutations in penicillin-binding proteins leading to elevated MICs (nonsusceptibility) to β-lactam antibiotics.[99] Ampicillin, together with an aminoglycoside, is the primary recommended therapy for infants up to 7 days of age. The empirical addition of broader-spectrum therapy should be considered if there is strong clinical concern for ampicillin-resistant infection in a critically ill newborn, particularly among neonates with very low birth weight.[100–102] Among previously healthy infants in the community, if the infant is not critically ill and there is no evidence of meningitis, ampicillin and ceftazidime together are recommended as empirical therapy for those 8 to 28 days of age; ceftriaxone therapy is recommended under these circumstances for infants 29 to 90 days of age. For all previously healthy infants in the community from 8 to 90 days of age, vancomycin should be added to recommended empirical therapy if there is evidence of meningitis or critical illness to expand coverage, including for β-lactam–resistant *Streptococcus pneumoniae*. The choice of empirical therapy among continuously hospitalized preterm infants beyond 72 hours of age is guided by multiple factors, including the presence of central venous catheters and local hospital microbiology. The empirical choice for such infants should include an antibiotic to which group B streptococci are susceptible, such as a β-lactam, cephalosporin, or vancomycin. When group B streptococci are identified in culture, penicillin G is the drug of choice, with ampicillin as an acceptable alternative therapy.

See Table 1 for dose and interval guidance. The length of antibiotic treatment is generally 10 days for bacteremia without focus and 14 days for uncomplicated meningitis; antibiotics should be given intravenously for the entire course. Longer therapy is used when there is a prolonged or complicated course. Some experts recommend a second lumbar puncture for CSF culture 24 to 48 hours after the start of antibiotics. Additional lumbar punctures and intracranial imaging are advised if there is not resolution of CSF infection, if neurologic abnormalities persist, or if focal deficits develop. Osteoarticular infection should be treated for 3 to 4 weeks and ventriculitis should be treated for at least 4 weeks. Consultation with a pediatric infectious disease specialist should be considered for meningitis and for cases with site-specific infection. Audiology testing and ongoing

TABLE 1 Recommended Intravenous Antibiotic Treatment Regimens for Confirmed Early- and Late-Onset GBS Bacteremia and Meningitis

	GA ≤34 wk		GA >34 wk	
	PNA ≤7 d	PNA >7 d	PNA ≤7 d	PNA >7 d
Bacteremia				
Ampicillin	50 mg/kg every 12 h	75 mg/kg every 12 h	50 mg/kg every 8 h	50 mg/kg every 8 h
Penicillin G	50 000 U/kg every 12 h	50 000 U/kg every 8 h	50 000 U/kg every 12 h	50 000 U/kg every 8 h
Meningitis				
Ampicillin	100 mg/kg every 8 h	75 mg/kg every 6 h	100 mg/kg every 8 h	75 mg/kg q 6 h
Penicillin G	150 000 U/kg every 8 h	125 000 U/kg every 6 h	150 000 U/kg every 8 h	125 000 U/kg every 6 h

Adapted from Table 4.2. Antibacterial Drugs for Neonates (<28 Postnatal Days of Age). In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:915-919. GA, gestational age; PNA, postnatal age.

audiologic monitoring, if indicated, should be arranged before discharge.

Multiple Births

When invasive GBS infection occurs in an infant who is 1 of multiple births, the birth siblings should be observed carefully for signs of infection and treated empirically if signs of illness occur. There is no evidence to support full antibiotic treatment courses in the absence of confirmed GBS disease.

Recurrent GBS Disease

Recurrent neonatal and young infant GBS disease can occur after completed appropriate treatment of the primary infection.[103,104] Authors of a population-based study conducted in Japan[53] during 2011 to 2015 found that recurrence occurred in 2.8% of cases of neonatal GBS infection. Recurrent cases were identified 3 to 54 days after completion of the therapy for the first occurrence. Recurrent cases are generally caused by the same GBS serotype that caused the primary infection, and persistent mucosal colonization and poor neonatal antibody responses to the first infection likely contribute to the pathogenesis of recurrent infection. Recurrent disease is not preventable by extension of recommended antibiotic courses nor by the addition of rifampin to eradicate mucosal colonization.[105] Parents should be counseled about the possibility of recurrent GBS disease after treatment of both GBS EOD and LOD.

FUTURE DIRECTIONS

Intrapartum Antibiotics, the Microbiome, and Childhood Health

GBS IAP and the administration of intrapartum antibiotics because of concern for maternal intraamniotic infection combined result in approximately 30% of pregnant women receiving antibiotics around the time of delivery. The composition of the gut microbiota develops and diversifies from birth through early childhood, and disruption of the microbiota during this critical period may have enduring health consequences. Perinatal antibiotic administration is associated with abnormal host development in animal models.[106–108] Human epidemiological studies have associated early infant antibiotic exposures with increased risks of atopic and allergic disorders as well as increases in early childhood weight gain.[109–112] Several human studies report differences in the composition of the maternal vaginal[113] and infant gut microbiome associated with the use of IAP, with effects on both the diversity and richness of identified species.[114–119] The differences observed vary with the mode of delivery and duration of breastfeeding; differences were detected as long as 12 months after birth in 1 study.[115] Changes in the initial constitution of neonatal gut microbiota in response to IAP are not unexpected; GBS IAP is administered with the intent of altering the content of the newborn infant's initial microflora exposure at delivery to decrease colonization with a significant neonatal pathogen. Whether the secondary effects of IAP on the microbiome influence short- and long-term childhood health outcomes is unknown and an area of active investigation.

GBS Vaccine Development

Multiple gaps remain in GBS disease prevention. Neonatal EOD continues to occur in the United States, primarily among preterm infants, term infants born to women with cultures negative for antenatal GBS, and infants born to mothers with reported β-lactam allergy that precludes maximally effective IAP. The incidence of GBS LOD has not been affected by IAP. In addition, group B *Streptococcus* is a cause of stillbirth and of invasive infection among pregnant and postpartum women as well as among the elderly and those whose health is compromised by diabetes or malignancy.[15,120] Furthermore, GBS disease is a worldwide problem, particularly among resource-limited countries where IAP is not a readily available preventive strategy. Effective, multivalent vaccines administered to pregnant women and at-risk nonpregnant adults could potentially prevent many of these issues. Preclinical and human phase I and II studies have been completed revealing the safety and immunogenicity of glycoconjugate GBS vaccines.[121–123] Current ABCs reveals that 99% of infections are caused by 6 GBS serotypes, suggesting that a hexavalent vaccine could be widely effective.[6]

SUMMARY OF RECOMMENDATIONS

1. The AAP supports the maternal policies and procedures for the prevention of perinatal GBS disease as recommended by the ACOG.
2. For the purpose of neonatal management, the administration of intrapartum penicillin G, ampicillin, or cefazolin can provide adequate IAP against neonatal early-onset GBS disease. For women at high risk of anaphylaxis to β-lactam antibiotics, clindamycin and vancomycin should be administered as recommended by the ACOG and will likely provide some protection against GBS EOD in exposed newborn infants. However, there is currently insufficient clinical efficacy evidence to consider the administration of these antibiotics equivalent to β-lactam antibiotics for the purpose of neonatal risk assessment.
3. Risk assessment for early-onset GBS disease should follow the general principles established in the AAP clinical reports on management of neonates with suspected or proven early-onset bacterial sepsis.[83,84] These principles include the following:
   - separate consideration of infants born at ≥35 0/7 weeks'

gestation and those born at ≤34 6/7 weeks' gestation;

- infants born at ≥35 0/7 weeks' gestation may be assessed for risk of early-onset GBS infection with a categorical algorithm by using multivariate models such as the Neonatal Early-Onset Sepsis Calculator or with enhanced clinical observation; and
- infants born at ≤34 6/7 weeks' gestation are at highest risk for early-onset infection from all causes, including group B streptococci, and may be best approached by using the circumstances of preterm birth to determine management.

4. Early-onset GBS infection is diagnosed by blood or CSF culture. Common laboratory tests such as the complete blood cell count and C-reactive protein do not perform well in predicting early-onset infection, particularly among well-appearing infants at lowest baseline risk of infection.
5. Evaluation for late-onset GBS disease should be based on clinical signs of illness in the infant. Diagnosis is based on the isolation of group B streptococci from blood, CSF, or other normally sterile sites. Late-onset GBS disease occurs among infants born to mothers who had positive GBS screen results as well as those who had negative screen results during pregnancy. Adequate IAP does not protect infants from late-onset GBS disease.
6. Empirical antibiotic therapy for early-onset and late-onset GBS disease differs by postnatal age at the time of evaluation. Penicillin G is the preferred antibiotic for definitive treatment of GBS disease in infants; ampicillin is an acceptable alternative.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
ABCs: Active Bacterial Core surveillance
ACOG: American College of Obstetricians and Gynecologists
CDC: Centers for Disease Control and Prevention
CSF: cerebrospinal fluid
EOD: early-onset disease
EOS: early-onset sepsis
GBS: group B streptococcal
IAP: intrapartum antibiotic prophylaxis
LOD: late-onset disease
MIC: minimum inhibitory concentration
NAAT: nucleic acid amplification test
PROM: prelabor rupture of membranes
ROM: rupture of membranes

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