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Perinatal Group B Streptococcal Infections and the New Guidelines: An Update

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Author Disclosure
Drs Tumbaga and Philip did not disclose any financial relationships relevant to this article.

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

1. Describe the current literature on surveillance studies and patient outcomes regarding group B Streptococcus (GBS) disease.
2. Discuss the current perinatal GBS prevention guidelines.
3. Describe the limitations of the “limited evaluation” in assessing newborns at risk for GBS disease.
4. Delineate the proposed management of asymptomatic infants at risk for GBS disease, with the goal of decreasing unnecessary testing and avoiding prolonged hospitalization.

Introduction

Group B Streptococcus (GBS), also known as *Sagalactiae*, is an encapsulated gram-positive bacterium that is a common inhabitant of the human gastrointestinal and genitourinary tracts. Despite recent reductions in incidence, it remains the most common cause of neonatal bacterial infections in most developed countries.

The most desirable approach suggested to eliminate neonatal GBS infection is the use of GBS vaccines prior to or early in pregnancy. However, until effective GBS vaccines become available, screening pregnant women for GBS colonization and providing intrapartum antibiotic prophylaxis (IAP) will continue to be the mainstay for prevention of GBS infection in neonates, as suggested by the Centers for Disease Control and Prevention (CDC).

A 70% decline in the rate of early-onset GBS disease followed the introduction of the first national consensus guidelines in 1996. In 2002, new national guidelines were released based on evidence that the screening-based strategy was superior to a risk factor-based strategy for preventing GBS infections in the neonate. As a result of many obstetricians adopting the screening-based strategy, CDC data from 2004 showed a further decline in the incidence of early-onset GBS infection to 0.34 cases per 1,000 live births. This surpasses the Healthy People 2010 objective of a reduction in the incidence of early-onset disease to 0.5 cases per 1,000 live births for all races. It should be mentioned that different countries may demonstrate different results, but it is noteworthy that a recent report of a national study from Germany documented an actual incidence of 0.24 cases per 1,000 live births, which was corrected to 0.47 per 1,000 live births for underreporting. These results were achieved using a combined screening and risk factor-based approach.

Effective GBS screening with improved implementation and compliance as well as the potential use of either a GBS antigen detection assay or the highly sensitive and specific polymerase chain reaction (PCR) assay (approved by the United States Food and Drug Administration in 2002) for rapid detection of GBS in women whose GBS status is unknown at the time of labor could yield even better results. The effect that positive PCR results for GBS may have on the outcome of neonates has yet to be determined.

The 2002 guidelines proposed the use of “limited evaluation” for at-risk newborns. Data obtained over the last 5 years suggest decreased usefulness of this evaluation. The 2002 guidelines and current literature regarding the usefulness of the limited evaluation are reviewed in this article.

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For purposes of this article, limited evaluation is defined as a complete blood count (CBC) and blood culture. At-risk newborns are defined as newborns of at least 35 weeks’ gestation born to mothers colonized with GBS or to mothers who have fever, have had premature rupture of membranes of at least 18 hours, have given birth to a previous infant who had GBS disease, and who did not receive adequate IAP. Adequate IAP is defined as the mother having received appropriate antibiotics (penicillin, ampicillin, or cefazolin) 4 or more hours prior to delivery. Use of erythromycin or clindamycin is acceptable if prior sensitivity testing was confirmed.

Background
GBS was considered a commensal organism until the late 1930s, when severe infections affected both parturient women and newborns. By the 1960s, the organism emerged as a prominent cause of neonatal infections. By the 1970s, GBS surpassed Escherichia coli as the leading cause of neonatal infections and emerged as an important cause of maternal infections. Although there has been an increasing incidence of E coli sepsis in very low-birthweight infants, GBS remains the leading cause of early-onset neonatal bacterial infections in the United States.

Early-onset neonatal sepsis presents as a systemic illness within the first 7 days after birth. GBS predominantly invades the blood, lungs, or cerebrospinal fluid. Infants become ill after passage through a colonized birth canal, via aspiration of contaminated amniotic fluid, via ascending infection through ruptured membranes, or very rarely through the maternal bloodstream. Maternal GBS colonization is a prerequisite for early-onset neonatal infections in nearly all cases.

As stated previously, GBS is a common inhabitant of the human gastrointestinal and genitourinary tracts. Approximately 30% of women have asymptomatic GBS colonization at some time during pregnancy, and about 20% are colonized at the time of labor. GBS colonization usually is constant but can be transient or intermittent. Nearly 50% of infants who pass through a colonized birth canal become colonized. However, only 1% to 2% of colonized infants develop invasive disease.

Early-onset Disease
Invasive disease in young infants is categorized according to the time of onset after birth as early-onset and late-onset disease. Early-onset disease occurs within the first week after birth (range, 0 to 6 d). Most affected infants become ill within the first 24 hours. The clinical spectrum involves respiratory distress, apnea, poor perfusion, and shock. Approximately 75% of cases of GBS infection are early-onset. Septicemia occurs in 25% to 40% of cases, pneumonia in 35% to 55%, and meningitis in 5% to 10%. The mortality rate is 4% to 6% and higher in preterm infants. An increased incidence among preterm infants probably is due to opsonin deficiency and limited maternal antibody transfer. Lack of maternal capsular antibody also increases the risk of infection.

African-American infants are at increased risk for early-onset GBS infection compared with other racial groups, but there is no clear reason for this disparity. CDC surveillance studies revealed a dramatic decline in reported GBS infection in African-American infants in response to antibiotic prophylaxis. Maternal obstetric complications frequently are associated with early-onset neonatal disease, but maternal complications also have waned with IAP.

Late-onset Disease
Late-onset disease typically occurs at 3 to 4 weeks after birth (range 7 d to 3 mo). Term and preterm infants are equally susceptible to late-onset disease, but maternal obstetric complications are uncommon. Late-onset GBS disease frequently presents with bacteremia or meningitis. Focal infections such as osteomyelitis, septic arthritis, and cellulitis occur less commonly than sepsis or meningitis but are typical of late-onset disease.

Unlike early-onset disease that is transmitted vertically in most or nearly all cases, horizontal transmission is the major source of late-onset disease. Infants acquire the organism in the hospital or the community as well as horizontally from a colonized mother. Late-onset infection is transmitted vertically in less than 50% of cases. Late-onset GBS transmission via human milk also has been reported. Not surprisingly, IAP has not decreased the incidence of late-onset GBS infections.

Screening
The opportunity to prevent GBS transmission to the neonate is greater when antibiotic prophylaxis is started early in the intrapartum period. When antibiotics were given less than 1 hour prior to delivery, 46% of infants were colonized, a rate similar to infants of untreated GBS-colonized mothers. When the interval was 2 to 4 hours prior to delivery, the infant colonization rate decreased significantly to 2.9%. When antibiotics were administered more than 4 hours prior to delivery, only 1.2% of infants were colonized. Therefore, antibiotic prophylaxis is beneficial 2 to 4 hours prior to delivery but more reassuring when administered more than 4 hours prior to delivery.
Because of the superiority of the culture screening strategy in preventing early-onset GBS disease compared with the risk-based approach, universal screening of all pregnant women at 35 to 37 weeks gestational age is now the recommended standard of care. Intrapartum prophylaxis is indicated for all GBS carriers except for those in whom cesarean delivery is planned in the absence of labor or membrane rupture (Fig. 1). Penicillin G remains the drug of choice for prophylaxis, with ampicillin as the alternative agent. For patients who are allergic to penicillin but do not have a history of anaphylaxis, cefazolin is the preferred choice. Otherwise, vancomycin is a viable alternative for those who have a history of anaphylaxis.

In the case of maternal chorioamnionitis, early treatment of the mother with broad-spectrum antibiotics is indicated because infection is already present. Full diagnostic evaluation and empiric therapy of the neonate are recommended (Fig. 2). The duration of treatment depends on the infant’s clinical course and laboratory results.

The presence of maternal chorioamnionitis must be based on solid evidence to avoid unnecessary evaluations and antibiotic usage. Criteria for maternal chorioamnionitis include maternal fever plus one of the following: uterine tenderness, fetal tachycardia, foul-smelling amniotic fluid, prolonged rupture of membranes (≥18 h), and maternal leukocytosis. The presence of fever alone is not enough to diagnose suspected chorioamnionitis. Fever may develop after epidural analgesia and, therefore, may provide less reliable evidence in this situation.

Management of Infants Born to Mothers Who Received IAP

The management of infants whose mothers received IAP remains controversial. The CDC and the American Academy of Pediatrics provide an algorithm for the management of infants born to mothers who have received IAP (Fig. 2).

Some of the guidelines are simple and straightforward. For example, a symptomatic neonate at any gestation, regardless of whether the mother received adequate IAP or not, should receive full diagnostic evaluation and treatment with intravenous ampicillin and gentamicin. Chest radiography should be obtained if there are respiratory symptoms. Lumbar puncture should be performed if sepsis is suspected as the primary diagnosis. Length of therapy depends on the infant’s clinical course and laboratory results. Similarly, infants born to mothers who have suspected or proven chorioamnionitis should receive full diagnostic evaluation, including lumbar puncture and initiation of ampicillin and gentamicin, even if the baby appears clinically well, because the frequency for sepsis is high in this group. Lumbar puncture should be performed; a recent study suggests that up to 38% of infants who have culture-proven meningitis have negative blood cultures. Similar results were published a decade ago.

Asymptomatic Preterm Infants

Because preterm infants (<35 weeks’ gestation) remain at high risk for mortality and morbidity from GBS infec-
tion, limited evaluation should be obtained in asymptomatic infants of GBS-colonized mothers or in the presence of other risk factors regardless of whether the mother received adequate IAP. These infants usually are admitted to the neonatal intensive care unit and receive close observation without antibiotic treatment. Full diagnostic evaluation, including lumbar puncture, and initiation of empiric intravenous antibiotic therapy are prudent for high-risk asymptomatic preterm infants born to mothers who have suspected or proven chorioamnionitis, the presence of preterm premature rupture of the membranes (PPROM) and GBS colonization, or the presence of PPROM alone. Frequency of sepsis is high in the presence of these risk factors, even if infants are asymptomatic.

**Asymptomatic Term or Near-term Infants**

Asymptomatic at-risk newborns born at 35 or more weeks’ gestation whose mothers were treated inadequately require limited evaluation and observation for at least 48 hours without antibiotic treatment. However, recent studies suggest that limited evaluation is no more helpful than clinical observation. Therefore, based on newly available data, the infant should be observed for at least 24 to 48 hours without laboratory evaluation or two serial CBCs (and C-reactive protein [CRP] measurements) should be obtained within 24 hours after birth. Blood culture is not necessary. If the values are within normal limits, the infant may be discharged after 24 hours with close outpatient follow-up. If the infant becomes symptomatic, blood culture should be obtained because the greatest organism yield occurs when an infant is symptomatic rather than when an infant appears well. Empiric intravenous antibiotics should be administered promptly. Duration of therapy depends on the infant’s clinical course and laboratory results (CBC, CRP, and blood culture).

Healthy near-term or term infants whose mothers received adequate IAP should be observed for at least 24 to 48 hours without laboratory evaluation. The infant may be discharged after 24 hours with close outpatient follow-up if he or she meets readiness for discharge criteria and the parents are competent.

As mentioned earlier, not every infant who passes through a colonized birth canal becomes colonized. Approximately 50% become colonized, and 1% to 2% develop invasive disease. Moreover, if the mother received appropriate antibiotics more than 4 hours prior to delivery, the colonization rate decreases significantly to 1.2% compared with 47% (colonized infants of untreated GBS colonized mothers). Therefore, the rate of invasive disease decreases markedly, making the risk of infection extremely low.

**Recent Studies**

Recent data suggest decreased utility of the limited evaluation compared with clinical observation in predicting infection in asymptomatic at-risk infants. Few studies in the last decade have addressed the usefulness of obtaining a blood culture in the asymptomatic population.

In a large retrospective/prospective study of asymptomatic at-risk newborns, Safer and associates concluded that it would take approximately 10,000 blood cultures to identify one case of GBS sepsis. This was based on the rate of GBS bacteremia and blood cultures performed for both clinical indications and screening in asymptomatic infants born to mothers who received intrapartum antibiotic prophylaxis (IAP) for prevention of early-onset GBS disease or suspected chorioamnionitis.
at-risk newborns. This result is not surprising because most mothers have received IAP in this era.

In a study by Ottolini and colleagues of 19,320 newborns, 134 infants had symptoms of sepsis immediately after birth. Of the 19,186 who initially were asymptomatic, 1,665 were considered at risk and 17,521 were considered not at risk. A total of 17 at-risk infants (1%) and 149 (0.8%) not at-risk infants developed clinical signs of sepsis. Therefore, a total of 300 infants became ill immediately or soon after birth. In this subpopulation of 300 infants, the yield of culture was low (14 infants had positive blood cultures, 6 of which were regarded as probable contaminants). Moreover, none of the 1,665 asymptomatic at-risk newborns, including 17 (1%) who subsequently developed symptoms of sepsis, had positive blood cultures. The 1% rate of sepsis in the asymptomatic at-risk newborn was similar to the results reported by Escobar and associates for infants whose birthweights were greater than 2 kg. The 1% rate of sepsis for this asymptomatic at-risk newborn population is still low compared with the 0.1% risk in the general population.

Ottolini and colleagues also showed poor sensitivity and positive predictive value of the CBC for predicting which newborns will develop sepsis. The sensitivity and specificity of an abnormal CBC result were 41% and 73%, respectively. Positive predictive value was 1.5%, and the negative predictive value was 99%. Therefore, the CBC, like the CRP, may be a useful laboratory test when results are normal because of its high negative predictive value. Escobar and associates found similar results. A more recent prospective observational study of 856 near-term or term newborns by Jackson and colleagues concluded that neutrophil values are not helpful in diagnosing early-onset infection or dictating duration of antibiotic therapy in asymptomatic, culture-negative neonates of at least 35 weeks’ gestation whose mothers had suspected chorioamnionitis. The CBC result may be normal in the early phase of infection. Therefore, a second CBC should be obtained within 8 to 24 hours following birth. If both CBC results are normal, it is very unlikely that the infant has GBS infection. However, as mentioned previously, abnormal CBC results are less helpful, and the clinician should rely on the clinical status of the infant when making treatment decisions.

Another important finding in the study by Ottolini and associates was that all infants diagnosed with clinical sepsis had clinical signs of sepsis immediately or soon after birth. Other earlier studies showed similar findings. In a study of 30,000 births at five military medical centers performed by Ascher and coworkers, most infants who had GBS infection became ill immediately after birth. The authors inferred that IAP failed. A study by Bromberger and associates indicated that IAP does not alter the timing of the development of clinical signs of early-onset infection. In their study of 319 infants who had culture-positive or clinically suspected early-onset GBS infection, 95% presented in the first 24 hours after birth, regardless of obstetric risk or IAP. Moreover, Escobar and associates demonstrated that presentation of early-onset sepsis after 48 hours is unlikely.

### Summary and Recommendations

1. Healthy near-term or term asymptomatic infants whose mothers received adequate IAP should be observed for at least 24 to 48 hours without laboratory evaluation. Infants may be discharged after 24 hours with close outpatient follow-up if they meet readiness for discharge and the parents are competent.

2. Healthy near-term or term infants whose mothers received inadequate IAP should be observed for at least 24 to 48 hours without laboratory evaluation or have serial CBC (and CRP) × 2 obtained within 24 hours after birth. Blood culture is not necessary. Infants may be discharged after 24 hours with close outpatient follow-up if they meet readiness for discharge and the parents are competent. If an infant becomes symptomatic, blood culture should be obtained because the greatest organism yield occurs when the infant is symptomatic rather than when the infant appears well. Empiric intravenous antibiotics should be started promptly. Duration of therapy depends on the infant’s clinical course and laboratory results.

3. Because of the high frequency of sepsis among asymptomatic infants born to mothers who have suspected or proven chorioamnionitis, even if the mother received adequate IAP, full sepsis evaluation, including lumbar puncture, and empiric antibiotic therapy are recommended in the newborn. Duration of treatment depends on the infant’s clinical course and laboratory results.

4. Because of the high frequency of sepsis among asymptomatic preterm infants born to mothers who have PPROM plus GBS colonization or PPROM alone, full sepsis evaluation, including lumbar puncture, and empiric antibiotic therapy are recommended in the newborn, even if the mother received adequate IAP. The duration of treatment depends on the infant’s clinical course and laboratory results.
Suggested Reading


NeoReviews Quiz

5. Group B Streptococcus (GBS) remains the leading cause of early-onset neonatal bacterial infections in most developed countries. Of the following, the most accurate statement regarding perinatal GBS disease is that:

A. Asymptomatic GBS colonization occurs in approximately 10% of women at some time during pregnancy.
B. Invasive disease occurs in approximately 25% of infants colonized by GBS during passage through the birth canal.
C. Maternal immunization with GBS vaccine is the current mainstay for prevention of GBS infection in neonates.
D. Preterm neonates are more susceptible to late-onset GBS infection and related mortality than term infants.
E. The decline in incidence of early-onset GBS infection has surpassed the Healthy People 2010 objective with the advent of a screening strategy.

6. Invasive GBS infection in young infants is categorized into two classes based on the time of onset of clinical manifestations after birth. Early-onset disease occurs within the first week after birth and late-onset disease occurs at 3 to 4 weeks after birth. Of the following, the most prevalent clinical manifestation of late-onset GBS disease is:

A. Arthritis.
B. Cellulitis.
C. Meningitis.
D. Osteomyelitis.
E. Pneumonia.

7. The incidence of early-onset GBS infection varies among neonates of different racial/ethnic groups. Of the following, the highest risk of early-onset GBS infection involves infants who are:

A. African-American.
B. Asian.
C. Caucasian.
D. Hispanic.
E. Native American.

8. A 28-year-old primiparous woman, whose GBS status is unknown, is in labor at 35 weeks of estimated gestational age. She has had amniotic membrane rupture for 20 hours and a fever. She is allergic to penicillin, but has no history of anaphylaxis. Of the following, the preferred antibiotic for intrapartum prophylaxis against GBS infection in this woman is:

A. Ampicillin.
B. Cefazolin.
C. Clindamycin.
D. Erythromycin.
E. Vancomycin.
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