

Group B Streptococcal Infections

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Author Disclosure
Dr Sass has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Educational Gap

In 2010, revised guidelines were published with updated algorithms for group B *Streptococcus* screening, intrapartum prophylaxis, antibiotic doses, and revised management for newborns.

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

1. Know the mode of transmission of group B *Streptococcus* (GBS) and the peripartum risk factors associated with a high risk of infection.
2. Know the major clinical manifestations of GBS and be able to differentiate the epidemiology and clinical presentation of early onset GBS disease from that of late-onset disease.
3. Know the laboratory testing for GBS: isolation, antigen detection, and susceptibility tests.
4. Know the treatment of GBS infections: drugs of choice, alternative drugs, and ineffective drugs.
5. Review the most recent guidelines for the prevention of perinatal GBS disease.
 - a. Understand the importance of maternal screening tests for GBS.
 - b. Know the criteria for the treatment of mothers known to be GBS carriers at the time of delivery.
 - c. Differentiate the prevention of early onset disease from that of late onset.

Introduction

Group B *Streptococcus* (GBS), or *Streptococcus agalactiae*, is an encapsulated gram-positive diplococcus that produces a narrow zone of β -hemolysis on blood agar and generally is resistant to bacitracin. GBS can be further differentiated by type-specific capsular polysaccharides (CPS) and protein antigens. Current circulating serotypes include Ia, Ib, Ia/c, II, III, IV, V, VI, VII, VIII, and IX. GBS initially was believed to be a bovine mastitis pathogen, but cases of puerperal sepsis in humans were described in the 1930s. The organism then became more prominent in the 1970s as a cause of maternal and neonatal disease.

The most common maternal manifestations are asymptomatic bacteriuria, urinary tract infection (UTI), bacteremia, chorioamnionitis, and endometritis. In infants, GBS classically presents as early onset disease (EOD; before 7 days after birth), late onset disease (LOD; up to 89 days after birth, but generally within first month after birth), and late-late onset disease (usually in the context of pre-term birth, up to 6 months of age).

Transmission

Over the past decades, GBS has been a dominant human pathogen, especially in neonates. There is no evidence for

Abbreviations

CDC:	Centers for Disease Control and Prevention
CPS:	capsular polysaccharides
CSF:	cerebrospinal fluid
EOD:	early onset disease
GBS:	group B <i>Streptococcus</i>
IAP:	intrapartum antibiotic prophylaxis
NAAT:	nucleic acid amplification test
UTI:	urinary tract infection

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zoonotic transmission. Both adults and children can be colonized with GBS. The primary reservoir in adults is the lower gastrointestinal tract, followed by the genitourinary tract. In children, the gastrointestinal tract also is a frequent site of colonization. The throats of children are more frequently colonized than those of adults. Genital colonization is uncommon before puberty. Carriage can be intermittent or chronic. Factors associated with increased adult colonization include age <20 years, women having had less than three pregnancies, increased sexual experience, and nonwhite race. (1)(2)(3) Carriage is not influenced by the use of oral contraceptives, marital status, vaginal discharge, or presence of other sexually transmitted infections.

The presence of GBS in the maternal genital tract at birth is the significant determinant of colonization and infection in the infant. Vertical transmission occurs when the neonate passes through a colonized birth canal or when bacteria ascend into the uterus. Ascending bacteria can enter the amniotic sac through ruptured membranes or by translocating through intact membranes. Rates of transmission range from 29% to 85%, with a mean of 50% in infants born to women who have positive GBS cultures. The risk of transmission is linked directly to the amount of GBS present but not to maternal age, race, parity, or method of delivery. (4)(5) Maternal bacteriuria and UTI are predictive of high density colonization. Horizontal transmission from hospital or community sources can occur but is much less common and is likely fecal-oral.

Clinical Manifestations

EOD typically occurs within the first 24 hours after birth but can occur up to 1 week of age. Infants can present with a range of illness, from asymptomatic bacteremia to septic shock. Bacteremia without a defined focus accounts for 80% to 85% of cases, pneumonia for 10% to 15%, and meningitis for 5% to 10%. Respiratory symptoms, such as tachypnea, grunting, flaring, apnea, and cyanosis, are the initial clinical findings in more than 80% of neonates, regardless of the site of infection. Hypotension is present in 25%. Other clinical findings are nonspecific and include lethargy, poor feeding, temperature instability, abdominal distention, pallor, tachycardia, and jaundice.

Virtually all infants who have pneumonia will have respiratory symptoms. Infiltrates can be seen on chest radiograph in up to one-third of infants, although this finding can be difficult to distinguish from surfactant deficiency associated with respiratory distress syndrome. It

is difficult to determine clinically which neonates have central nervous system disease, because the clinical presentation can be the same as that of bacteremia or pneumonia. Only examination of the cerebrospinal fluid (CSF) can exclude the diagnosis. Seizures can occur in 50% of infants within the first 24 hours. The case fatality rate has improved dramatically over the decades but still remains at 3% to 10%.

Risk factors for EOD include maternal colonization at birth, preterm birth <37 weeks' gestation, rupture of membranes >18 hours before delivery, lack of maternal antibodies to type specific CPS, chorioamnionitis, multiple gestation, nonwhite maternal race, intrapartum fever >38°C, intrauterine monitoring, postpartum maternal bacteremia, and having had previous infant with invasive GBS disease. (6)(7) As mentioned, the higher the maternal inoculum, the greater the risk to the infant. Maternal bacteriuria and UTI are related to high density colonization. Preterm birth increases the incidence for invasive disease compared with term infants.

LOD occurs between 7 and 89 days but presents most commonly within the first 4 to 6 weeks after birth. Unlike EOD, there is usually a lack of maternal obstetric and nursery complications. Bacteremia without a defined focus remains the most common manifestation, representing ~65% of cases. Meningitis is more common in LOD than EOD, representing 25% to 30% of cases. Other manifestations include pneumonia, cellulitis, and osteoarticular infections. Infants with bacteremia present with nonspecific signs and symptoms, including fever, poor feeding, and irritability. These infants generally are mildly ill upon presentation but can progress rapidly to shock if not treated promptly. Those who have meningitis present with fever, irritability or lethargy, poor feeding, and tachypnea. A preceding upper respiratory infection occurs in 20% to 30% of infants with LOD. The presence of seizures, poor perfusion, neutropenia, large numbers of organisms on CSF gram stain, hypotension, coma, and elevated CSF protein >300 mg/dL can be predictive of a poor outcome. (8)

Infants who have septic arthritis tend to present sooner and with a shorter duration of symptoms than those with osteomyelitis. Decreased motion of the involved extremity and pain with manipulation are the most common presenting signs, with the occasional presence of erythema and warmth of the infected area. Generally, these infants are not systemically ill. GBS joint disease tends to occur more commonly in the lower extremities, especially the hip, knee, and ankle. This pattern is in contrast to GBS osteomyelitis, in which the humerus is the most common site, followed by the femur and tibia. It is important

to evaluate the joints above and below the site of osteomyelitis because 75% of infants can have septic arthritis of the contiguous joints. The prognosis for osteo-articular disease generally is good, with no residual joint movement restriction or growth impairment of the affected limb.

Cellulitis and adenitis are less common presentations of LOD. There is a male predominance, unlike the other manifestations, which have no predisposition to either gender. Peak incidence generally is at a mean of 5 weeks of age. The typical presentation involves unilateral facial, preauricular, or submandibular swelling, usually with erythema, along with poor feeding, fever, and irritability. These children usually are bacteremic as well.

Late-late onset infection occurs in infants >89 days of age. Most of these infections occur in infants born at <35 weeks' gestation who have had prolonged neonatal hospitalizations. The most common presentation is bacteremia without a focus. Occurrence in a term infant without any risk factors should prompt an immunologic evaluation, including HIV testing.

Laboratory Testing

The definitive diagnosis of invasive GBS infection is the isolation of the organism from a normally sterile body site, such as blood or CSF. Culture of skin and mucosal surfaces may not indicate disease. Cultures traditionally are placed on blood agar media and reveal a narrow zone of β -hemolysis. When obtaining vaginal and rectal cultures, there is increased yield when using broth rather than solid media. Selective media include Todd-Hewitt broth with gentamicin or colistin and nalidixic acid (Lim broth), with or without sheep red blood cells. GBS can then be identified by using latex agglutination techniques.

Antigen detection is not a substitute for bacterial culture and can be used only for blood and CSF. A positive antigen indicates only that GBS surface antigens are detectable, not that viable organisms are present. Antigen testing may be useful in the cases in which there has been antibiotic pretreatment but should not be the sole method of diagnosis. Nucleic acid amplification tests (NAATs) such as polymerase chain reaction are being investigated for rapid diagnosis of antepartum colonization, but these procedures are not widely available clinically.

Other laboratory tests, such as C-reactive protein level and white blood cell count, are not specific for the diagnosis of GBS but may be helpful for determination of the extent of disease and clinical response to treatment. Clindamycin treatment failures can occur when used in infections caused by D-zone positive organisms. In general,

GBS is susceptible to ampicillin, penicillin, meropenem, imipenem, vancomycin, cephalosporins, and levofloxacin. Ceftriaxone is the most active cephalosporin in vitro. Resistance is expected to bacitracin, nalidixic acid, trimethoprim-sulfamethoxazole, metronidazole, and aminoglycosides.

Susceptibility testing of GBS isolates is imperative if an alternative treatment to penicillin is to be used and may require specific instruction to the clinical microbiology laboratory. There is no known resistance to penicillin, but resistance to erythromycin and clindamycin is increasing and can be present in up to 40% of colonizing strains. It is important to perform D-zone testing to recognize those isolates that are erythromycin-resistant that have inducible clindamycin resistance, because they will initially test clindamycin susceptible. Inducible clindamycin resistance patterns also are seen in strains of *Staphylococcus aureus*.

Treatment

Initial treatment for EOD usually is ampicillin plus gentamicin, until the identity of the pathogen is determined. If meningitis is not suspected, the ampicillin dose should be 150 to 200 mg/kg per day and the gentamicin dose is 7.5 mg/kg per day. The ampicillin dose for treating meningitis is higher to obtain appropriate drug levels in the CSF: ampicillin 300 to 400 mg/kg per day plus gentamicin 7.5 mg/kg per day. Although GBS is resistant to aminoglycosides, synergistic killing of GBS often is achieved when aminoglycosides are used in combination with either ampicillin or penicillin. The same initial drug choices are appropriate for treating LOD unless there is concern for *Streptococcus pneumoniae* disease, in which case empiric therapy should be vancomycin and cefotaxime. Once a definitive bacterial diagnosis of GBS is confirmed, antibiotic therapy can be tailored, generally after 24 to 48 hours.

The drug of choice for treatment of proven GBS infections is penicillin. The recommended dosage for treatment of bacteremia without meningitis is 200,000 units/kg per day and increases to 300,000 to 500,000 units/kg per day for meningitis. Length of treatment depends on the site of infection. Bacteremia without a focus requires 10 days of therapy. Meningitis requires a minimum of 14 days. In cases of meningitis in which response to therapy is unclear after 48 to 72 hours, a repeat lumbar puncture is indicated to document sterility of the CSF. Diagnostic neuro-imaging should be considered in this instance to evaluate for the presence of subdural effusions and other suppurative complications, which would prolong treatment.

Septic arthritis requires 2 to 3 weeks of therapy and osteomyelitis, 3 to 4 weeks. Drainage of any suppurative focus is an important adjunct to antibiotic therapy.

If the patient is penicillin allergic, cefazolin or cefotaxime can be used. Clindamycin should not be used unless D-zone testing has been performed. Neither cefazolin nor clindamycin would be appropriate if meningitis is present. Aminoglycosides alone are not appropriate.

Supportive care of the infant also is important for a successful outcome. Respiratory and pressor support may be needed in addition to antibiotic therapy. Adjunctive therapies such as granulocyte transfusions, granulocyte colony-stimulating factor, and intravenous immunoglobulin have been used in the research setting but with variable results and concern for adverse effects. Commercially available intravenous immunoglobulin contains low levels of CPS antibodies, which give additional protection to infected infants.

Recurrent infection does occur, although it is not common. Appropriate antibiotic therapy does not always eliminate mucosal colonization; the infant can be re-exposed in the community and invasive infection does not result in protective levels of CPS antibodies. Recurrent GBS infection occurring in healthy infants merits an immune evaluation, including HIV. Treatment for recurrent infection is dependent on the type of infection. In infants who experience recurrent disease, an attempt to eradicate colonization with the use of rifampin for 5 days can be considered after the appropriate treatment course of intravenous antibiotics.

Prevention Guidelines

Although the rate of maternal GBS colonization has not changed over the past several decades, the rate of EOD has decreased significantly due to the use of intrapartum antibiotic prophylaxis (IAP) after the implementation of antenatal screening and prophylaxis of colonized mothers. In 1996, the Centers for Disease Control and Prevention (CDC) published the first guidelines for the prevention of perinatal GBS disease by using two different approaches: risk factor screening or universal culture screening. These guidelines were updated in 2002 to recommend universal culture-based screening of all pregnant women between 35 and 37 weeks' gestation to identify those who would benefit from IAP. In 2010, revised guidelines were published with updated algorithms for GBS screening, intrapartum prophylaxis, antibiotic doses, and revised management for newborns. (9) The American Academy of Pediatrics published a policy statement in 2011 containing recommendations as well. (10)

The use of the guidelines has decreased substantially the incidence of early onset sepsis, from 1.7 cases per 1000 live births in the early 1990s to 0.28 cases per 1000 live births in 2008. Antenatal screening and IAP have not changed the incidence of LOD.

Universal screening of all pregnant women is now standard practice. Cultures should be obtained at 35 to 37 weeks of gestation from both the lower vagina and rectum and placed in appropriate media for growth. The 2010 guidelines now allow use of NAATs as an option for GBS status identification.

Maternal IAP is indicated in any of the following situations: a history of a previous infant with invasive GBS disease (regardless of current cultures); GBS bacteriuria during the third trimester; or positive GBS cultures during this pregnancy. In addition, if the GBS status is unknown at the onset of labor, prophylaxis is indicated if delivery is <37 weeks, rupture of membranes is >18 hours, intrapartum temperature is >38°C, or an intrapartum NAAT is positive for GBS. Women do not need to be treated if they have a history of GBS colonization or bacteriuria during a previous pregnancy but have negative cultures for the current one. If a cesarean delivery is performed before the onset of labor in a woman with intact membranes, she does not require prophylaxis, regardless of gestational status or culture results.

If preterm labor is present, cultures from the mother should be obtained and prophylaxis begun. If true labor occurs, antibiotics should be continued; if not, GBS prophylaxis should be stopped. If the cultures are positive, she should be treated when true labor occurs. If preterm premature rupture of membranes occurs, cultures should be obtained and the patient treated either until the delivery occurs if true labor is present; or per standard practice if antibiotics are being given to prolong latency (avoiding the preterm birth); or for 48 hours while awaiting GBS culture results. Repeat screening should occur at 35 to

Table. Maternal Intrapartum Antibiotic Dosing

Intrapartum Antibiotic	Dose (Intravenous Only)
Penicillin G	5 million units initially then 2.5–3 million units every 4 h
Ampicillin	2 g initially then 1 g every 4 h
Cefazolin	2 g initially then 1 g every 4 h
Clindamycin	900 mg every 8 h
Vancomycin	1 g every 12 h

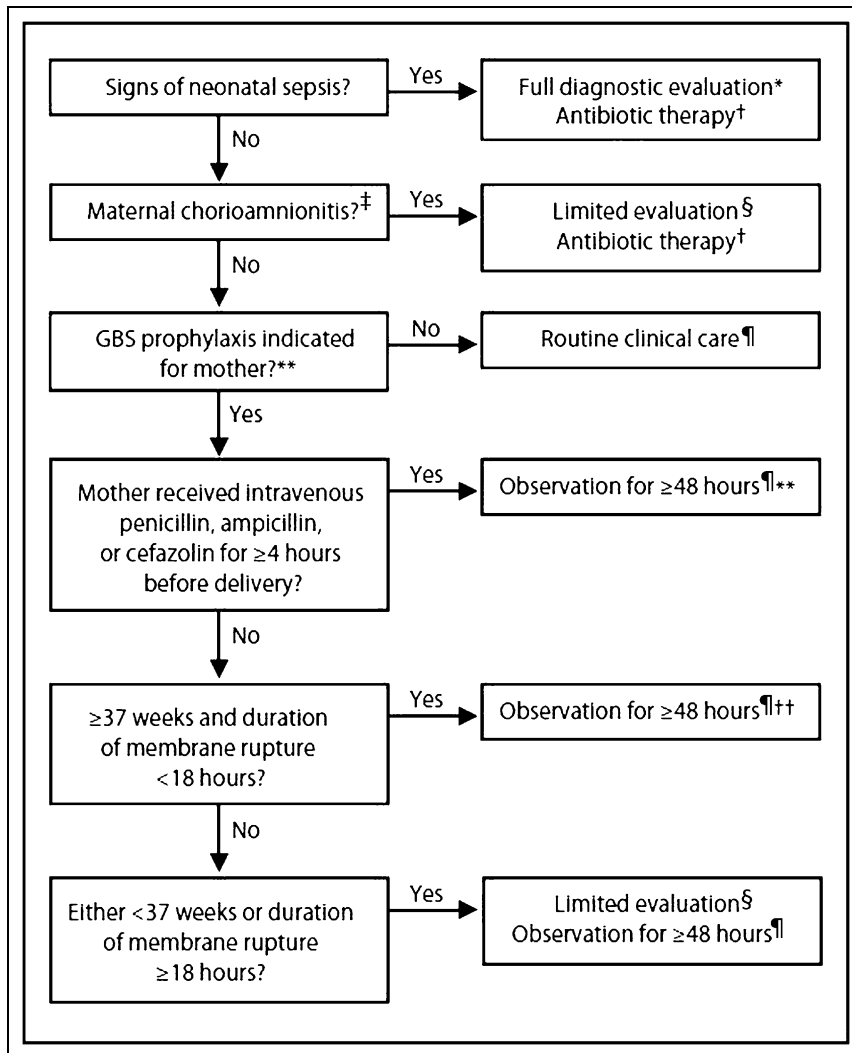


Figure. CDC algorithm for secondary prevention of early-onset GBS disease among newborns. (9) * Full diagnostic evaluation includes a blood culture, a complete blood count (CBC) including white blood cell differential and platelet counts, chest radiograph (if respiratory abnormalities are present), and lumbar puncture (if patient is stable enough to tolerate procedure and sepsis is suspected). † Antibiotic therapy should be directed toward the most common causes of neonatal sepsis, including intravenous ampicillin for GBS and coverage for other organisms (including *Escherichia coli* and other gram-negative pathogens) and should take into account local antibiotic resistance patterns. ‡ Consultation with obstetric providers is important to determine the level of clinical suspicion for chorioamnionitis. Chorioamnionitis is diagnosed clinically and some of the signs are nonspecific. § Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6 to 12 hours after birth). ¶ If signs of sepsis develop, a full diagnostic evaluation should be conducted and antibiotic therapy initiated. ** If ≥ 37 weeks' gestation, observation may occur at home after 24 hours if other discharge criteria have been met, access to medical care is readily available, and a person who is able to comply fully with instructions for home observation will be present. If any of these conditions is not met, the infant should be observed in the hospital for at least 48 hours and until discharge criteria are achieved. †† Some experts recommend a CBC with differential and platelets at age 6 to 12 hours.

37 weeks' gestation or at the time of readmission for subsequent preterm labor in women whose initial GBS screens during preterm labor are negative.

The drug of choice for intrapartum prophylaxis remains intravenous penicillin, with ampicillin as an acceptable alternative. Both agents are given every 4 hours until delivery, with at least one dose administered 4 hours before birth. If the patient is penicillin allergic, she should be given cefazolin every 8 hours if there is no history of anaphylaxis, angioedema, respiratory distress, or urticaria to penicillins or cephalosporins. For patients having a high risk for anaphylaxis to the first-line agents, antenatal GBS cultures should include appropriate susceptibility testing, including D-zone testing to determine clindamycin susceptibility. If the isolate is susceptible, clindamycin is the appropriate choice, given every 8 hours. Erythromycin is no longer an acceptable alternative given the high rates of resistance. If the isolate is resistant to clindamycin, or appropriate susceptibility testing was not done or available, vancomycin is the next best option given every 12 hours. The Table gives the intrapartum antibiotic dosing.

Evaluation of the Neonate

The next step in prevention of early onset sepsis is the assessment of the infant. After delivery, the newborn must be evaluated thoroughly to determine his or her risk for early onset sepsis. The 2010 guidelines provide an easy to follow clinical algorithm to aid the clinician in the most appropriate management (Fig). The decision is simple if the newborn is ill appearing. Any infant showing signs suggestive of sepsis should be evaluated with a complete

blood count, blood culture, urine culture, CSF studies and cultures, and chest radiograph if respiratory symptoms are present. Antibiotic therapy should be directed toward the most common causes of neonatal sepsis.

The evaluation is more difficult for those infants who are clinically well but are born to mothers with potential risk factors. If maternal chorioamnionitis is present, a limited evaluation of the newborn that includes a complete blood count and blood culture should be obtained and antibiotic therapy given pending culture results. Chorioamnionitis is a clinical diagnosis, and consultation with the obstetric service is important to determine the degree of clinical suspicion that the condition is present.

If both the mother and the infant are well, the clinician should determine if maternal IAP was indicated. If IAP was indicated, the type of antibiotic used and the timing of administration should be evaluated. If no GBS prophylaxis was needed, the infant should be managed with routine newborn care. If IAP had been indicated, therapy with penicillin, ampicillin, or cefazolin should have been initiated >4 hours before delivery, with at least one dose administered 4 hours before birth.

If IAP had not been given at the appropriate times, the infant should be observed for at least 48 hours for signs of sepsis if born after 37 weeks' gestation and if rupture of membranes was <18 hours before delivery. If these criteria are not present, the infant should undergo a limited evaluation (complete blood count/blood culture) and be observed for at least 48 hours.

If the mother was treated adequately before delivery, the infant may be observed at home after 24 hours as long

as the family can readily access medical care and can comply with medical instructions.

If there are any concerns, the child should remain in the hospital for a full 48 hours. In a change from previous guidelines, infants who are well appearing but born between 35 and 36 weeks' gestation whose mothers did receive adequate prophylaxis do not need routine diagnostic evaluations.

Summary

- GBS remains an important neonatal pathogen despite a dramatic decline in the incidence of invasive disease.
- Strong evidence exists demonstrating the importance of obtaining maternal cultures to determine who requires intrapartum prophylaxis in an attempt to prevent early onset sepsis.
- Unfortunately, this approach has not changed the incidence of LOD, so it is important to keep GBS as part of the differential diagnosis when evaluating infants who show late signs consistent with infection.
- Prevention measures as outlined in the 2010 CDC guidelines (9) and the 2011 American Academy of Pediatrics Policy Statement (10) should be followed in clinical practice.

To view the references and the suggested reading list for this article, visit <http://pedsinreview.aappublications.org> and click on "Group B Streptococcal Infections."

PIR Quiz

This quiz is available online at <http://www.pedsinreview.aappublications.org>. NOTE: Since January 2012, learners can take *Pediatrics in Review* quizzes and claim credit online *only*. No paper answer form will be printed in the journal.

New Minimum Performance Level Requirements

Per the 2010 revision of the American Medical Association (AMA) Physician's Recognition Award (PRA) and credit system, a minimum performance level must be established on enduring material and journal-based CME activities that are certified for *AMA PRA Category 1 Credit™*. In order to successfully complete 2012 *Pediatrics in Review* articles for *AMA PRA Category 1 Credit™*, learners must demonstrate a minimum performance level of 60% or higher on this assessment, which measures achievement of the educational purpose and/or objectives of this activity.

Starting with 2012 *Pediatrics in Review*, *AMA PRA Category 1 Credit™* can be claimed only if 60% or more of the questions are answered correctly. If you score less than 60% on the assessment, you will be given additional opportunities to answer questions until an overall 60% or greater score is achieved.

1. You are discussing the importance of hand washing, gowning, and other efforts to minimize the spread of infection to a group of medical students. In listing appropriate precautions for various organisms, you remind them that the most common mode of horizontal transmission of GBS is by
 - A. Air-borne inhalation.
 - B. Blood-borne infection.
 - C. Fomites.
 - D. Sexual contact.
 - E. The fecal-oral route.
2. Routine screening for GBS infection in pregnant women has been recommended by many agencies and organizations including the American Academy of Pediatrics. Isolation of the organism is essential for definitive diagnosis. To confirm a diagnosis of invasive GBS, you would culture the
 - A. Blood.
 - B. Oral mucosa.
 - C. Rectum.
 - D. Skin.
 - E. Vagina.
3. In selecting a drug to treat a pregnant woman with confirmed GBS infection, you recall that, in general, the organism is resistant to
 - A. Ampicillin.
 - B. Bacitracin.
 - C. Ceftriaxone.
 - D. Penicillin.
 - E. Vancomycin.
4. The 27-year-old mother of a 4-year-old patient of yours is 12 weeks pregnant with her second child. She tells you that her sister lost a full-term infant to an undiagnosed GBS infection last year. She is understandably anxious about her own current pregnancy and wonders what steps she should take. While recommending that she talk with her obstetrician about her concerns as soon as possible, you also inform her that, according to CDC guidelines, the optimal time for her to have a screening test for GBS is
 - A. 29 to 31 weeks.
 - B. 31 to 33 weeks.
 - C. 33 to 35 weeks.
 - D. 35 to 37 weeks.
 - E. 37 to 39 weeks.
5. In women whose GBS status is unknown and who have risk factors, intravenous penicillin is the drug of choice for intrapartum prophylaxis for GBS infection. Among the following, the drug of choice for treating a penicillin allergic mother in this situation is
 - A. Cefazolin.
 - B. Erythromycin.
 - C. Gentamicin.
 - D. Metronidazole.
 - E. Trimethoprim/sulfa.