Group B Streptococcus: Perinatal Considerations

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Group B streptococcal (GBS) infections are responsible for significant perinatal morbidity and mortality in the United States. It has been proposed that to prevent neonatal sepsis, all pregnant women be screened for GBS colonization, and that intrapartum antibiotics be used in certain high-risk situations. These recommendations are controversial, as is the current management of the asymptomatic newborn of a GBS-colonized mother.

Key words. Streptococcus agalactiae; infant, newborn; prenatal care. (*J Fam Pract 1994; 39:171-177*)

Neonatal sepsis caused by *Streptococcus agalactiae*, or Group B streptococcus (GBS), is a major problem around the world.[1–6] It is estimated that each year in the United States alone, GBS will cause disease in 12,000 to 15,000 infants (0.6 to 3.7 cases per 1000 live births) and 50,000 pregnant women,[3,7–9] at a cost of over $726 million.[8,10] Maternal manifestations of GBS disease are listed in Table 1.[4,10–25]

Between 15% and 40% of women of child-bearing age are colonized with GBS.[7,26] All three serotypes of GBS (I, II, III) are equally represented.[11] Approximately 50% (range, 40% to 75%) of infants born to these women will also become colonized, but only 1% to 2% of these will become infected.[4,7,11,26]

Group B streptococcus is the most common cause of neonatal infectious morbidity and mortality.[1,5,6,9,27] There are two distinct syndromes: early-onset disease, which accounts for two thirds of GBS infections, and late-onset disease.[9,11] These presentations are compared in Table 2.[4,9,11,28,29] Most experts believe that early-onset disease is usually acquired in utero, with membranes intact. Intrauterine infection may result in fetal demise. Transmission of GBS infection at the time of delivery is less common. Late-onset disease is usually horizontally transmitted, possibly nosocomially; only one half of late-onset cases can be attributed to intrapartum transmission.[9,30–32] The long-term consequences of GBS infection can be devastating. Between 25% and 50% of survivors will be left with permanent neurodevelopmental problems, including cognitive dysfunction, deafness, and seizures.[11,28]

Maternal Screening

Given the severity of the problem, what can be done to decrease the incidence of neonatal GBS infection? Screening for GBS colonization and the use of intrapartum antibiotics have been the subjects of recent debate.[7,10,26,33,34]

Some authorities, such as the American Academy of Pediatrics, recommend that all pregnant women be cultured for GBS colonization of the lower genital tract during pregnancy.[7,10,26,33] Arguing against universal screening, the American College of Obstetricians and Gynecologists has pointed out that universal screening cultures may not be the most cost-effective strategy in the prevention of GBS disease,[34] and are not the standard of care.[31] However, a recent study[35] has shown universal screening and the selective use of intrapartum antibiotics to be a cost-effective method of preventing GBS disease. The conflict is further complicated by nonmedical groups, such as the Association of Trial Lawyers of America and the lay Group B Strep Association, which recommend universal screening.[34,36]

Risk factors for GBS colonization include frequent intercourse with multiple partners, concurrent candidal infection, lower educational level, and Hispanic (especial-

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Table 1. Maternal Manifestations of Group B Streptococcal Infection

Asymptomatic colonization
Urinary tract infection/asymptomatic bacteriuria
Postpartum endometritis
Chorioamnionitis
Wound infections
Puerperal sepsis
Endocarditis
Osteomyelitis
Peritonitis
Meningitis
Preterm labor
Preterm, premature rupture of membranes
Premature rupture of membranes

Table based on data from Fletcher and Gordon,[4] Greenspoon et al,[10] Haft and Kasper,[11] Hueston,[12,13] Vartian and Septimus,[14] Atri and Cohen,[15] Berkowitz and McCaffrey,[16] Lefèvre,[17] McGregor et al,[18] Gjerdingen,[19,20] Hillier et al,[21] Greenwald,[22] Romero et al,[23] Maxwell and Watson,[24] and Maxwell.[25]

ly Caribbean) ethnicity or black race.[11,31,33,37] However, risk-factor analysis is neither sensitive nor specific enough to allow for selective screening for GBS.[37]

If cultures are to be taken, important methodological questions need to be addressed. The only way to identify most of the carriers is to grow both lower vaginal (labial and periurethral) and anorectal cultures in selective media (ie, Todd-Hewitt broth containing gentamicin and nalidixic acid). Cervical cultures alone may miss up to one half of colonized women.[7,32,33]

Most authors suggest that screening should take place between 26 and 28 weeks of gestation.[7,26] Two thirds of women with a positive test at this time will still be colonized at delivery (range, 60% to 75%).[11,26] Approximately 8% (range, 0% to 13%) of women whose cultures are negative at this time will be colonized at term.[7,10,11] Other authors[10,31] point out that the predictive value of culturing increases as the time between screening and delivery decreases, and therefore suggest obtaining cultures between 4 and 10 weeks before delivery (30 to 36 weeks' gestation).

Although cultures are the "gold standard," there is an interest in tests for rapid intrapartum detection of GBS. Numerous rapid tests have been studied. These tests have good specificities (95% to 99%) but poor sensitivities (33% to 65%). A positive test can be used to guide management, but a negative test needs confirmation by culture.[3,8,11,33,38,39]

Management

Intrapartum Antibiotics

Because the carrier state cannot be eradicated and because neonatal chemoprophylaxis is ineffective,[31,33] chemoprophylaxis is used during labor. Studies have clearly shown that intrapartum antibiotics are an effective means for preventing early-onset disease as well as maternal morbidity caused by GBS. There is no proof, however, that chemoprophylaxis prevents late-onset disease.[7,10,26,30,33]

If a patient is known to be GBS-positive, intrapartum antibiotics are indicated in the high-risk situations listed in Table 3.[7,26,31,33] Selective chemoprophylaxis has been proposed to prevent the adverse effects of antibiotics that might occur if all GBS carriers were treated; however, this selective treatment of GBS carriers is not without risk. It is estimated that this approach will fail to prevent 25% to

Table 2. Neonatal Manifestations of Group B Streptococcal Infection

	Early-Onset Disease	Late-Onset Disease
Onset	First 7 days	1 week to 3 months
Incidence	2/1000 live births	0.7–1.0/1000 live births
Fatality rate	11%–55%	7%–23%
Most common presentations	Pneumonia Respiratory distress Sepsis	Sepsis Meningitis
Serotypes	I, II, III	III in 85%
Risk factors	PROM PTL Premature birth Multiple gestation Maternal GBS bacteriuria Chorioamnionitis Heavy maternal GBS colonization	Prematurity Black race Primiparity Heavy maternal GBS colonization Absence of protective maternal antibody Maternal age <20 years

Table based on data from Fletcher and Gordon,[4] Ferrieri,[9] Haft and Kasper,[11] Yagupsky et al,[28] and Cabal et al.[29] PROM denotes premature rupture of membranes; PTL, preterm labor; GBS, group B streptococcus.

Table 3. Risk Factors for Neonatal Sepsis and Indications for Intrapartum Chemoprophylaxis in GBS-Positive Women

AAP-identified risk factors for neonatal sepsis and indications for intrapartum chemoprophylaxis
Preterm labor <37 weeks' gestation
Preterm premature rupture of membranes <37 weeks' gestation
Fever during labor or suspected endometritis chorioamnionitis (T≥37.5°C)
Multiple gestation
Membranes ruptured >12 to 18 hours*
History of a previous newborn with GBS disease
Other risk factors for neonatal sepsis
History of GBS bacteriuria during the pregnancy
Polyhydramnios (controversial)
Maternal diabetes (controversial)

**After 12 hours of ruptured membranes, antibiotics should be started if it is likely for labor to continue beyond 18 hours after ruptured membranes.*
Table based on data from the American Academy of Pediatrics committees on Infectious Diseases and on Fetus and Newborn[7]; Gibbs et al[26]; Katz[31]; and Hueston.[33]
GBS denotes group B streptococcus.

30% of the early-onset cases and 10% of deaths.[7,10,35] Therefore, some suggest that all GBS-colonized patients, with or without risk factors, receive intrapartum antibiotics.[16]

If a patient presents in labor with GBS status unknown and develops any of the risk factors listed in Table 3, one approach would be to perform a GBS culture and treat the patient as if she were GBS-positive until proven otherwise.[10,26] At this time, rapid tests for GBS cannot be recommended because of their low sensitivity.[7,26,38] In an area with a low incidence of GBS colonization, it may be more prudent to consider patients GBS-negative until culture results are available.[10]

Ampicillin sodium has been the most commonly studied antibiotic in the treatment of GBS. A regimen of 2 g intravenously (IV) for an initial dose followed by 1 g IV every 4 hours has been shown to be most effective.[7,26] Alternatives to ampicillin include penicillin, erythromycin, clindamycin hydrochloride, vancomycin hydrochloride, and the first-generation cephalosporins.[10–12,33] Clindamycin crosses the placenta better than erythromycin and is the suggested alternative in cases of penicillin allergy.[31,32,40] Clindamycin can be given intravenously at 150 to 900 mg every 6 to 8 hours. No specific dosing regimens have been prospectively studied.[7] Erythromycin is given 250 mg orally every 6 hours or 15 to 20 mg/kg/d IV.[32] Intravenous dosing is preferred.[7] It is suggested that the first dose of antibiotics be given at least 1 hour[10] and optimally 4 hours[7] before delivery.

The Newborn

The question of how to manage asymptomatic infants of GBS-positive mothers has not been addressed by carefully controlled studies. In the evaluation of neonatal sepsis, the risk of increased morbidity and mortality associated with delayed diagnosis and treatment must be weighed against the financial and emotional costs of overtreatment, as well as the risks associated with antibiotic use (eg, alterations in normal flora, medication errors, and IV infiltration).

A survey sent to fellowship program directors in neonatology and pediatric infectious diseases failed to demonstrate any consensus on the appropriate evaluation and treatment of these infants. Therefore, any recommendations at this time are only empiric.[7,41] However, the literature can provide some guidance concerning which tests constitute an appropriate sepsis evaluation.

Laboratory Evaluation for Sepsis

Cultures of body fluids are the "gold standard" for the evaluation of sepsis. Blood cultures, however, may be negative in up to 18% of clinically septic patients and in up to 50% of neonates with pneumonia.[2,42,43] Other limitations include delay in bacterial growth and contamination that may interfere with results.[44] There is disagreement about whether a single blood culture is sufficient[2,30] or whether multiple or quantitative blood cultures should be performed.[43,45] Ninety-six percent of positive blood cultures will be identified by 48 hours of incubation. This number increases to 98% at 72 hours. Therefore, it is prudent to wait at least 2 days, if not 3, before considering a blood culture negative.[2,30]

Lumbar punctures are another source of controversy. Although cerebrospinal fluid (CSF) cultures are helpful, other CSF tests, such as cell counts and protein or glucose levels, are not useful because they have a wide range of normal values that overlap with values found in infants with meningitis. Indications for lumbar puncture vary among physicians.[2,30]

Urine cultures are not recommended because they have a low yield during the first 72 hours of life. Tracheal aspirate cultures in intubated infants are useful only if obtained in the first 12 hours of life. Neither gastric aspirate Gram stain and culture nor skin cultures are useful indicators of neonatal sepsis.[2,30,46,47]

The urine latex particle agglutination (LPA) test for GBS antigen has become a popular method to screen for neonatal sepsis. According to some authors,[7,26,30,48] however, this test has limited usefulness and should be used only in clinically septic neonates rather than to screen an asymptomatic population. Others[2] base treatment on LPA results.

An LPA test positive for GBS should reflect GBS bacteremia with subsequent antigen excretion,[42] and when the urine LPA results correlate with the blood culture, management is straightforward. The major dilemma arises when a patient has a positive urine LPA screen but a negative blood culture. The blood culture may be falsely negative if sampling is insufficient or intrapartum antibiotics inhibit growth.[2,42,49] A false-positive LPA test for GBS may be caused by GBS from swallowed amniotic fluid[48] or from mucosal colonization,[49] cross-reacting antigens, and contamination of the urine during collection.[49] Some suggest that local perineal contamination, even in bag-collected urine, does not appear to increase the false-positive rate[42]; others disagree.[30] A negative test is reliable, independent of collection method.[48] The urine LPA test for GBS has a sensitivity of 88% to 100% and a specificity of 81% to 100% for detecting GBS antigen in the urine. When compared with blood cultures, the positive predictive value for sepsis is 17% to 20% and the negative predictive value is 98% to 100%.[42,48–50]

Hematologic tests and tests for acute phase reactants are important adjunctive tests in the evaluation of neonatal sepsis. No single test is a perfect screen for sepsis. When combined in a "sepsis screen," however, sensitivity and specificity are increased.[2,5]

Total white blood cell (WBC) counts, total neutrophil counts, immature neutrophil counts, and the immature-to-total (I:T) neutrophil ratio have been used to screen for sepsis. As single measurements, with the possible exception of the I:T ratio, they are insufficiently sensitive or specific for sepsis.[2,5] The reported sensitivity for an I:T ratio ≥ 0.2 is 90% to 100%. The specificity, positive predictive value, and negative predictive value are 50% to 78%, 11% to 51%, and 99% to 100%, respectively.[2]

Serial hematology measurements over a 24-hour period may help to differentiate between septic and uninfected neonates.[5] Many factors can affect hematologic values, however, including maternal conditions, source of blood (central vs capillary), and timing of the sampling.[2] Because noninfectious conditions in the mother and neonate may cause changes in the WBC count and WBC differential similar to sepsis, investigators have turned to acute-phase reactants as alternative screening methods.[44] The C-reactive protein (CRP) measurement has been shown to be very specific for serious bacterial infection in both term and preterm infants.[44,51,52]

Pourcyrous et al[40] found that uninfected neonates had normal CRP values on serial testing. Among those with positive blood cultures, 15 of 16 (94%) mounted a CRP response, and among those with a negative blood culture but presumed sepsis, 13 of 14 (93%) had elevated CRP values.[44] False-positive tests were caused by meconium aspiration.[2,44,53] Analysis of their data shows that serial CRP testing has a sensitivity of 93%, specificity of 94%, positive predictive value of 80%, and negative predictive value of 98% for sepsis. The reported ranges for a single CRP test are: sensitivity 47% to 100%; specificity 83% to 94%; positive predictive value 6% to 83%; and negative predictive value 71% to 99%.[2]

Some research has shown an association between elevated CRP values and prolonged rupture of membranes, shock, and asphyxia[2,44]; others have not.[52] Infants with viral infections or those with false-positive blood cultures do not mount a CRP response.[44,53] The CRP may be helpful in differentiating a false-positive urine LPA from a true-positive, although no studies have specifically addressed that question.

The CRP level may not be elevated early in sepsis, as it usually takes the liver 6 to 24 hours after an inflammatory stimulus to synthesize the protein.[2,44] Therefore, serial testing over 24 to 36 hours is suggested to increase sensitivity and specificity.[44,53] The CRP level will decrease with appropriate treatment, and thus can be used to gauge response to antibiotics.[2,44] Also, if antenatal antibiotics are given or if the infection is mild, the CRP response may not be very dramatic.[44] The data[44,53] suggest that if a newborn without signs or symptoms of sepsis has three normal CRP measurements within 24 hours, it is probably safe to discontinue antibiotics. However, no controlled trials have been conducted to specifically address this question.

According to one author,[2] normal CRP values should be <1.6 mg/dL during the first 2 days of life and <1.0 mg/dL thereafter. Others use 0.8 mg/dL to 1.0 mg/dL as the upper limit of normal, regardless of age.[44,51,53,54] Normal values may vary from one institution to another.

The microerythrocyte sedimentation rate is less sensitive than the CRP (range, 27% to 50%), but is very specific (range, 83% to 97%). The positive and negative predictive values for sepsis are 24% to 43% and 94% to 97%, respectively. Normal value is defined as day of life plus 3 mm/h, with a maximum of 15 mm/h. Other tests,

such as haptoglobin, orosomucoid, prealbumin, and fibronectin, have not been shown to be helpful in screening for sepsis.[2,44,54]

Indications for Antibiotics

The decision as to when to start antibiotics in the asymptomatic neonate born to a GBS-colonized mother varies from practitioner to practitioner, and is based on an analysis of existing risk factors for sepsis. Predisposing factors for neonatal sepsis are additive. For example, infants born to GBS-colonized mothers have a 1 in 200 risk for sepsis. If other risk factors are present, as outlined in Table 3,[7,26,31,33] the risk for sepsis can range from 4% to 10% or higher.[2,31]

If the only risk factor for neonatal sepsis is maternal GBS colonization, and the infant is asymptomatic, antibiotics are not indicated. The practitioner may choose to evaluate the infant for possible infection. One approach is to perform serial sepsis screens consisting of complete blood cell counts, with or without CRP levels, at 12-hour intervals for the first 24 hours. If the three sepsis screens are normal and the child is well, infection is unlikely. The evaluation for possible sepsis also may include a urine LPA test for GBS, a blood culture at birth, or both. Abnormal test results would prompt the completion of a sepsis evaluation and the initiation of antibiotic therapy until sepsis is ruled out.[2] Another approach would be to simply follow the infant clinically.[32]

If other risk factors from Table 3 are present, and if intrapartum antibiotics were not given, sepsis should be ruled out through serial sepsis screens and appropriate cultures. Antibiotics may be started while waiting for laboratory results, especially in infants of less than 34 weeks' gestational age.[2,7]

If intrapartum antibiotics were given, treatment may be continued until sepsis is ruled out.[2] On the other hand, some authors have stated that if intrapartum antibiotics have been given more than 4 hours before delivery, they do not need to be continued during the neonatal period.[7,32] However, the practitioner may still want to evaluate the infant for possible infection. Infants born before 34 weeks' gestation are candidates for continued empiric antibiotic therapy.[7]

Of course, any newborn demonstrating the signs of sepsis should be evaluated and treated appropriately, regardless of whether risk factors are present.[2,5,32] The physical signs of sepsis in the neonate are nonspecific (Table 4[2,5,29,54]).

The most commonly used antibiotic regimen for presumed neonatal sepsis is ampicillin with gentamicin. Group B streptococci are uniformly sensitive to the penicillins, and GBS killing appears to be enhanced by the addition of an aminoglycoside to the antibiotic regimen.[55] For the term neonate weighing more than 2500 g, the dose of ampicillin is 50 to 100 mg/kg every 12 hours. The upper dosage range is used if meningitis is proven or strongly suspected. Gentamicin is given at 2.5 mg/kg every 12 hours. The length of treatment is variable, depending on symptoms and laboratory results.[2]

Table 4. Signs and Symptoms of Neonatal Sepsis

Temperature instability (fever or hypothermia)
Loss of glucose homeostasis
Respiratory distress (grunting, retractions, apnea, cyanosis)
Cardiovascular instability or shock (tachycardia, hypotension, poor perfusion, acidosis)
Neurologic findings (hypotonia, seizures, lethargy, irritability, changes in level of consciousness)
Feeding intolerance (eg, vomiting and abdominal distension)
Petechiae, purpura
Jaundice (especially direct hyperbilirubinemia)

Table based on data from Gerdes,[2] Greenberg and Yoder,[5] Cabal et al,[29] and Bell.[54]

The Future: Immunotherapy

Although the use of intrapartum antibiotics is an effective means of preventing GBS sepsis in neonates, it is dependent on knowledge of the mother's GBS carrier status or on appropriate rapid tests. Active immunization of the mother and passive immunization of the neonate against GBS have been proposed as adjunctive or alternative methods to prevent or treat GBS sepsis. Research is ongoing.[4,9,33,54,56–58] Active immunization against GBS in pregnancy would be theoretically cost-effective.[35] Passive transfer of immunity by breast-feeding has been shown to protect against neonatal sepsis in certain populations.[59]

Conclusions

The issue of universal screening for GBS colonization is controversial. There is disagreement about which screening and management strategy should be used: universal antepartum screening, screening at the onset of labor, or treatment only for high-risk individuals without GBS culture. Experts agree, however, on the efficacy of and guidelines for the use of intrapartum chemoprophylaxis for the prevention of neonatal sepsis caused by GBS.

The management of asymptomatic infants born to GBS-positive women, whether treated with intrapartum chemoprophylaxis or not, is also controversial. Each clinician must decide how to evaluate these infants, and which infants require antibiotics. Until appropriate studies can be performed, recommendations will remain empiric.

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