

Guidelines for Prevention of Group B Streptococcal (GBS) Infection by Chemoprophylaxis

Committee on Infectious Diseases and Committee on Fetus and Newborn

BACKGROUND

For two decades streptococci classified serologically as Lancefield group B *Streptococcus agalactiae* (GBS) have been a leading cause of perinatal infections. In neonates and young infants these infections include congenital pneumonia, sepsis, or meningitis; in pregnant women they include urinary tract infection, chorioamnionitis, early postpartum endometritis, postcesarean section febrile morbidity, and—less frequently—pelvic thrombophlebitis or endocarditis. Although the incidence varies somewhat by geographic region, 12 000 infants and 50 000 pregnant women in the United States are estimated to develop GBS-associated morbidity or mortality annually.¹ Overall mortality for early-onset (less than 7 days of age) and late-onset (7 days to 3 months of age) infant disease is approximately 15% and 10%, respectively.²⁻⁴ Gestational age significantly correlates with mortality among early-onset cases and is approximately 25% to 30% in preterm infants and 2% to 8% in term infants. Thus, every year approximately 1 600 infants die and an equal number have permanent neurologic sequelae following meningitis.¹ This substantial GBS-associated perinatal mortality and morbidity make prevention strategies imperative. Among proposed strategies, including chemoprophylaxis and immunoprophylaxis, only intrapartum maternal chemoprophylaxis has been evaluated for safety and efficacy.

EPIDEMIOLOGY

GBS are frequently harbored in the genitourinary and lower gastrointestinal tracts of adults. When sensitive culture methods are used for their detection (ie, antibiotic-containing or selective broth media) and both lower vaginal and anorectal sites are sampled, GBS are found in 15% to 40% of pregnant women.⁵⁻⁸ Direct plating of swabs from body surfaces onto solid media or sampling of the cervix as a single genital tract site fails to identify as many as 50% of women who are culture-positive for GBS.⁴ When selective broth media are used for lower vagina and anorectum cultures, virtually 100% of GBS carriers are detected.⁴ Colonization rates do not vary by trimester, and carriage may be chronic (40%), transient, or intermittent.⁶ However, when both the lower vagina and anorectum are cultured for GBS in selective broth medium on a single occasion late in the second trimester, only 4% to 7% of women who are apparently culture-negative at that time are subsequently GBS-positive at delivery.^{6,9} Colonization rates

may be higher in women who are less than 20 years old, primigravida, medically indigent, black, or Hispanic of Caribbean origin, but these associations are not definitive enough to allow their use in selective screening as a basis for chemoprophylaxis.^{2,4,6,8}

Vertical transmission of GBS to neonates occurs in 40% to 73% of culture-positive women, but only 1% to 2% of their infants develop early-onset disease.⁴ Maternal factors that significantly increase the risk for GBS sepsis include gestation of less than 37 weeks, rupture of membranes more than 18 hours before delivery, fever during labor, multiple births, GBS bacteriuria, high inoculum of GBS in genital cultures ("heavy colonization"), age less than 20 years, low concentration of serotype-specific antibody to the GBS capsular polysaccharide in the serum, and, perhaps, black race and diabetes mellitus.^{2-4,9-11} The presence of one or more of these factors in a pregnant GBS carrier is associated with a 5-fold to 35-fold increase in risk for sepsis in her offspring.

CHEMOPROPHYLAXIS STRATEGIES

Several regimens have been suggested to decrease vertical transmission of GBS, early-onset neonatal septicemia, especially in the setting of preterm labor or premature rupture of membranes, and maternal puerperal infection. Major differences in approaches have resulted from unanswered questions and controversies concerning existing data. Agreement exists that the target population should be selected by risk factors. The usual approach has been to identify women who are colonized with this potential pathogen and to attempt eradication of GBS colonization. However, consensus on many operational issues is lacking. These issues include the optimal time during gestation to assess GBS colonization; the usefulness (or lack thereof) of vaginal swab GBS antigen detection tests during labor; and whether selection of women for intrapartum chemoprophylaxis should be based on presence of GBS colonization and risk factors or on the presence of risk factors alone. Despite these uncertainties, published data support maternal intrapartum chemoprophylaxis.

Multiple studies employing oral antibiotics to eradicate GBS colonization antepartum have resulted in high rates of recurrences at delivery, even when sexual partners are treated concurrently (67%).^{4,5} Neonatal prophylaxis with parenteral ampicillin or penicillin G at birth is ineffective because more than 60% of infants are symptomatic at or within a few hours of birth.^{2,4,11,12}

Antepartum oral antibiotic therapy is indicated for the woman with GBS bacteriuria. This entity is significantly associated with heavy GBS genital colonization and the associated increased risk for early-onset infant sepsis. Women treated antenatally have resolution of bacteriuria and less risk for preterm labor, but genital colonization is likely to persist.⁹ Further benefit from treatment of GBS bacteriuria is indicated by some studies demonstrating that women treated antenatally are significantly less likely to develop preterm labor or premature rupture of membranes at term or preterm.¹⁰

Most experts believe that intrapartum maternal chemoprophylaxis is the ideal method to prevent neonatal and maternal morbidity.^{3,4,11} Also, because GBS colonization rates are high (15% to 40%) and attack rates are low in term neonates (0.5 to 1.5 per 1000), selection of "high-risk" GBS carriers has been recommended to avert the occurrence and high cost and likelihood of rare but serious adverse effects of antibiotics that would be encountered if all women colonized with GBS were given prophylaxis. Intravenous ampicillin or penicillin G given during labor does reduce vertical transmission of this organism and prevents both early-onset (less than 7 days of age) neonatal sepsis and GBS-associated maternal morbidity.¹¹ Despite these data, selective maternal chemoprophylaxis for GBS infection has not been widely adopted, and its usefulness in preventing late-onset disease, if any, has not been studied.

EFFICACY OF MATERNAL CHEMOPROPHYLAXIS

The first documentation that intrapartum chemoprophylaxis prevented early-onset neonatal disease as well as GBS-associated maternal morbidity was reported in 1986.¹¹ Women at 26 to 28 weeks gestation had lower vaginal and anorectal cultures obtained for GBS. Women who were GBS-positive who had preterm labor at less than 37 weeks gestation, rupture of membranes more than 12 hours, or intrapartum fever were randomized to receive routine care or intravenous ampicillin intrapartum (2 g initially, 1 g every 4 hours until delivery). Women not randomized to receive ampicillin who developed intrapartum fever (greater than 37.5°C) were dropped from the study and were treated with ampicillin. Of 79 infants born to untreated women, 5 developed GBS septicemia, but none of 85 infants born to ampicillin-treated women developed it ($P = 0.024$). Another study employed the same approach and noted that 1.8% of infants born to treated women and 13% born to untreated women had GBS septicemia ($P = 0.04$).¹³ Recently, this approach was reported to be cost-effective.¹⁴ Similar studies employing agents other than ampicillin or penicillin G in penicillin-allergic women have not been performed.

Despite its efficacy, selective chemoprophylaxis given to GBS carriers detected antepartum fails to prevent an estimated 25% to 30% of cases of early-onset neonatal sepsis and about 10% of deaths.^{2,11} These infants represent the number of term babies who had been delivered within 12 hours of rupture of membranes and whose mothers were not febrile

during labor. Efficacy of this selected approach might be improved by expanding the risk factors for selection to include multiple births, GBS bacteriuria, and insulin-dependent diabetes mellitus.^{2,4,9} Almost certainly, however, a few "failures" with any selective approach will occur, although the majority of cases, and most deaths, can be prevented.

Another approach to selecting a target population by maternal risk factors would be to test women for GBS when admitted for labor at less than 37 weeks gestation or due to preterm premature rupture of membranes.¹⁵ If labor is not stopped and if either the GBS test is positive or the test result is pending, therapy with intravenous ampicillin is initiated. If labor is inhibited, GBS carriers are given intravenous therapy for 24 hours, and then oral ampicillin is given for an additional 14 days. This strategy would deliver prophylaxis to an estimated 7.5% of pregnant women; however, it fails to consider neonates with gestations beyond 36 weeks who account for 66% to 92% of the cases of early-onset GBS sepsis and it has not been tested for efficacy.

Other investigators propose testing of women for GBS colonization intrapartum with a rapid GBS antigen assay performed on a vaginal swab.¹⁶ The women with positive GBS antigen assays are given intravenous penicillin G (5 mU every 6 hours) until delivery whether or not risk factors are present. If delivery does not occur within 18 hours, oral penicillin V (1 mU every 8 hours) is administered until parturition. This approach lowers the rate of early-onset neonatal disease, and is believed to be cost-effective.¹⁷ However, a few women with risk factors who had positive GBS cultures and negative antigen assays were not given chemoprophylaxis; subsequently, they had infants with GBS septicemia.¹⁶ This nonselective approach, while including both term and preterm infants, is hampered by the occurrence of delivery before test results are available. A greater problem, however, is the poor sensitivity of the currently available detection methods for GBS antigen (approximately 20% to 60% overall; 65% to 88% for "heavily colonized" women).¹⁸⁻²⁰ While attack rates are higher in heavily colonized women, some risk for those with a lower inoculum and their infants exists.²¹ If positive, these tests are reliable because their reported specificity is 98% to 99%.¹⁸⁻²⁰

Whether selective or nonselective strategies are employed, chemoprophylaxis ideally should be administered at least 4 hours before delivery. This allows sufficient time to achieve optimal concentrations of ampicillin or penicillin G in the amniotic fluid as well as in the placental circulation.²² This ensures a sufficient reduction in the number of GBS in amniotic fluid and maternal genital secretions unless the amniotic fluid inoculum is very high.²³ Intrapartum detection of GBS carriers would potentially delay initiation of prophylaxis and thereby theoretically decrease its efficacy. More importantly, the currently available GBS antigen-detection latex agglutination or enzyme immunoassay methods do not detect women colonized with low concentrations of GBS^{16,18-20} whose infants are at risk, albeit lower, for GBS septicemia.

MANAGEMENT OF INFANTS WHOSE MOTHERS RECEIVED CHEMOPROPHYLAXIS

Numerous questions arise concerning the evaluation and treatment of infants born to GBS carriers given intrapartum chemoprophylaxis. This concern is well founded because GBS are penicillin-susceptible, and high doses of maternal ampicillin or penicillin G may sterilize the blood of a neonate in the early phase of septicemia. False-negative blood cultures could occur in symptomatic neonates born to mothers receiving prophylaxis, but the infants' clinical courses dictate the need for empiric antimicrobial therapy for septicemia (10 days of parenteral antibiotics) despite negative blood cultures. In asymptomatic neonates, however, this theoretical concern is unlikely to be of any practical consequence. In efficacy studies, initially asymptomatic infants who were either treated with intramuscular ampicillin for the first 48 hours^{11,13} or received nothing¹⁶ did not have a clinical course consistent with septicemia or later occurrence of GBS bacteremia.

One major source of confusion is the use of GBS antigen detection tests on urine specimens from these asymptomatic infants. These laboratory tests were developed for rapid diagnosis of GBS sepsis in symptomatic infants, not for "sepsis screening" of asymptomatic infants. Urine GBS latex methods result in a false-positive rate of 5% to 12%. This results in most instances either from contamination of bag specimens of urine with GBS from perineal and rectal colonization²⁴ or gastrointestinal absorption of antigen,²⁵ or both. Testing of urine for GBS antigen is unsuitable to "screen" for sepsis in asymptomatic infants, especially in the setting of known maternal GBS colonization and intrapartum chemoprophylaxis. Thus, most experts believe that treatment of the term neonate with a positive urine GBS antigen test is not indicated when the clinical course is benign; this test does not prove invasive infection.

No studies on the management of infants whose mothers received intrapartum chemoprophylaxis have been published. Thus, the recommendations are empiric.²⁶ Management should be based on assessment of the infant's risk of sepsis as indicated by clinical manifestations and gestational age. For example, symptomatic infants born to women given chemoprophylaxis should be evaluated for invasive infection caused by GBS and other causes of early-onset neonatal infections; these infants should be treated with broad-spectrum antibiotic regimens while cultures results are pending. Asymptomatic term infants whose mothers have received therapy with one or more doses of ampicillin (2 g initially) or penicillin G (5 mU) initiated more than 4 hours before delivery need not be treated. Asymptomatic preterm infants of GBS-colonized mothers with a gestation less than 34 weeks are candidates for empiric antibiotic therapy, whether or not maternal chemoprophylaxis was given. In all cases in which antimicrobial therapy is initiated, it should be administered for no more than 72 hours unless blood or cerebrospinal cultures are positive or unless the subsequent clinical course suggests sepsis or pneumonia.

RECOMMENDATIONS FOR PREVENTION OF EARLY-ONSET NEONATAL GBS INFECTION

1. Screening of all pregnant women for GBS at 26 to 28 weeks gestation is a method upon which effective, selective intrapartum chemoprophylaxis can be based.

2. If GBS cultures are performed, a single swab of the lower vagina and anorectum should be placed into selective broth medium, transported to the laboratory, and subcultured onto solid media for optimal detection.

3. Antepartum treatment of asymptomatic women for GBS regardless of maternal colonization status is not recommended except for those with GBS bacteriuria.

4. At hospital admission, such as for preterm labor or premature rupture of membranes, women who have no prenatal GBS culture result available may be tested for GBS, either by rapid antigen test (if an appropriate test is available) or by culture.

5. Maternal GBS carriers, identified either antepartum or intrapartum, with one or more of the following risk factors should be given intrapartum intravenous ampicillin (2 g initially; 1 to 2 g every 4 to 6 hours) or penicillin G (5 mU every 6 hours) until delivery; penicillin-allergic women may be given clindamycin or erythromycin intravenously. Risk factors include (1) preterm labor at less than 37 weeks gestation; (2) premature rupture of membranes at less than 37 weeks gestation; (3) fever during labor; (4) multiple births; and (5) rupture of membranes beyond 18 hours at any gestation. When membranes have been ruptured for 12 hours, an assessment of the likely duration of labor should be made so that chemoprophylaxis can be initiated if rupture is considered likely to extend beyond 18 hours. If maternal GBS colonization status is unknown, chemoprophylaxis may be appropriate for one or more of the aforementioned risk factors.

6. Previous delivery of a sibling with invasive GBS disease warrants intrapartum maternal chemoprophylaxis in each subsequent pregnancy.

7. Management of infants of mothers receiving chemoprophylaxis should be based on the clinical findings and gestational age of the infants.

8. As maternal GBS chemoprophylaxis is implemented in an area, active surveillance and determination of risk-benefit ratios by public health agencies should be performed so that future approaches might be modified to enhance safety and efficacy.

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