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# *Group B Streptococcus and Intraamniotic Inflammation and Infection*

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**Abstract:** Intraamniotic inflammation and infection complicate 2% to 5% of term deliveries. Group B *Streptococcus* (GBS) is a common cause of intraamniotic infection associated with invasive neonatal disease and maternal morbidity. Universal vaginal-rectal screening for GBS colonization is recommended between 36 and 37 weeks. Intrapartum antibiotic prophylaxis is recommended for individuals with positive GBS screens and other risk factors. Intravenous penicillin is the preferred antimicrobial agent. Individuals with penicillin allergies may receive cefazolin for low-risk allergies and either clindamycin or vancomycin for high-risk allergies, depending on their antimicrobial susceptibilities. Clinical trials are underway to evaluate the safety and immunogenicity of maternal anti-GBS vaccine candidates.

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## *Introduction*

The condition of intraamniotic inflammation and infection, commonly known as "chorioamnionitis," complicates 2% to 5% of term deliveries and is associated with adverse maternal and neonatal outcomes.[1] A common pathogen involved in intraamniotic infection and a primary cause of early-onset neonatal sepsis is *Streptococcus agalactiae* or group B *Streptococcus* (GBS).[1] With the advent of intrapartum antibiotic prophylaxis for patients with positive GBS cultures in 1986 and universal screening for GBS colonization between 35 and 37 weeks in 1996, the incidence of neonatal sepsis


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secondary to GBS has decreased significantly.[2,3] Recommendations for screening during pregnancy, intrapartum prophylaxis, and treatment of intraamniotic inflammation and infection have evolved over the years to improve both maternal and neonatal outcomes. The purpose of this review is to provide an overview of epidemiologic data and clinical sequelae of GBS infection, as well as present current guidelines for the management of GBS and intraamniotic inflammation and infection.

## CLINICAL PRESENTATION AND SEQUELAE

### *Intraamniotic Infection and Inflammation*

Intraamniotic infection and inflammation (Triple I), still commonly referred to as "chorioamnionitis" in clinical practice,[4] is defined as the resultant inflammation of any combination of the amniotic fluid, placenta, fetus, fetal membranes, or decidua.[1] Infection is often polymicrobial in origin and results from ascent of vaginal flora into the amniotic cavity.[1,5] Triple I has been reported to complicate 2% to 5% of term deliveries,[6,7] and risk for infection has been found in some studies to increase after 40 0/7 weeks gestation.[6–8] Triple I is a well-known risk factor for both maternal and neonatal adverse outcomes, including postpartum hemorrhage, wound infection, neonatal sepsis, and neonatal seizures, among other complications.[9]

Recent efforts to stratify risk and better define the disease processes resulted in the coining of the terms "intraamniotic infection and inflammation" (IAI or Triple I), which have had variable uptake in clinical settings. Intraamniotic infection and inflammation can be divided into 3 clinical categories: isolated parturient fever, suspected intraamniotic infection, and confirmed intraamniotic infection.[1,4] Isolated parturient fever is defined by a single temperature reading above 39°C or multiple readings between 38°C and 39°C 30 minutes apart with no associated infectious symptoms.[4] Isolated parturient fever has been associated with both short- and long-term poor neonatal outcomes in some studies, to include lower Apgar scores at delivery and higher rates of neonatal hypotonia.[10] Suspected intraamniotic infection has previously been defined as a temperature above 38°C with no other obvious source of infection and any of the following: baseline fetal tachycardia (fetal heart rate $>160$ beats per minute baseline), maternal leukocytosis (WBC $>15{,}000/m^3$ in the absence of corticosteroids), and purulent fluid from the cervical.[1,4] Although clinical guidance has traditionally incorporated maternal fever as a required criterion for suspected intraamniotic infection, fever is not uniformly present in all cases. The American College of Obstetrics and Gynecology (ACOG) has removed the requirement of maternal fever for diagnosis of suspected intraamniotic infection and recommends intervention with antibiotics if other clinical signs and symptoms are present to suggest infection for improvement of maternal morbidity.[11] Confirmed intraamniotic infection includes all the features previously mentioned and also includes amniocentesis-proven infection via positive gram stain, low glucose within amniotic fluid, positive amniotic fluid culture, or placental pathology confirming findings of infection.[4]

Risk factors for intraamniotic infection include lower parity, multiple vaginal exams, intrauterine monitoring, prolonged labor, meconium-stained amniotic fluid, colonization with GBS, and sexually transmitted infections.[12,13] Intraamniotic infection has been associated with dysfunctional labor, requiring more interventions as well as further maternal complications, including uterine atony, endometritis, peritonitis, sepsis, adult respiratory distress syndrome, and, in some cases, death.[14,15]



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### *GBS Epidemiology*

GBS is a facultative anaerobic gram-positive bacterium known to colonize the rectovaginal tract. It is associated with maternal urinary tract infections, intrapartum and postpartum infections, and sepsis. Rectovaginal colonization with GBS has been reported in 15% to 30% of women.[16,17] Colonization can be intermittent, transitory, or persistent. GBS colonization in a prior pregnancy increases the likelihood of colonization in subsequent pregnancies to 50%.[18] Of neonates born to individuals with GBS colonization, 50% will be infected with GBS by vertical transmission, and 1% to 2% of those infected will develop early-onset invasive disease.[17,19] GBS colonization is associated with higher rates of pre-term birth and stillbirth. Bianchi-Jassir et al demonstrated that when colonization is evident as maternal GBS bacteriuria, patients have almost a 2-fold increase in the rate of preterm birth (RR 1.98, 95% CI, 1.45-2.69).[20]

### *GBS Neonatal Disease*

GBS is associated with both short- and long-term sequelae in neonates. It can be associated with invasive disease in infants, classified as early-onset disease (EOD) or late-onset disease (LOD). In 2021, the Centers for Disease Control and Prevention reported 0.21 cases per 1000 live births of invasive EOD in the first week of life, and 0.23 cases of LOD per 1000 live births in days 7 to 90 of life.[21]

The timing of EOD is characterized by the onset of disease between birth and 7 days of life. EOD can present as neonatal pneumonia, meningitis, or sepsis,[22–24] and is the most common cause of early-onset sepsis in neonates.[22] Maternal colonization with GBS is associated with increased risk for EOD.[22,25] Independent risk factors for EOD include preterm birth, very low birth weight, prolonged rupture of membranes, intraamniotic infection, young maternal age, and African American race.[5,20,22,26–29] Studies have reported that 72% of GBS EOD occurs in term infants;[26] however, morbidity and mortality are higher in preterm infants.[30] Preterm infants with GBS EOD are more likely to require neonatal intensive care, including respiratory support.[30]

LOD is defined as neonatal bacteremia, meningitis, or less commonly, organ or soft tissue infection between 7 and 90 days of life.[31] LOD is typically caused by horizontal transmission or environmental sources, such as in the cases of hospital- or community-acquired pneumonia.[31] Similar to EOD, most cases of LOD occur in term infants. Risk factors for LOD are not as well known when compared to EOD.[31] One meta-analysis found that HIV exposure in utero was associated with increased rates of LOD but had no significant effect on cases of EOD.[32] Some studies have shown that the administration of IAP can also affect rates and the severity of LOD. Berardi et al, showed that infants born to mothers who received IAP and later developed LOD presented significantly later (median 45 d vs 20 d of life, $P < 0.01$) and often had more mild infections.[31]

In recent years, there has been concern that obstetric interventions may increase the risk for GBS-related neonatal complications. Studies have reported mixed results on GBS-related outcomes with immersion in water,[25,33] membrane sweeping,[34] mechanical cervical ripening,[35–38] repeat vaginal examinations,[39,40] artificial rupture of membranes,[40,41] and intrauterine monitoring.[41,42] One challenge in illuminating the risk of GBS colonization associated with obstetric intervention is that interventions tend to be indicated in women who are also at higher risk for GBS colonization. Literature on these risks is sparse, and there is not sufficient data to make recommendations on labor-management about the risk of GBS complications.


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## MANAGEMENT

### *Screening*

Since 1996, the Centers for Disease Control and Prevention has collaborated with several professional societies to create recommendations for GBS screening. As of 2019, the American College of Obstetrics and Gynecology (ACOG) and the American Academy of Pediatrics (AAP) have assumed the role of curators of the guidelines for prophylaxis and treatment of GBS infection.[3] Screening and appropriate intrapartum antibiotic prophylaxis have become the mainstay of prevention of GBS EOD. In terms of screening, studies have shown that a screen-to-birth interval of 5 weeks is optimal.[43,44] Beyond this time frame, there may be discrepancies in GBS status at the time of screening versus delivery.[44,45] As of 2019, ACOG recommends universal screening for GBS colonization between 36 0/7 and 37 6/7 weeks of gestation.[40] This is updated from previous guidelines that recommended screening starting at 35 weeks. Given that 6.7% of individuals deliver at 41 weeks or later,[46] screenings as early as 35 weeks would require repeat screening for those gestations that go beyond 40 weeks.[43,44] Patients with a prior history of a neonate with GBS EOD or GBS bacteriuria at any point during the current pregnancy are exempt from screening and require intrapartum antibiotic prophylaxis (IAP).[40]

GBS vaginal-rectal swab culture is the gold standard for GBS screening as it produces the best colony yield.[47] A recent meta-analysis found that vaginal-perineal swabs produce similar colony yield with less patient discomfort.[48] Sensitivity and specificity of vaginal-perineal swabs were not compared with those of vaginal-rectal swabs in this study. ACOG still recommends vaginal-rectal swabs as the gold standard for screening. Another meta-analysis has shown that patient self-collected swabs have similar specificity but lower sensitivity compared with provider-collected swabs. Data looking at the effects of self-collection on health outcomes and trials directly comparing the accuracy of provider-collected to self-collected swabs is limited.[49] ACOG does not recommend against or for self-collected cultures but does comment that if patients are educated on how to complete the collection, colony yields are similar.[40]

Per ACOG guidelines, swabs should be labeled to indicate samples for GBS from pregnancy and penicillin allergy if present to prompt susceptibility testing to alternative antibiotics.[40] Samples should be incubated in GBS-selective broth on blood agar to optimize culture yield and can be tested via latex agglutination with group B streptococcus antisera, chromogenic agar, DNA probes, and nucleic acid amplification tests (NAAT).[50–52] Swabs from patients with penicillin allergies may also undergo D-zone testing for susceptibility to clindamycin and macrolides.[53] Of note, susceptibility results may include erythromycin, however, erythromycin is no longer accepted for IAP and should not be administered.[26,54]

Although culture is considered the standard for GBS screening, NAAT testing is equivalent, and, in some cases better than culture when a 14 to 24-hour incubation in enrichment broth is performed before testing.[55–58] Culture should still be performed for patients with penicillin allergy because antibiotic susceptibility testing cannot be performed on NAAT samples.[56,58] Point-of-care NAAT may be performed at the delivery encounter and takes 1 to 2 hours; however, without an incubation step, there have been reported failure rates of 7% to 10%.[55,59,60] Survey data from 2019 reported that about 18.7% of laboratories use NAAT for GBS screening, 39% of which use it for antepartum screening only, 22% for intrapartum screening only, and 17% for both antepartum and intrapartum screening.[50] 82% of laboratories performing NAAT reported using an enrichment step before polymerase chain reaction.[50]



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### *Prenatal GBS Bacteriuria*

Patients with asymptomatic GBS bacteriuria at a level of at least 100,000 CFU/mL should be treated to decrease the risk of pyelonephritis, birth weight below 2500 g, and preterm birth.[61,62] Some laboratories may report GBS levels of 10,000 CFU/mL, but studies have found no correlation of preterm birth with GBS levels below 100,000 CFU/mL, so treatment is not recommended.[63–65] However, levels of 10,000 CFU/mL indicate a high level of vaginal GBS colonization, so intrapartum antibiotic prophylaxis is recommended on initiation of labor.[40]

### *Indications for Intrapartum Antibiotic Prophylaxis*

Intrapartum antibiotic prophylaxis (IAP) is recommended in certain situations by ACOG to decrease rates of GBS colonization, risk of intrauterine infection, and neonatal early-onset disease (Fig. 1).[40] IAP has been shown to decrease the risk for GBS-associated neonatal sepsis and other early-onset disease.[66–70] From the 1990s to 2011, the implementation of IAP resulted in an approximate 80% reduction in the incidence of early-onset neonatal sepsis from GBS.[71]

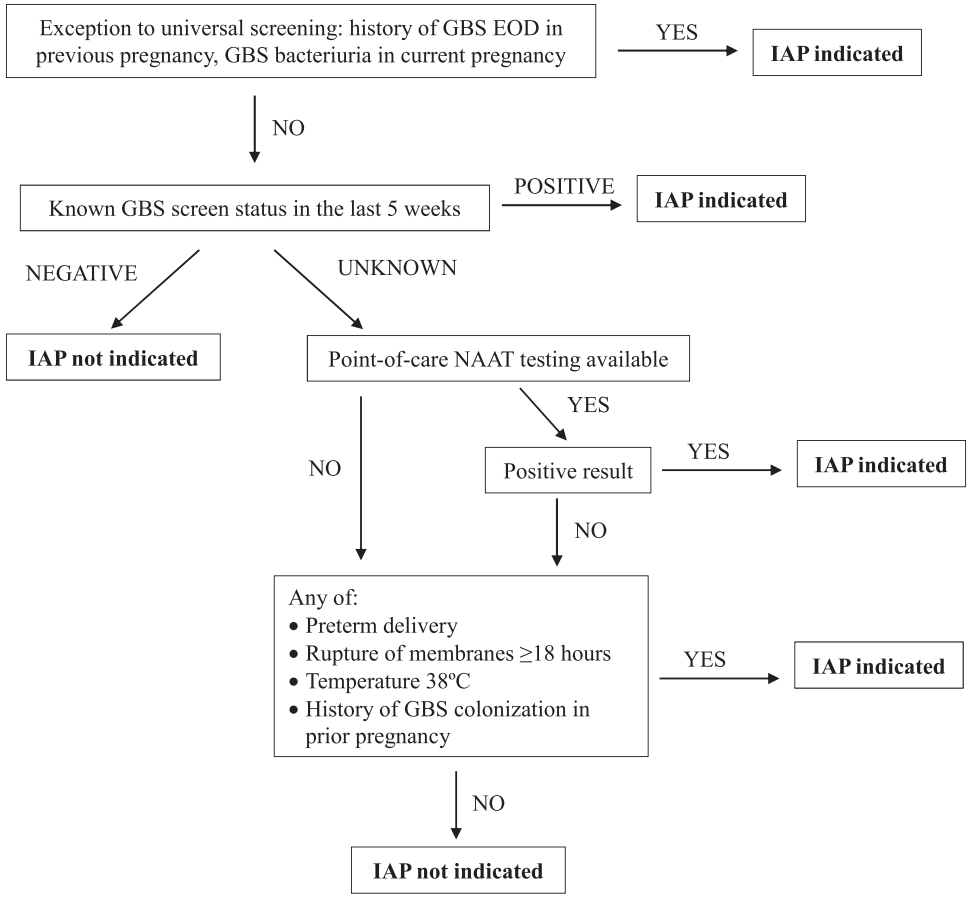


***FIGURE 1.*** Indications for intrapartum antibiotic prophylaxis according to GBS vaginal-rectal screening culture result and additional risk factors. GBS indicates Group B *Streptococcus*; IAP, intrapartum antibiotic prophylaxis.


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ACOG recommends IAP for women with positive GBS cultures or GBS bacteriuria during the current pregnancy unless pre-labor cesarean with intact membranes is planned.[40] For women with unknown GBS status, risk factors are used to determine whether intrapartum GBS prophylaxis is indicated. These include preterm birth <37 weeks, prelabor rupture of membranes for 18 or more hours at term, intrapartum fever (whether considered intraamniotic inflammation, infection, or chorioamnionitis), or history of GBS in a prior pregnancy.[40,72,73] In patients who undergo point-of-care NAAT testing, all patients with positive tests and those with negative tests who meet the above clinical risk factors should receive IAP because NAAT is not 100% sensitive.[55]

IAP is not indicated for patients with negative GBS culture screens in the current pregnancy, regardless of colonization status in prior pregnancies or clinical risk factors. This excludes patients with a history of a prior neonate with invasive GBS disease who should receive intrapartum prophylaxis regardless of screening culture result. Patients with unknown GBS colonization status with negative point-of-care NAAT and no clinical risk factors do not require IAP.[40] Importantly, regardless of GBS screening results or known colonization, treatment of an intrapartum infection is still provided when fever is diagnosed or clinical infection is suspected.[1] Patients with planned cesarean section should still undergo GBS screening at 36 0/7 weeks in case of labor or prelabor rupture of membranes (PROM).[40] Patients in active labor or with PROM before cesarean section should receive one dose of IAP and presurgical prophylaxis. It is not recommended to delay cesarean section to give additional doses of GBS IAP.[40]

Special consideration is given to patients at risk for preterm delivery, as prematurity is a risk factor for GBS EOD.[20,27,74] Patients who present with preterm labor or premature prelabor rupture of membranes (PPROM) should undergo vaginal-rectal swab for NAAT or culture with antibiotic susceptibility testing if a penicillin allergy is reported.[40] IAP is administered during initial management while waiting for NAAT or culture results.[40] In patients with PPROM after 34 weeks, the risk of neonatal GBS infection may be decreased if labor is induced immediately.[75] Patients with planned preterm induction should undergo a GBS screen 5 weeks from the planned induction date.[25,76]

### *Antibiotic Recommendations*

The recommended antibiotic for preventing early-onset GBS disease in neonates is intravenous (IV) penicillin.[4,40] ACOG recommends a loading dose of 5 million units followed by 2.5 to 3 million units every 4 hours until delivery. Penicillin is the antibiotic of choice given its narrower spectrum of activity against gram-positive bacteria. However, IV ampicillin is an acceptable alternative, with a 2 g loading dose followed by 1 g every 4 hours until delivery.[40] It has been shown that IAP has the highest effectiveness against neonatal disease when initiated at least 4 hours before delivery.[67,70] However, 2 hours of IAP has been shown to reduce GBS colony counts and the frequency of a clinical neonatal sepsis diagnosis.[70,77] All accepted agents for IAP, including penicillin, ampicillin, cefazolin, clindamycin, and vancomycin, have been shown to achieve bactericidal levels in amniotic fluid and cord blood after 2 hours.[31,66,77] A recent cohort study among patients who received at least 2 hours of antibiotics found no difference in GBS colonization after 1 versus multiple doses of IAP.[78] ACOG recommends initiating IAP as soon as possible when indicated but recommends against delaying necessary obstetric interventions.[40] Intramuscular or oral antibiotic administration



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and vaginal cleansing with chlorhexidine alone during labor have not been shown to reduce rates of neonatal sepsis and therefore should not be considered substitutes for intravenous prophylaxis.[40]

A recent prospective study found that IAP is not always prescribed when an indication is present, representing opportunities for improved delivery of care.[74] However, intrapartum antibiotics may not be benign,[79,80] and assessment of risk and clinical indicators should be performed to guide management.[8,28] Providers should use the guidelines set out by ACOG to engage in shared decision-making with patients where GBS colonization status is unknown and risk factors for GBS invasive disease are low to mitigate the risk of invasive disease.

### *Treatment of Intraamniotic Infection and Inflammation*

In cases of isolated fever, it may be appropriate to avoid antimicrobial agents but in most cases of suspected or confirmed Triple I, antimicrobial agents should be started, with choice of agent guided by the prevalent microorganisms causing intrauterine infection. Generally, ampicillin and gentamicin will cover the most likely pathogens and are thus often the antibiotic regimens of choice. In cases of cesarean delivery, the addition of anaerobic coverage with clindamycin or metronidazole can be considered to reduce the risk of endometritis.[1,4] Antibiotics should not be continued automatically postpartum, and administration may be guided by institutional protocol or clinical infection resolution. Antibiotics may be continued if the risk of postpartum endometritis is suspected to be high.[81,82] Specifically, in the case of cesarean delivery, at least one additional dose of antimicrobial agents after delivery should be given, but the ultimate decision on the length of treatment should again be based on the further risk of infection following delivery.[1,4]

### *Penicillin Allergy*

A recent review reported that among penicillin use in all patients, the rate of IgE-mediated reaction is 1% to 2%, and the risk of anaphylaxis is even lower.[83] The rate of anaphylactic reactions to penicillin in pregnancy is estimated to be approximately 2.7 per 100,000 deliveries.[84] Allergy testing in individuals with reported penicillin allergy may decrease morbidity and cost, in addition to adverse reactions to alternative antibiotic therapy.[79,80,85] An estimated 95% of individuals with reported penicillin allergies can tolerate drugs in the penicillin class.[86]

In patients with a reported penicillin allergy, the most important first step prenatally is to categorize the nature of the allergy as low or high risk for anaphylaxis or other severe non-IgE reaction. Low-risk allergic reactions include nonspecific reactions such as GI upset, headache, vaginal candidiasis, and nonurticarial morbilliform rash or pruritis without rash. This category also includes individuals with family history but no personal history of severe reaction, and those who report a history of allergy without recollection of their symptoms or treatment.[83,87] High-risk allergies include those with a high risk for anaphylaxis, defined by a history of pruritic rash, hives, flushing, hypotension, angioedema, respiratory distress, or anaphylaxis occurring within the first few hours of receiving penicillin or cephalosporin. Additionally, high-risk allergies include a history of recurrent reactions, reactions to multiple beta-lactams, or a positive penicillin allergy test. Severe non-IgE-mediated reactions considered contraindications to penicillin administration include severe, delayed-onset cutaneous and systemic reactions with eosinophilia (DRESS) or Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS-TEN).[79,83,87]

ACOG's recent guidelines regarding GBS IAP include recommendations for management for patients with penicillin


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allergy (Fig. 2). For individuals with low-risk penicillin allergies, the alternative drug of choice is cefazolin. GBS is susceptible to cefazolin, as it has pharmacokinetic properties similar to penicillin and yields similar therapeutic intraamniotic and fetal blood levels.[78,88] Although previous studies have reported 8% to 10% cross-reactivity between penicillin and cephalosporins,[79] more recent studies have shown that the rates of cross-reactivity are much lower (4.3% with first- and second-generation cephalosporins such as cefazolin, and less than 1% with third- and fourth-generation cephalosporins).[89] Cefazolin is preferred over third- or fourth-generation cephalosporins in GBS IAP to avoid antibiotic resistance associated with broad-spectrum antibiotics.[90] Patients should be given a 2 mg IV loading dose of cefazolin, followed by 1 g IV every 8 hours until delivery.[40]

In patients with high-risk penicillin allergies, IV clindamycin 900 mg every 8 hours is the preferred alternative antibiotic only if the colonizing GBS is susceptible according to resistance testing performed on a prenatal screening culture positive for GBS.[40,70,91] Erythromycin was a previously accepted alternative, but reports of increasing resistance have made this no longer an acceptable choice.[26,54] GBS resistance to clindamycin may be as high as 20% according to recent reports,[26,54] and in high-risk patients with GBS colonization resistant to clindamycin, IV vancomycin is the acceptable alternative.[77,92] Institutional antibiograms

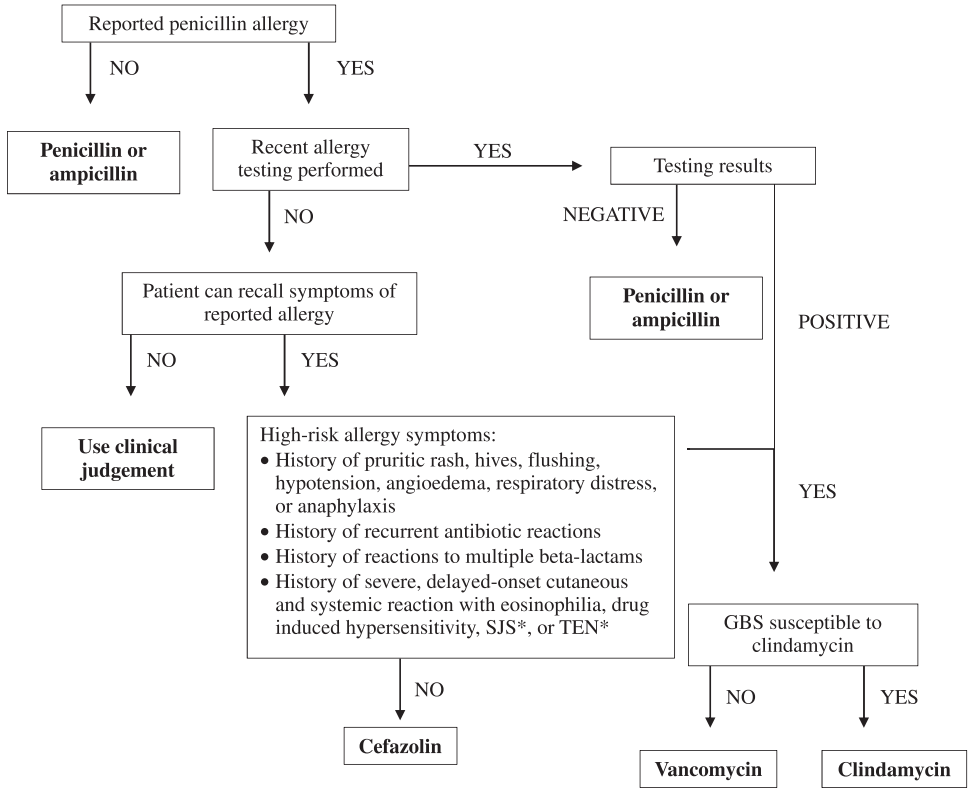


***FIGURE 2.*** Intrapartum intravenous antibiotic prophylaxis in patients reporting penicillin allergy. SJS indicates Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.


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may dictate rates of clindamycin resistance among GBS isolates, and clinicians should refer to local resistance patterns if GBS clindamycin sensitivity testing is not available for an individual with reported penicillin allergy. According to newer recommendations, IV vancomycin should be dosed based on weight (20 mg/kg every 8 h) and renal function for improved parturient and fetal blood levels.[40,92] There is currently no evidence to support a particular choice of alternative antibiotics in patients with a reported history but no recall of symptoms. In the absence of allergy testing, providers may use clinical judgment, with the understanding that true Ig-E mediated penicillin allergy is quite rare and that only Ig-E mediated or severe non-IgE-mediated reaction (DRESS or SJS-TEN) warrants a non-cephalosporin alternative.[40]

### *Vaccination and Other Forms of Prevention*

While significant improvements in outcomes have been made with the use of IAP, prevention of neonatal GBS disease through maternal vaccination is desired to further improve outcomes and decrease the need for antibiotic use. Multiple phase 2 trials are currently underway to evaluate the safety and immunogenicity of candidate vaccines. Madhi and colleagues demonstrated detectable serotype-specific antibodies to GBS among infants delivered to vaccinated women through 90 days of life, with no reduction of antibodies elicited by routine infant diphtheria toxoid and pneumococcal vaccination.[93] Another recent study reported 50% awareness and median 9/10 acceptance rates of this novel vaccine among pregnant individuals.[94] There is currently no clear evidence demonstrating that prenatal probiotics are effective in reducing GBS colonization, with mixed results from recent studies.[95–97] More work is needed to determine whether probiotics should be recommended to pregnant individuals to reduce GBS colonization or, more importantly, neonatal GBS disease.

## *Conclusions*

Group B S*treptococcus* and intraamniotic infection and inflammation portend increased risk for serious complications to pregnant individuals and their infants. Screening for GBS colonization and prophylaxis with intrapartum antibiotics has led to a decrease in neonatal and maternal morbidity and mortality associated with GBS infection. Screening guidelines have evolved to identify individuals who may be colonized with GBS near the time of delivery. Antibiotic recommendations reflect the need to target the GBS organism and achieve therapeutic levels in the fetus while reducing the risk of antibiotic resistance. Although a future GBS vaccine will likely reduce the risk of neonatal GBS disease, clinical guidelines for GBS screening and intrapartum prophylaxis will still be needed.

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