



Prophylaxis Against Early-onset Group B Streptococcus Infections in Pregnant Women Who Are Allergic to Penicillin

**HUGH C.G. NADEAU, MD,
and RODNEY K. EDWARDS, MD, MS**

*Section of Maternal-Fetal Medicine, Department of Obstetrics
and Gynecology, University of Oklahoma College of Medicine,
Oklahoma City, Oklahoma*

Abstract: Group B *Streptococcus* (GBS) infection remains a significant cause of neonatal morbidity and mortality. Adoption of screening for maternal genital tract colonization and intrapartum antibiotic prophylaxis has significantly reduced early-onset neonatal GBS infections. For women with an allergy to penicillin, recommended agents for prophylaxis have been well-outlined, but compliance with guideline recommendations is poor. There have been ongoing efforts in vaccine development, but no vaccination currently is available for either preconception or antenatal administration. This article will review established screening techniques, intrapartum antibiotic prophylactic regimens, and management specifically of the penicillin-allergic pregnant woman who is colonized with GBS.

Key words: group B *Streptococcus*, pregnancy, penicillin allergy, beta-lactam allergy, intrapartum antibiotic prophylaxis, early-onset neonatal infection

Overview

The gram-positive coccus, group B *Streptococcus* (GBS), also known as *Streptococcus agalactiae*, has long been known to be a major contributor to neonatal morbidity and mortality. In the United States, this bacterium has genitourinary and gastrointestinal colonization rates ranging between 10% and 30% and typically acts as nonpathogenic flora associated with the host's microbiome. Despite this, GBS has been described as a source pathogen in maternal infections

Correspondence: Hugh C.G. Nadeau, MD, University of Oklahoma College of Medicine, 800 Stanton L. Young Boulevard, Suite 2000, Oklahoma City, OK. E-mail: hugh-nadeau@ouhsc.edu

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including asymptomatic bacteriuria, cystitis, pyelonephritis, bacteremia, chorioamnionitis, endometritis, postcesarean wound infections, and more rarely pneumonia and meningitis.¹⁻³ Maternal mortality due to GBS infection is rare.

GBS was distinguished from group A *Streptococcus* (*Streptococcus pyogenes*) in the 1930s. The association between maternal GBS colonization and puerperal infection, which typically follows transmission during delivery, was noted later that decade and was reported sporadically through the 1960s before becoming the most frequent bacterium associated with neonatal pneumonia, meningitis, and sepsis in the 1970s, leading to mortality rates as high as 50%.⁴ Neonatal infections due to GBS are described as early-onset, occurring within the first week of life, or late-onset, occurring after the first week of life. Early-onset neonatal GBS infections have been associated with a variety of antenatal and intrapartum factors including intrapartum fever, having a prior infant with early-onset neonatal GBS infection, African American race, maternal age below 20 years, limited prenatal care, GBS bacteriuria (associated with heavy genital tract colonization), preterm delivery, and prolonged rupture of membranes <18 hours.⁵ The risk factor most highly associated with early-onset neonatal GBS infection is maternal genital tract colonization. Early-onset neonatal GBS infections typically are due to vertical transmission from mother to infant. Late-onset infections are due to horizontal transmission.

In the 1970s, rates of early-onset neonatal GBS infections were as high as 2 per 1000 live births, with a mortality rate of 25% to 50%.⁴ Clinical trials that took place in the 1970s and 1980s led to the discovery that administration of intravenous intrapartum antibiotic prophylaxis (IAP) to women at risk of transmitting GBS led to decreased rates of early-onset neonatal infection.

The American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) first emphasized the need for development of a highly reliable, rapid screening test for GBS and the utilization of risk-based IAP in 1992.⁶ Subsequently, in 1996 in conjunction with the AAP and ACOG, the Centers for Disease Control and Prevention (CDC), released guidelines suggesting the use of either risk-based or screening-based strategies and the choice of appropriate IAP to prevent early-onset neonatal GBS infections. These guidelines described the use of IAP based either on risk factors (previously affected infant with early-onset GBS infection, delivering at a gestational age less than 37 wk, intrapartum temperature of $\geq 100.4^{\circ}\text{F}$ or greater, or rupture of membranes for 18 h or longer) or the results of screening cultures taken from the lower vagina and anorectum at 35 to 37 weeks gestation and administering IAP for women with a positive screening culture or with GBS bacteriuria during the pregnancy, or in the absence of a screening culture result, 1 or more risk factors.⁷

The CDC released updated consensus guidelines in 2002 with changes including the recommendation for universal prenatal GBS screening at 35 to 37 weeks' gestation and an update to the prophylaxis regimens for women with a penicillin allergy. In addition, the CDC recommended against the use of IAP, regardless of maternal GBS colonization status, for women undergoing planned cesarean deliveries in the absence of labor or amniotic membrane rupture. The guidelines did support screening, at 35 to 37 weeks, of women before planned cesarean deliveries, as labor or rupture of membranes may occur before the planned surgery.⁸ Following widespread adoption of screening-based IAP, early-onset neonatal GBS infection rates dropped from 1.8 per 1000 live births in 1990 year to 0.3 per 1000 live births in 2008.^{1,7}

Further updates were made in 2010, leading to the most current edition of the CDC's Guidelines for the Prevention of Perinatal GBS Disease. These most recent modifications (1) expanded the options for laboratory detection of GBS, (2) changed the threshold for which laboratories should report the bacterium in screening urine cultures of pregnant women, (3) clarified the screening and IAP administration algorithms for special populations of pregnant patients, (4) updated the neonatal assessment and management algorithm, and (5) tailored the presentation of recommended IAP agents in an effort to facilitate the most appropriate antibiotic choice for penicillin-allergic women.⁹ These ongoing changes to recommendations for antibiotic choice for IAP for penicillin-allergic women have been due to the emergence of increased rates of resistance to erythromycin and clindamycin, the originally recommended options for this group of gravidas.

Screening

The CDC's 2002 publication, described above, initially outlined GBS screening using a culture-based method. This method uses serial culture in selective broth media followed by blood agar plates, which may take 72 hours or more to report. This process is initiated by culturing the collected sample for 18 to 24 hours in a specialized selective enrichment broth to enhance GBS growth by retarding growth of other organisms. Examples of such selective media include Todd-Hewitt broth that contains supplemental gentamicin and naldixic acid (Transvag Broth) or supplemental colistin and naldixic acid (Lim Broth). Subsequently, subculture to blood agar plates is undertaken, and presumptive identification is made by the Christie-Atkins-Munch-Petersen (CAMP) test or serologic identification using latex agglutination with GBS antisera, which can take an additional 18 to 24 hours.^{1,9} Antibiotic susceptibility testing can be performed on these isolates.

The use of chromogenic agars and pigmented enrichment broths, which change color in the presence of beta-hemolytic GBS colonies, can decrease the time to result for GBS screening cultures. However, they are not broadly utilized, since they do not typically detect nonhemolytic strains.⁹

Newer diagnostic technologies have been developed for the identification of GBS, but these have been inconsistently supported by the CDC, AAP, and ACOG. One such technology that does not require incubation uses a nucleic acid amplification technique (NAAT), such as polymerase chain reaction, to target a DNA region found in GBS. These tests, which have varying sensitivities (range: 62.5% to 98.5%) and specificities (range: 64.5% to 99.6%), take <4 hours to result. For early varieties of NAAT for GBS, sensitivity was decreased in the presence of light colonization. Adding an enrichment step before testing the sample resulted in an improved sensitivity of those early NAAT for GBS (range: 92.5% to 100%) but increased the time for sample throughput.⁹ Later iterations of NAAT for GBS produce results in as little as 75 minutes and have shown comparable test performance characteristics (sensitivity 91.1%, specificity 96.0%), even in the setting of light colonization, but these tests are unable to evaluate for antibiotic susceptibility of isolates.¹⁰

The AAP has endorsed the use of NAAT for GBS detection. However, the CDC guidelines, which has become the de facto standard of care since publication of the first version in 1996, outlines these as appropriate options for testing but still describes culture-based screening as the gold standard.^{9,11}

IAP

The 1996 iteration of the CDC guidelines described the use of either penicillin G (administered at an initial dose of 5 million units intravenously, then 2.5 to 3 million

units intravenously every 4 h until delivery) and ampicillin (administered at an initial dose of 2 g intravenously, then 1 g intravenously every 4 h until delivery) for IAP. Despite these 2 antibiotics having similar efficacy against GBS, penicillin G was described as the preferred agent, given its narrower spectrum of antimicrobial activity. It was postulated that this narrower spectrum of activity would cause widespread use of IAP to be less likely to cause selection of resistant organisms than if ampicillin were used preferentially. The described dosages of these agents are targeted to achieve adequate levels in the fetal circulation and amniotic fluid rapidly while avoiding potentially neurotoxic serum levels in the mother or fetus. Both agents, when administered intravenously for at least 4 hours before delivery, significantly reduce vertical transmission and risk of early-onset GBS disease in the neonate.^{7,8}

When prescribing IAP, the presence of a penicillin allergy and the severity of said allergy becomes an important consideration in antibiotic selection. The current method for determining antibiotic selection relies largely on the patient's report of whether or not a prior allergic reaction was noted following administration of penicillin or some other beta-lactam antibiotic. This reaction is classified as a mild or a severe allergy. A severe allergy, also known as a type 1 reaction or an IgE-mediated reaction, is defined by the CDC as anaphylaxis, angioedema, respiratory distress or urticaria. Nonurticarial rashes are classified as mild allergies. Symptoms including nausea, vomiting, diarrhea, and vaginitis are known side effects of antibiotic use and are not indicative of a penicillin allergy. A positive family history, but negative personal history, of a penicillin allergy also does not preclude penicillin use.

Per CDC estimates, ~10% of the population in the United States report having a penicillin allergy, but <1% of the population

reporting an allergy, when evaluated, have a true IgE-mediated reaction. In addition, 80% of patients with an IgE-mediated reaction lose their sensitivity to penicillins after 10 years. The CDC reports that of the allergic reactions that occur with an estimated 0.7% to 4.0% of treatment courses with penicillins, the most common reaction is a maculopapular rash, which is not typically IgE-mediated. Further, the CDC estimates the rate of anaphylaxis due to penicillin to be between 4 per 10,000 and 4 per 100,000. Anaphylaxis associated with penicillin administered as IAP for GBS is rare—there have been only 4 reported cases in the United States of maternal anaphylaxis since publication of the 1996 iteration of the CDC guideline, and none of these cases has been fatal.⁹

This increased perception of having a penicillin allergy compared with the actual prevalence of true penicillin allergies is noteworthy given the implications regarding the risk of developing drug-resistant bacteria and in providing suboptimal antibiotic therapy.¹² With 3,978,497 live births in 2015 in the United States reported by the National Center for Health Statistics, an estimated 397,850 to 1,193,549 were colonized with GBS (using a 10% to 30% colonization rate).¹³ Of these, 39,785 to 119,355 have a reported penicillin allergy (using a 10% rate of reported penicillin allergies). Per the above information, <3979 to 11,936 have a true IgE-mediated hypersensitivity. This number may, in actuality, be dramatically less given that this reaction is often transient in nature (Fig. 1).

Penicillin skin testing is a method to more accurately determine if a patient is truly penicillin-allergic, and some propose skin testing pregnant women with a reported penicillin allergy in order to utilize the most appropriate antibiotic for IAP. This test, which must be performed before the need for therapy, involves a small cutaneous exposure, with a skin prick or a scratch, to the reagents penicilloylpolym-

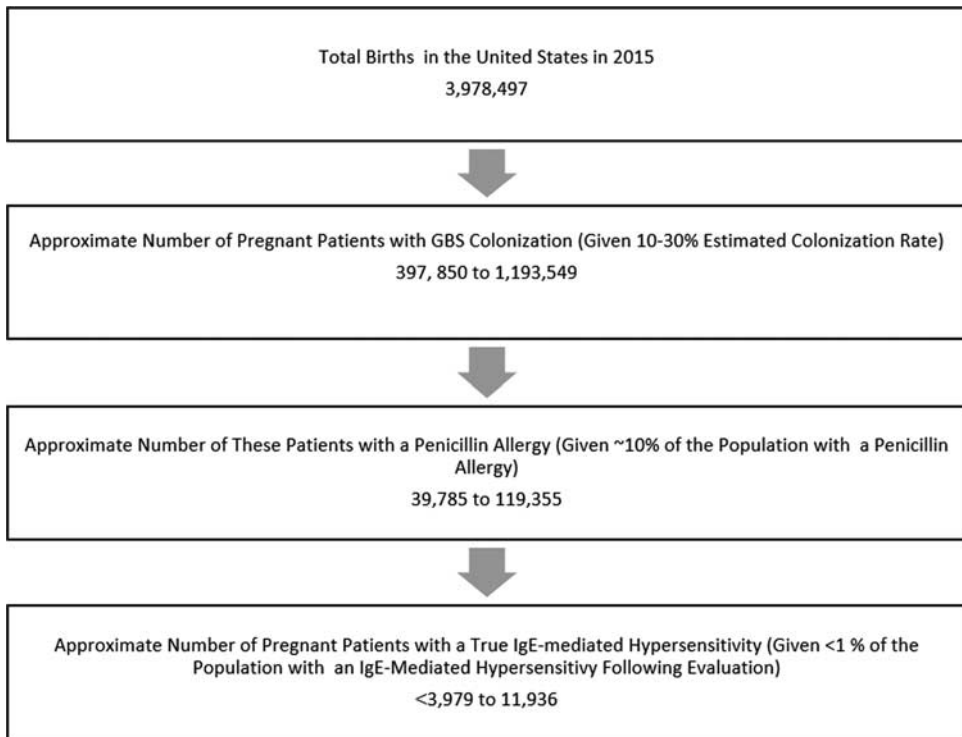


FIGURE 1. Approximate number of penicillin allergies in GBS colonized pregnant women as a proportion of total births in the United States in 2015, obtained from the US Centers for Disease Control and Prevention’s National Vital Statistics System.

lysine and commercially-available penicillin G. The test, which can be administered by a trained nurse, physician, or pharmacist, is said to have a positive response if a wheal is noted after this challenge. Patients with a positive skin test should not receive antibiotics from the beta-lactam class. In the absence of a wheal, an oral challenge dose with an antibiotic such as 250 mg of amoxicillin can be undertaken; if no symptoms in 1 hour following the oral challenge dose, the test is considered negative. Per the CDC, the negative predictive value of skin testing is >95% but approaches 100% when followed by an oral challenge dose.¹⁴

In a single-center study, 56 enrolled pregnant patients had penicillin skin testing performed. Of these, there were only 2

mild adverse reactions and 3 positive results. Of the 53 patients with negative skin testing, 47 were exposed to penicillin, and only 2 patients experienced any side effects, both having delayed-onset rashes.^{12,14,15}

It should be noted that penicillin skin testing should be avoided in women with a history of beta-lactam associated toxic epidermal necrolysis, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms syndrome, severe hepatitis, interstitial nephritis, or hemolytic anemia. These reactions are not IgE mediated. Therefore, a negative result on penicillin skin testing does not necessarily predict the risk of recurrence.

For women with a mild penicillin allergy, administration of the cephalosporin, cefazolin (administered at an

initial dose of 2 g intravenously, then 1 g intravenously every 8 h until delivery) is recommended for IAP. Similar to penicillin G and ampicillin, the drug reaches high intra-amniotic concentrations and has a narrow antimicrobial spectrum. Figure 2 shows the currently recommended algorithm for deciding which antibiotic to use for IAP. In addition, another clinical tool available is the free smart phone app from the CDC called “Prevent Group B Strep.”

Given that there is an estimated 10% risk of a hypersensitivity reaction to cephalosporins in patients with a severe penicillin allergy, pregnant women with a severe allergy to penicillin should have antimicrobial susceptibility testing performed along with antenatal GBS screening cultures in order to assess for GBS isolate susceptibility for the most commonly used alternative agents, clindamycin and erythromycin.⁹

In the past, both of these antibiotics were reasonable alternatives. In an article by Castor and colleagues that assessed 3471 GBS isolates collected as part of population-based surveillance for invasive GBS disease in 4 states during the period from 1996 to 2003, clindamycin resistance increased from 10.5% to 15.0% and erythromycin resistance increased from 15.8% to 32.8% during the study period. Concurrent resistance to both drugs was identified in 12.6% of evaluated isolates. All isolates were noted to be sensitive to all other antimicrobial agents recommended per the CDC guidelines, including penicillin, ampicillin, cefazolin, and vancomycin.¹⁶ Since that time, the proportion of GBS clinical isolates that are resistant to these antibiotics has increased further. In addition, most isolates testing as susceptible to clindamycin and resistant to erythromycin have inducible clindamycin resistance. Therefore, if the isolate is susceptible to both agents, clindamycin (administered at 900 mg intravenously every 8 h until delivery) may be

used. However, if an isolate is resistant to erythromycin but susceptible to clindamycin, or if susceptibility testing was not accomplished, then vancomycin (administered at a dose 1 g intravenously every 12 h until delivery) should be used for IAP.

Alternatively, D-zone testing can be used to assess for inducible clindamycin resistance. To accomplish this, erythromycin-impregnated and clindamycin-impregnated disks are placed on an agar plate a specified distance apart and exposed to a GBS isolate. These plates are incubated for 16 to 24 hours then inspected visually. If the zone of inhibition surrounding the clindamycin-impregnated disk is found to be flattened in the area adjacent to the erythromycin-impregnated disk, then the isolate is said to have positive D-zone testing. If this test is completed and the penicillin-allergic patient is found to have a GBS isolate that is susceptible to clindamycin with negative D-zone testing, then clindamycin may be used⁹ (Fig. 2).

While the use of alternatives to penicillin, ampicillin, and cefazolin for IAP has been well-established and are described in the CDC guidelines, the efficacy of alternate antibiotics for IAP and their ability to reach bactericidal levels in fetal tissues have limited supportive data. The pharmacokinetics, including the degree of placenta transport and the fetal circulatory levels following infusion, of clindamycin and erythromycin have not been well evaluated, leading to unclear recommendations for duration of dosing for adequate GBS prophylaxis. As such, when these agents are utilized for IAP, the neonate, per the CDC’s 2010 guidelines, is considered to have received inadequate treatment for the purposes of neonatal management—therefore, a limited evaluation and ≥ 48 hours of monitoring is indicated. IAP with these agents is classified as inadequate regardless of duration of IAP exposure before delivery.

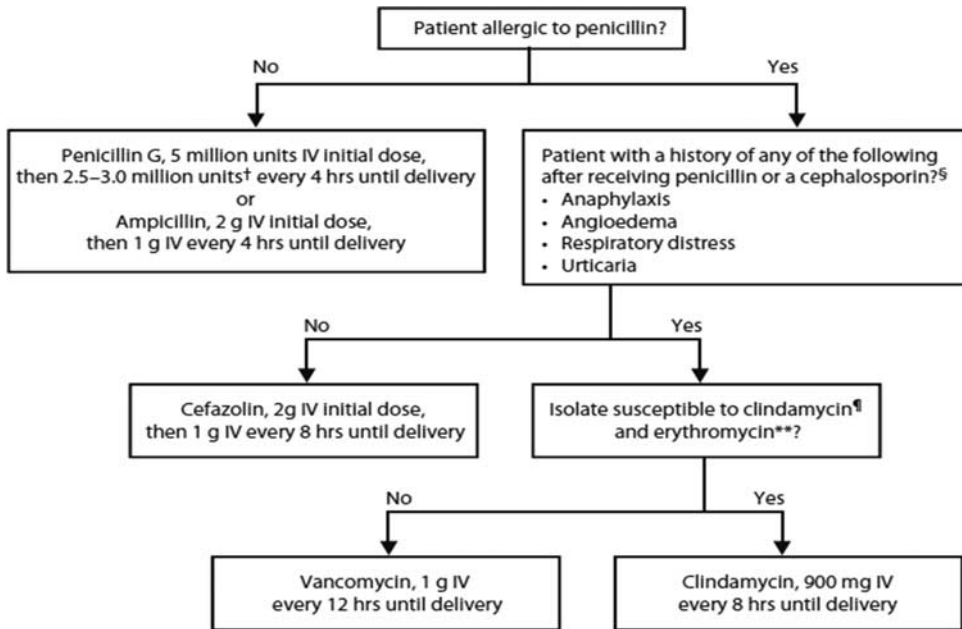


FIGURE 2. Algorithm from 2010 revision of the US Centers for Disease Control and Prevention's recommended regimens for intrapartum antibiotic prophylaxis for prevention of early-onset neonatal infections with group B streptococcus (GBS). †Doses ranging from 2.5 to 3.0 million units are acceptable for the doses administered every 4 hours following the initial dose. §These patients are considered to be at high risk for anaphylaxis and should not receive penicillin, ampicillin, or cefazolin for GBS intrapartum prophylaxis. ¶If no susceptibility testing was performed, or the results are not available at the time of labor, vancomycin is the preferred agent for GBS intrapartum prophylaxis for penicillin-allergic women at high risk for anaphylaxis. **Resistance to erythromycin is often but not always associated with clindamycin resistance. If an isolate is resistant to erythromycin, it might have inducible resistance to clindamycin, even if it appears susceptible to clindamycin. If a GBS isolate is susceptible to clindamycin, resistant to erythromycin, and testing for inducible clindamycin resistance has been performed and is negative (no inducible resistance), then clindamycin can be used for GBS intrapartum prophylaxis instead of vancomycin. IV indicates intravenously.

This lack of information is problematic given the noncompliant prescribing patterns noted earlier and referenced in the 2010 version of the CDC guidelines. Despite recommendations in the 2002 version of the guidelines, only 13.8% of penicillin-allergic women with a history of a mild penicillin allergy received cefazolin. Penicillin-allergic women were primarily given clindamycin (69.9% of those at low risk for anaphylaxis and 83.5% of those at high risk).⁹ Further, recommendations for antimicrobial susceptibility testing of prenatal

GBS isolates were not routinely followed before administration of clindamycin. A 2015 survey of 206 members of the ACOG sought to assess opinions and practice patterns involving GBS. For patients reporting a history of a mild penicillin allergy, respondents reported using cefazolin (51.2%; 95% CI, 44.1-58.3), clindamycin (36.3%; 95% CI, 29.7-43.4), vancomycin (7.5%; 95% CI, 4.2-12.0), and erythromycin (4.5%; 95% CI, 2.1-8.3) for IAP, despite CDC recommendation for cefazolin use in this clinical situation.

Interestingly, the authors noted that 94.3% of those reporting clindamycin use (95% CI, 86.0-98.4) stated that guideline compliance was important or somewhat important in deciding which agent to use.¹⁷

Evaluation of alternative agents for IAP in pregnant women with GBS colonization, including vancomycin, have demonstrated incomplete placental transfer where the resultant antimicrobial concentration is noted to be higher in the maternal than in the fetal/neonatal compartment. Typically used agents for women with no penicillin allergy or a mild penicillin allergy demonstrate complete placental transfer with rapid placental crossing and subsequent equilibration of antimicrobial concentration between maternal and fetal circulations.^{18,19}

A single small cohort study evaluated transplacental passage of vancomycin in 13 term, uninfected pregnant nonlaboring women undergoing scheduled cesarean delivery and noted incomplete transfer of vancomycin but reported levels in cord blood (range: 2.8 to 9.4 mcg/mL) following a 1 g infusion. All infants had cord blood concentrations of vancomycin above the GBS vancomycin minimum inhibitory concentration of 1 mcg/mL, which is the concentration of the agent that defines whether the bacterial species is susceptible or resistant to the drug. Following treatment with vancomycin at the recommended dosage, minimal inhibitory concentration was noted in the maternal serum within 30 minutes of infusion of the drug.¹⁸ Cord blood concentrations approached maternal serum concentrations 4 hours following the completion of the infusion, demonstrating an increased correlation of serum concentrations versus time.¹⁹

While penicillin-resistant and ampicillin-resistant GBS isolates have not been identified clinically, isolates with increasing minimal inhibitory concentrations have been documented both internationally and in the United States,⁹ indicating the potential for future resistance of GBS isolates to

standard agents for IAP. Further, selecting for resistant bacteria in the lower genital tract flora is a potential consequence of IAP. A single-center randomized trial obtained vaginal cultures from 352 women before and following treatment with ampicillin and penicillin administered as IAP and noted the presence of ampicillin-resistant *Enterobacteriaceae* and *Escherichia coli* isolates significantly more frequently following, compared to before, IAP. Notably, results in this trial were similar in the penicillin and ampicillin groups.²⁰

Vaccination

Despite great advances in reduction of early-onset neonatal GBS infections, widespread implementation of universal screening and IAP has not had a notable effect on late-onset GBS sepsis, which, while initially rarer than early-onset disease, now occurs at roughly similar rates.¹ This condition, for which there are not any prevention protocols in place, is multifactorial and not necessarily tied to the GBS status of the mother. Therefore, we infer that late-onset neonatal infections with GBS are due to horizontal, rather than vertical, transmission. Following late-onset GBS sepsis, as many as 50% of infants experience morbidity including neurocognitive and developmental delay. The rate of late-onset neonatal GBS infections has remained stable at 0.3 to 0.4 cases per 1000 live births for the past 20 years. A GBS vaccine is an antenatal intervention with the potential to reduce the burden of both early-onset and late-onset neonatal GBS infections, in addition to being of benefit in the reduction of invasive GBS infection in nonpregnant adults (albeit a less common pathogen in adults).⁴

The bacterium, GBS, has been subtyped into 10 serotypes on the basis of type-specific capsular polysaccharides. This capsular polysaccharide represents the major virulence factor, interfering with phagocytic clearance, with the majority of neonatal

GBS infection being attributable to 1 of 5 serotypes (Ia, Ib, II, III, and V). The goal of vaccine development has been to upregulate antibody production that could cross the placenta to provide protection against GBS infection by targeting specific capsular polysaccharides. The efficacy of these vaccines has been further augmented to increase immunogenicity by conjugating the polysaccharides to protein carriers, specifically tetanus toxoid. Additional efforts now involve the development of a multivalent conjugate vaccine to target more than a single serotype.

While there have been efforts focused on development of such a GBS vaccine for decades, limited studies are available demonstrating the efficacy of a GBS vaccine administered during pregnancy. One such report in 2003 described administration of a glycoconjugate generation vaccine at 30 to 32 weeks gestation that demonstrated functional activity against GBS in neonatal serum through 2 months of age. There is also an ongoing phase 2 clinical trial by the pharmaceutical company Novartis Vaccines to evaluate the tolerability and efficacy of a trivalent vaccine in pregnant women.⁴

Questions about vaccination that still need to be addressed include timing of administration and persistence of immunity following administration. Should vaccinations be given during pregnancy? Could they be given before childbearing? Would they need to be repeated during or before subsequent pregnancies? Vaccination administration during pregnancy would need to occur early enough to affect the ~30% of GBS infections that develop following premature births.

Summary

While GBS remains a notable cause of neonatal morbidity and mortality, rates of early-onset GBS infection have declined due to the widespread implementation of prenatal screening for maternal GBS colonization and administration of IAP to colonized women. Despite this success, there remain

areas for improvement, as research has demonstrated that adherence to recommendations for antimicrobial selection is not uniform. In addition, with greater utilization of penicillin skin testing, the need for/use of alternative antibiotics might be reduced. Further innovations in the assessment of pregnant patients for GBS colonization, including NAAT, may ultimately reduce puerperal infection rates. The limitation of current point-of-care technology remains that antibiotic susceptibility testing is not possible, thus making antepartum culture the continued test of choice, which limits screening in those with either limited prenatal care or delivery prior to the gestational age at which routine antenatal GBS screening occurs. Vaccine development has the potential to change the paradigm for prevention of GBS infections in the neonate, but further research in this area is still needed.

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