Prevention of Early-onset Neonatal Group B Streptococcal Disease

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Streptococcus agalactiae, also known as Group B *Streptococcus* (GBS), is an opportunistic pathogen that colonizes the gastrointestinal and genitourinary tracts of up to 50% of healthy adults and newborns; it is responsible for significant morbidity and mortality. Early detection can be used to establish the use of antibiotic prophylaxis to significantly reduce neonatal sepsis. This article reviews methods of detection and prevention of GBS infection in the neonate.

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KEY WORDS

Streptococcus • Neonatal sepsis • Prevention

Streptococcus agalactiae, also known as Group B *Streptococcus* (GBS), is a β-hemolytic Gram-positive streptococcus and an opportunistic pathogen that colonizes the gastrointestinal and genitourinary tracts of up to 50% of healthy adults[1,2] and newborns; it is responsible for significant morbidity in pregnant women and mortality in the immunocompromised.[3-5]

GBS infection produces two different clinical presentations: early-onset neonatal sepsis (EONS) and late-onset neonatal sepsis (LONS) (Table 1). In the 1970s, prevalence of EONS disease was 2 in 1000 live births, with a mortality rate of 50%.[6] Implementation of different antibiotic prophylactic policies during labor led to a reduction in incidence of 65% by the 1990s, from 1.7 to 0.6 in 1000 live births.[7] In recent years this number has continued to decrease, reaching figures of 0.30 and 0.39 per 1000 live births in the United States and United Kingdom, respectively.[8,9] It has been suggested,

TABLE 1

Clinical Comparison Between Early- and Late-onset Neonatal Sepsis

	Early-onset Neonatal Sepsis	Late-onset Neonatal Sepsis
Time of presentation	Within 24 hours of birth (range, to day 6 of life)	4-5 weeks of age (range, 7-89 days)
Clinical manifestations	Generalized sepsis, pneumonia, meningitis	Bacteremia without focus, meningitis, focal infection (septic arthritis, osteomyelitis, pneumonia, cellulitis, adenitis)
Profound shock	Likely	Less likely
Seizures in meningitis	Not likely	Likely

however, that the incidence could be higher than reported, given that the requirements for positive cultures in blood or cerebrospinal fluid can underestimate the real burden of the disease.[10] In developing countries, this pathology affects 2 to 4 per 1000 live births, and the incidence in centers without prevention protocols could reach up to 3.5 per 1000 live newborns, with a mortality rate near 15%.[11]

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Colonization during pregnancy is associated with miscarriage, premature labor, chorioamnionitis, and premature prelabor membrane rupture.[12] In the newborn, GBS produces EONS in the first week of life with a mortality rate of 10% to 15%[7] as a consequence of GBS exposure during labor,[4,13] and fetal aspiration of GBS contaminated amniotic fluid due to an ascendant infection from the maternal urogenital tract. By inhaling amniotic fluid the respiratory tract is colonized,[14] causing pneumonia and septicemia with the consequential dissemination to different organs.[15] When the infection is acquired later (LONS, at 70-90 days of life), the most frequent manifestation is meningitis and sepsis, causing permanent neurologic sequelae in 50% of patients that survive the infection, with an associated mortality rate of 2% to 6%.[4,7,14-16]

Microbiology

GBS is a Gram-positive, facultative coccus anaerobic bacterium associated in chains or pairs, unlike other Gram-positive cocci. It is also catalase-free, β-hemolytic, and very demanding in its requirement for growth. Its hemolysis is due to the action of two enzymes: streptolysin O and streptolysin S. These enzymes remain stable in the presence of oxygen and their production is induced by serum. GBS does not produce gas as a product of fermentation,[17] it does not form spores, and it has no capsule. It may remain viable for some hours at room temperature in the presence of organic material, although it survives longer at refrigeration temperatures (0°-4°C). It is vulnerable to iodine tincture, phenols, cresol, and mercury dichloride, and when exposed to temperatures $> 60°C$ for 30 to 60 minutes.[18]

The identification of different species of *Streptococci* is done based on serologic properties of Lancefield groups (A-H, K-M, O-V) and their hemolytic patterns. GBS belongs to Group B of this classification and is further subdivided into nine serotypes (Ia, Ib, II, III, IV, V, VI, VII, and VIII) based on the composition of the capsular polysaccharides.[18] In the United States and Europe the most prevalent serotypes in human infections are Ia, II, III, and V[13,19,20]; in Japan they are VI and VIII. In Latin American countries such as Chile, the most prevalent serotype in human infection is III.[21,22]

In addition to the capsular polysaccharides, different proteins with immunogenicity are immersed in the membrane, which are expressed variably in different serotypes. GBS has several virulence factors, such as production of hemagglutinin adhesin (hyaluronidase), which destroys the extracellular matrix to allow the advancement of the bacteria to other body cells, hemolytic toxins, deoxyribonuclease, proteases, neuraminidases, and glutamine synthetase.[16,18]

Streptococcus agalactiae is a ubiquitous bacterium, and therefore is widely distributed in the

environment; GBS infections in pregnancy have been described in women of all races and in all geographic areas in which they have been studied.[23] In humans, this bacterium is found as a reservoir in the gastrointestinal tract, colonizing the genitourinary tract of sexually active women.[24] Subsequently, these women convert into asymptomatic carriers, either chronic or intermittent, depending on several variables, including sex, age, socioeconomic status, diet, and intrauterine device use, among others.[14] Acquisition or recolonization is common in sexually active women.[25] GBS can be found in both sexes as flora in the urethra, rectum, and pharynx[16]; positive GBS cultures have been identified in 50% of male partners of women who are colonized.[14] The rates of maternal carriage of GBS reported in the literature vary, probably related to the use of suboptimal detection techniques.[23] Maternal colonization rates of up to 25% are reported in the United States and United Kingdom,[26] and rates of up to 20% are reported in Chile.[10,27] The highest colonization rates are obtained when performing bacterial cultures from the vaginal and perianal regions simultaneously, and using selective culture media (Todd Hewitt broth) that allow bacterial recovery between 14% and 38%.[10,28]

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Clinical Management for Prevention of Neonatal GBS Disease

Some clinical trials in the 1980s showed that early neonatal sepsis could be prevented by antibiotic prophylaxis during labor in women who are colonized at delivery.[29] This led the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics to establish policies for the prevention of early neonatal sepsis in 1992, which has allowed the decrease of the prevalence of this disease by 80% in the past 20 years.[30,31] During the 1990s, patients eligible to receive intrapartum chemoprophylaxis were identified through the use of rectovaginal detection methods for the presence of GBS between 35 and 37 weeks of gestation or by screening for the presence of risk factors. Screening included the use of antibiotics in all patients with a history of preterm birth, history of a previous child with GBS sepsis, GBS bacteriuria in the current pregnancy, premature rupture of membranes $>$ 18 hours, or intrapartum fever. Antibiotic prophylaxis based on risk factors resulted in a 68% fall in the incidence of GBS neonatal sepsis. However, when a culture-based protocol was used, this reduction was 89%. This, added to the fact that up to 65% of early neonatal sepsis is not associated with any risk factors,[32] led the Centers for Disease Control and Prevention (CDC) to change their clinical management guidelines in 2002, promoting a new approach that consisted of universal screening for GBS at 35 to 37 weeks of gestation with antibiotic prophylaxis in pregnant women who presented with a positive culture.[25,27,28,33] This prevention strategy has been recently reviewed by the CDC, and has remained essentially unchanged.[34]

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Methods for Detection of GBS

To determine asymptomatic perineal presence of GBS in pregnant women between 35 and 37 weeks of gestation, a culture is obtained using a swab of the vaginal and anal region, which is grown in Todd Hewitt broth supplemented with nalidixic acid and gentamicin to increase sensitivity by eliminating Gram-negative agents. After 24 hours, it is regrown on blood agar. The vaginal culture alone has a sensitivity that is 40% lower than that of the rectovaginal sample. The same applies if a universal culture is performed instead of using a selective culture medium. The sensitivity and specificity of a rectovaginal culture at 36 weeks of gestation to predict colonization at birth is 91% and 89%, respectively, compared with culture at $\geq$ 6 weeks before delivery, which has a sensitivity of 43% and a specificity of 85%.[25] Despite this high sensitivity and specificity, growing a culture at 35 to 37 weeks of gestation has several drawbacks. Premature births are missed; although these correspond to only 7% to 11% of all births, they have a higher risk for serious neonatal infection by neonatal GBS and represent 32% to 38% of GBS EONS.[35] However, 61.4% of term infants with neonatal GBS disease had mothers who tested negative for GBS.[36] These false-negative results can be explained by maternal recolonization after performing cultivation, poor sampling technique, or mishandling of the sample.[23] In addition, the rate of screening for GBS in the pregnant population is variable, reaching 85% to 99%[36] in American populations; rates are much lower in developing countries,[10] with variables depending on

TABLE 2

Different Methods of Group B *Streptococcus* Diagnosis

	Sensitivity (%)	Specificity (%)	Sample
Rectovaginal culture	91	89	35-37 weeks of gestation
Polymerase chain reaction	87-97	85	Labor time admission
Immunoassay	90	—	35-37 weeks of gestation

the hospital setting. When the culture is not performed, an antibiotic is administered in labor depending on the presence of the risk factors mentioned above, decreasing the effectiveness of prophylaxis and increasing the number of patients who are treated unnecessarily. This unnecessary antibiotic prophylaxis has disadvantages for mother and child, such as the risks of anaphylaxis, medicalization in childbirth and the neonatal period, and the production of antibiotic-resistant strains.[37] The disparity seen in the implementation of the CDC protocol may be due to (1) cost of culture; (2) need for qualified laboratory technicians; (3) the fact that testing between 35 and 37 weeks of gestation requires patients to visit a clinic setting at this stage of pregnancy, which is not always possible due to the existence of poorly controlled pregnancies, premature births, and the limited access of patients from rural areas to clinical facilities; and (4) a lack of awareness among professionals in charge of antenatal care, with respect to the importance of the patient reaching delivery with GBS detection.

The use of GBS screening and treatment is not innocuous, and thus, not completely accepted. In the United Kingdom, the guidelines of prevention of EONS GBS disease published in 2003 did not recommend routine screening for antenatal GBS carriage. They found that the incidence of EONS without screening or intrapartum antibiotic (0.5/1000 births) did not differ from the incidence seen in the United States after systematic screening and intrapartum antibiotic prophylaxis, despite comparable vaginal carriage rates. The Royal College of Obstetricians and Gynaecologists argued that there are no randomized, controlled trials comparing incidence of GBS neonatal sepsis with or without antenatal screening.[38] No study has yet been able to demonstrate that screening for GBS has any impact on neonatal sepsis as a whole. On the other hand, there are also possible risks associated with intrapartum penicillin prophylaxis. Severe anaphylaxis has been estimated to occur in as many as 1 in 10,000 women treated, and the incidence of fatal anaphylaxis has been estimated at 1 in 100,000 women treated.[38]

To overcome the difficulties of screening, as in cases of preterm labor, premature rupture of membranes, or patients in labor at term without previous cultures, rapid diagnostic tests have been developed for assessing carriage of GBS without the need to make cultures. In some studies the use of immunoassays has shown a sensitivity $>$ 90% in patients with a high presence of GBS, but this sensitivity decreases in patients without a high bacterial load (which can also cause neonatal sepsis).[39] The use of real-time polymerase chain reaction (PCR) is currently being evaluated for timely diagnosis of GBS in pregnant women, with a sensitivity of 87% to 97% and a specificity of 95% (Table 2).[5,25,40,41] Current studies have evaluated the effectiveness of PCR for detection of GBS, demonstrating that this technique can be highly sensitive and specific.[42] However, the major limitation for PCR is its high cost, which limits its widespread use, with a consequent inadequate coverage of the pregnant population. For a quick diagnostic test to be very useful, it would have to be performed on admission in labor, have a sensitivity and specificity comparable with the current standard (culture), and allow one to obtain information quickly enough to make an accurate and timely clinical decision at low cost. So far, the lack of a GBS test that meets these characteristics has been an impediment to the widespread use of rapid diagnostic techniques.[43] Immunoassays and PCR partly meet these characteristics, which transforms them into potential candidates for achieving this goal. However, before their

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application in clinical practice, technologic development is needed to improve their sensitivity and specificity (in the case of immunoassays) and lower their cost (in the case of PCR).[37]

Another way to address the problem would be the development of vaccines for GBS. In theory, this would allow prevention of GBS, obviating the need for screening with intrapartum treatment. Current research is oriented to the development of specific vaccines without adverse reactions that are affordable for everyone. Unfortunately, there is still no vaccine that meets all these requirements, and screening for GBS probably cannot be replaced in the near future.[39,44,45]

Conclusions

GBS colonization is a frequent finding during pregnancy. The importance of its detection resides in the possibility that a pregnant carrier has to infect the newborn during delivery, resulting in EONS or LONS, a disease that is associated with a high mortality rate. Early detection can be used to establish the use of antibiotic prophylaxis, to significantly reduce neonatal sepsis. The problem is that today the gold standard in screening is rectovaginal culture at 35 to 37 gestational weeks, which, despite having acceptable specificity and sensitivity, still produces false-negative results, mainly due to the time when the culture is taken. There is a need, therefore, to develop new tools with which to diagnose intrapartum GBS that would allow a decrease in unnecessary treatment and an increase in the coverage of the pregnant population. ■

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MAIN POINTS

- *Streptococcus agalactiae*, also known as Group B Streptococcus (GBS), is an opportunistic pathogen that colonizes the gastrointestinal and genitourinary tracts of up to 50% of healthy adults and newborns, and is responsible for significant morbidity and mortality.
- In the newborn, early-onset disease as a consequence of GBS exposure during labor carries a mortality rate of 10% to 15%. When the infection is acquired between 70 and 90 days of life, the most frequent manifestation is meningitis and sepsis, causing permanent neurologic sequelae in 50% of patients that survive the infection.
- Early clinical trials showed that early neonatal sepsis could be prevented by antibiotic prophylaxis during labor in women who are colonized at delivery. More recently, patients eligible to receive intrapartum chemoprophylaxis were identified through the use of rectovaginal detection methods for the presence of GBS between 35 and 37 weeks of gestation or by screening for the presence of risk factors. Antibiotic prophylaxis based on risk factors alone resulted in a 68% fall in the incidence of GBS neonatal sepsis; however, when a culture-based protocol was used, this reduction was 89%.
- The sensitivity and specificity of a rectovaginal culture at 36 weeks of gestation to predict colonization at birth is 91% and 89%, respectively. Current studies have evaluated the effectiveness of polymerase chain reaction (PCR) for detection of GBS, demonstrating that this technique can be highly sensitive and specific. However, the primary limitation for PCR is its high cost, which limits its widespread use.
- Removing the need for screening altogether through the administration of a vaccine would allow prevention of GBS, obviating the need for screening with intrapartum treatment, which carries inherent risks. Current research is oriented toward the development of specific vaccines without adverse reactions.

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