Group B Streptococcal Disease in the Newborn – Maternal Screening Methods and Antimicrobial Prophylaxis

a report by

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In industrialised countries, Group B streptococci (*Streptococcus agalactiae*, GBS) have been a leading cause of morbidity and mortality among newborns for more than 30 years. Resulting in pneumonia, sepsis and meningitis, GBS affects 0.5 to three of every 1,000 live births in different populations.[1–6] Over 80% of cases occur in the first six days after birth – early-onset disease (EOD) – and of these most occur within 12–24 hours of birth.[3,7] EOD is typically related to maternal carriage of GBS in the genital tract, with vertical transmission occurring prior to or during labour and delivery. A second peak of disease incidence occurs around one month after birth – late-onset disease (LOD) – and accounts for the remaining 20% of cases.[2] In LOD, GBS is acquired peri-natally, nosocomially or from community sources. GBS is also an important cause of maternal illness, a well-recognised cause of stillbirth and a risk factor for pre-term delivery, although its prevalence in these areas is more difficult to quantify.[10]

During the past decade, major initiatives have been proposed to prevent EOGBS disease. The main goal of preventative strategies is to reduce or eliminate transmission of GBS to the infant by giving antibiotics to GBS-colonised women during delivery. As in the US, prevention strategies have been implemented in various European countries,[11,12] and the overall incidence of EOGBS infection has progressively dropped in line with the adoption of specific policies for intra-partum antimicrobial prophylaxis (IAP).[3,7,10,13] However, despite the considerable effort and economic resources spent on IAP for EOGBS disease, cases continue to occur.

This article reviews the evolution to screening-based strategies and the different options available to improve GBS screening.

Epidemiology and Transmission

GBS are Gram-positive bacteria commonly present in the gastrointestinal and genital tracts.[14] Among pregnant women, GBS carriage rate in the vaginal and rectal flora ranges from 7 to 37%.[2,8,15,16] This colonisation can be intermittent, transient or persistent. At birth, 40–60% of neonates born to a GBS carrier are colonised. Fortunately, the attack rate of EOGBS disease among colonised infants is low, with only 1–3% becoming infected.[3,12,17,18] Additional factors that increase the risk of infection include:

- prolonged interval (18 hours or more) between rupture of membranes and delivery;
- pre-term labour or pre-term rupture of membranes at less than 37 weeks of gestation;
- GBS bacteriuria at any time during pregnancy;
- having had a previous infant with invasive GBS infection; or
- intra-partum maternal temperature of 38.0°C or greater.[17–22]

In the last decade, the overall case fatality rate has fallen under 10%; however, among pre-term affected neonates it remains substantially higher, at 20–30%. GBS meningitis leaves one-third of those infected with adverse long-term neurodevelopmental outcomes.[2,3,10,23]

Evolution of Guidelines for Prevention

As infants with GBS disease are already septicaemic at birth, limiting the opportunity for timely interventions, the focus for reducing the burden of GBS disease lies in disease prevention rather than treatment. In the late 1980s, clinical trials demonstrated that appropriate intravenous intra-partum treatment of GBS-colonised women using penicillin or ampicillin resulted in reduced rates of neonatal colonisation and sepsis.[1,7,24–26] Despite the availability of this effective intervention, the challenge was to agree on a strategy for identifying candidates for IAP. Different strategies based on the presence of risk factors associated with increased risk of EOGBS disease, GBS-positive late antenatal cultures or combinations of the two were then recommended to identify women at risk of delivering a GBS-infected infant.[27] Surveillance studies documented a decline of over 70% in EOGBS disease in the 1990s, which coincided with increased use of IAP. During the same period, invasive GBS disease among pregnant women declined by 20%.[10,25,26]

However, in 2002 a large systematic review showed that, although the risk factor approach is the less expensive option, universal GBS screening at 35–37 weeks of gestation and treating all colonised women during labour is more than 50% more effective.[25] Therefore, in 2002 the US Centers for Disease Control and Prevention (CDC), referring to these findings, issued revised guidelines recommending universal late antenatal GBS screening at 35–37 weeks of gestation and intra-partum prophylaxis for women with GBS colonisation, the risk factor approach being reserved for cases in which maternal GBS status is unknown at presentation for delivery.[4] These recommendations have been endorsed by the American College of

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Obstetrics and Gynecology[22] and the American Academy of Pediatrics. Since the end of the 1990s, as in the US, in several European countries different protocols have been recommended and implemented for the prevention of peri-natal GBS disease.[11,12,28–30] In several European countries the recommendations are very similar to those of the CDC,[11,12] while in others the risk factor approach is still a recommended alternative.[31–33]

In part due to the increased use of antibiotics and concerns that β-lactam resistance may emerge in GBS or other important pathogens in neonates, IAP is considered as an interim strategy for the prevention of EOGBS disease.[4,12,34] A practical alternative and desirable approach might be immunoprophylaxis. GBS vaccines hold great promise for disease prevention as they may prevent all GBS-associated diseases, including EOGBS disease but also LOGBS disease, spontaneous abortion, stillbirth and maternal bacteraemia. Vaccination of women before or during pregnancy is likely to be the most durable and cost-effective approach of all, and would avoid the issues around screening and antibiotic use. Today, although the use of GBS vaccines has yielded promising results, it remains an investigational approach.[19,35]

Recommended Guidelines

Guidelines recommended by the CDC and some European countries, such as Spain and Belgium, are very similar in terms of their main features and are based around IAP and antenatal GBS screening culture. Indications and regimens for IAP are summarised in *Table 1* and *Figure 1*. Further details, other conditions and clinical management of infants at risk of EOGBS disease are given and proposed in the full text of these guidelines.[4,11,12]

Limitations in the Era of Intra-partum Antimicrobial Prophylaxis

Widespread implementation of IAP in pregnant women colonised with GBS has been shown to be successful at reducing the rate of EOGBS sepsis and meningitis in neonates, yet GBS continues to be a major cause of life-threatening infections in newborns and cases continue to occur despite routine screening, leading to significant morbidity and mortality. Several aspects of antenatal and peri-natal clinical practice – including insufficient pre-natal care, inaccurate GBS screening, deficits in the communication of GBS screening results, improper implementation of IAP or microbiologic factors such as antibiotic resistance – may all contribute to the ongoing problem. However, studies have indicated that the majority of continued EOGBS disease in term infants occurs in those delivered to mothers screened negative for GBS colonisation.[36] Whether these negative cultures were false-negative results or whether the mothers acquired GBS in the interval between the screening culture and the time of delivery is unknown. Furthermore, it is possible that negative GBS screens provide a false sense of reassurance to obstetrical providers. Improving microbiologic procedures for screening should contribute to further decreasing the incidence of EOGBS disease.

Group B Streptococci Screening

Selective Cultures

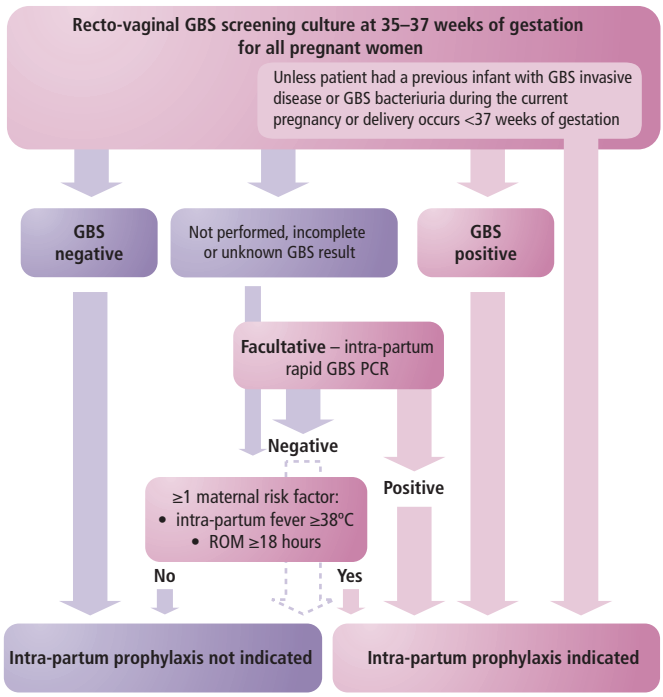
Culture techniques that maximise the likelihood of GBS recovery are required for pre-natal screening. Important factors that influence the accuracy of detection of GBS maternal colonisation are the choice of culture media, the body sites sampled and the timing of the sample.[17] The yield of GBS-positive culture is increased by sampling the anorectum in addition to the lower vaginal area, because the gastrointestinal tract is a major reservoir of GBS.[15] This can be performed using a single swab or two different swabs. After collection, swabs must be placed in a non-nutrient transport medium such as Amies or Stuart. The use of a selective broth medium that inhibits the growth of competing organisms, Gram-negative enteric bacilli and other normal flora significantly increases the yield of GBS culture and is recommended.[4,12,15] The most widely used selective medium is Todd-Hewitt broth, with gentamicin or colistin and nalidixic acid (LIM broth) further sub-cultured on blood agar plate. However,

Table 1: Recommended Regimens for Intra-partum Antimicrobial Prophylaxis for the Prevention of Peri-natal Group B Streptococcal Disease

Recommended	**Penicillin G**, 5 million units IV initial dose, then 2.5 million units IV every 4 hours until delivery
Alternative	Ampicillin, 2g IV initial dose, then 1g IV every 8 hours until delivery
If allergic to penicillin:	
Patients not at high risk of anaphylaxis	Cefazolin, 2g IV initial dose, then 1g IV every 8 hours until delivery
Patients at high risk of anaphylaxis	
• GBS susceptible to clindamycin and erythromycin	Clindamycin, 900mg IV every 8 hours until delivery or eythromycin, 500mg IV every 6 hours until delivery
• GBS resistant to clindamycin and erythromycin	Vancomycin, 1g IV every 12 hours until delivery

GBS = group B streptococci; IV = intravenous.
Adapted from revised CDC guidelines, 2002.[4]

Figure 1: Indications for Intra-partum Antibiotic Prophylaxis to Prevent Peri-natal Group B Streptococcal Disease Under a Universal Pre-natal Strategy



GBS = group B streptococcus; PCR = polymerase chain reaction.
Adapted from revised CDC guidelines, 2002[4] and the Belgian guidelines.[12]

this enrichment broth is not totally selective for GBS, and other Gram-positive cocci may also be enriched by this method, possibly leading to false-negative results.

For this reason, the use of selective and differential media for sub-cultures can improve screening sensitivity as well as shortening the turnaround time: for example, Belgian guidelines recommend the use of such media for antenatal GBS screening cultures.[12] Several options are now available. Granada agar, a modified Islam agar also known in the US as Carrot medium, was the first and most widely used medium in Spain and Belgium. On Granada agar, β-haemolytic strains of GBS produce orange colonies that are clearly differentiated from the background flora. For recto-vaginal cultures, the sensitivity of Granada agar for the detection of GBS is superior to that of blood agar. Easy to read and with 100% specificity, workload and turnaround time are reduced. Recently, two selective and differential chromogenic media have been launched: Strepto B ID (bioMérieux, France) in 2006 and Strep B Select (Biorad, France) in 2007. Compared with the recommended culture, these new chromogenic media significantly increased the sensitivity of GBS screening and can also replace the currently recommended blood agar.[37]

> Important factors that influence the accuracy of detection of group B streptococci maternal colonisation are the choice of culture media, the body sites sampled and the timing of the sample.

The optimal time for performing antenatal cultures is between 35 and 37 weeks of gestation.[38] However, as GBS carriage is highly variable, GBS antenatal cultures are not always good predictors of maternal GBS status at presentation for delivery.[39,40] Another true limitation of culture is the turnaround time, with 24–72 hours required before results can be issued, making it impractical when the patient presents in labour. In addition, even with ideal sampling and culture procedures, maternal factors such as use of oral antibiotics or a variety of feminine hygiene products before specimen collection can lead to failure to culture GBS.

Rapid Diagnostic Tests

A potential alternative to antenatal GBS screening culture is the identification of GBS colonisation at presentation for delivery. Using a reliable, sensitive, easy-to-use, rapid test should be cost-effective, and should lead to the prevention of more EOGBS cases while reducing the number of women receiving unnecessary IAP. In order for an intra-partum screening strategy to be successful, the turnaround time – from sample to result – should not exceed one hour, allowing timely and targeted IAP to be administered to a larger proportion of GBS-positive screened women. Such tests should be available 24 hours a day, seven days a week.

Antigenic and Hybridisation-based Tests

Rapid diagnostic tests based on identification of the GBS group-specific antigen from swab specimens using latex agglutination, enzyme-linked immunosorbent or optical immuno-technology or DNA hybridisation have been developed for intra-partum GBS screening. Although these techniques have good specificity (95%), they tend to have low sensitivity (33–65%), which is improved only in cases of heavy colonisation. Therefore, a negative test cannot rule out GBS colonisation.[41,42] In 2003, the Belgian guidelines[12] recommended the Strep B OIA (ThermoBiostar, US), the best rapid antigenic test available,[43] as an optional alternative for women presenting for delivery with no antenatal culture result, with a positive test result being considered as an indication for IAP.

Polymerase Chain Reaction-based Tests

Advances in polymerase chain reaction (PCR) and fluorescence labelling technologies have provided new detection platforms for bacterial identification.[44] Recent data suggest that realtime PCR-based tests such as the BD GeneOhm™ StrepB Assay (Becton Dickinson, US) or the Xpert™ GBS test (Cepheid, US) can equal or surpass the sensitivity of antenatal culture at 35–37 weeks of gestation; such tests also compare favourably with standard peri-natal culture methods for the detection of GBS colonisation at presentation for delivery (intra-partum).[16,45] Therefore, the commercialisation of rapid detection of GBS through realtime PCR offers the potential for GBS detection among women without pre-natal care or among those in whom no antenatal culture was collected.

The IDI Strep B test, now the BD GeneOhm StrepB Assay, was the first realtime PCR test for GBS detection cleared by the US Food and Drug Administration (FDA); it received approval in 2003. This assay specifically detects GBS DNA directly from a vaginal–rectal swab, with specimen preparation, analysis and results taking 30–45 minutes.[16] The test has to be performed in a specialised PCR laboratory and is therefore dependent on laboratory opening hours, and the turnaround time from patient to result availability for practical reasons generally exceeds 24 hours. A later generation of this test – the Xpert GBS – is characterised by an extremely low workload (two minutes' hands-on time), is highly sensitive and was cleared by the FDA in 2006. This realtime PCR assay is simple enough for even inexperienced technicians to perform, but use of this relatively new and more expensive technology is not yet widespread among European hospitals.[47]

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It has already been suggested that the cost-effectiveness of a PCR test performed in less than one hour at time of delivery would be superior to that of the recommended antenatal screening-based approach;[48] however, further studies are needed. Studies evaluating the cost and benefits of IAP based on these new rapid PCR testing methods during labour are ongoing in North American and European hospitals. A desired evolution of these tests would be the combined detection of

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resistance to clindamycin and macrolides, which is necessary for the choice of the appropriate IAP for penicillin-allergic women at high risk of anaphylaxis.

> The use of selective differential media can improve antenatal culture sensitivity and has been recommended in some European countries, such as Spain and Belgium.

Conclusion

In the setting of a maternal GBS screening programme, efforts to improve screening for GBS status remain important. Correct laboratory processing of culture specimens plays a critical role in successful implementation of any screening policy. The use of selective differential media can improve antenatal culture sensitivity and has been recommended in some European countries, such as Spain and Belgium. Despite efforts related to sampling and culture procedures, false-negative GBS screening results contribute to continuing EOGBS cases, while false-positive screening results lead to unnecessary IAP. Rapid GBS tests have been developed: antigenic tests are not sensitive enough to replace antenatal screening cultures, but realtime PCR tests have fared better in the detection of GBS; the latter could improve the effectiveness of the screening-based strategy and lead to a further reduction of the incidence of EOGBS disease. However, questions of costs and logistics remain unanswered at this time.

Could such rapid intra-partum tests replace existing screening strategies, or could they be used in conjunction with them? A key issue when addressing these questions relates to the accuracy with which the rapid test not only identifies mothers with GBS colonisation, but also detects antimicrobial resistance to GBS in specimens from penicillin-allergic women at high risk of anaphylaxis. ■

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