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ON DEMAND

report

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by Cepheid

Group B Streptococcal Neonatal Disease:
Mission Accomplished??

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ON DEMAND report

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Cepheid's ON DEMAND Report is distributed four times a year. We welcome communication from users of Cepheid systems and tests and invite suggestions for articles in future issues. Send correspondence to:
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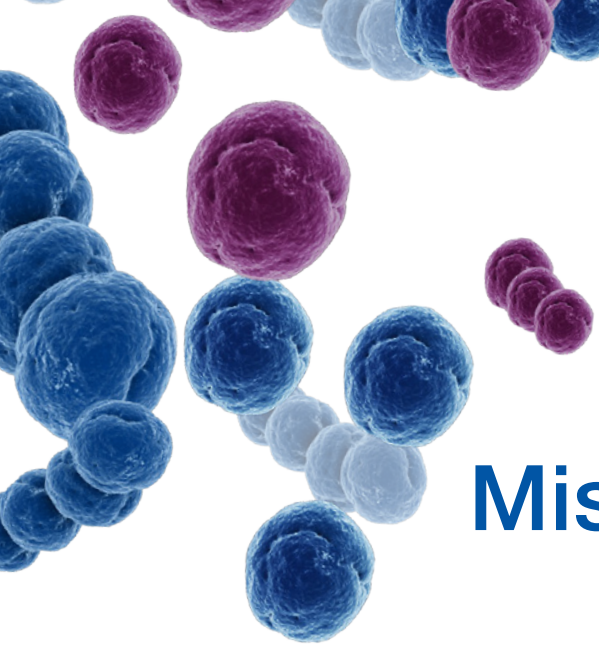
David Persing M.D., Ph.D.

Chief Medical and Technology Officer, Cepheid

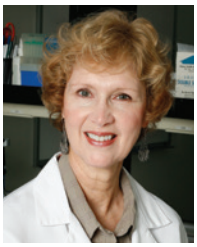
From the Editor

In this issue of On Demand, Dr. Ellen Jo Baron provides a comprehensive summary of the public health challenge posed by Group B Streptococcus (GBS) and the "Test and Treat" strategies that have been highly effective in interrupting transmission of this pathogen. Cepheid is pleased to be able to offer comprehensive GBS testing options for the antepartum and intrapartum setting; our most recently cleared GBS testing option, Xpert® GBS LB, combines ease of use with superior sensitivity. We think you will find this issue to be highly informative.

David H Persing



Group B Streptococcal Neonatal Disease: **Mission Accomplished??**



Ellen Jo Baron Ph.D., D(ABMM)

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Testing pregnant women for their group B streptococcal (GBS) colonization status was not a widespread practice in U.S. clinical microbiology laboratories, even after the Centers for Disease Control and Prevention published their initial draft guidelines in 1994 and recommendations in 1996.[12] Since seminal publications appeared in the 1970's, it was known that early onset GBS disease (EOGBSD) was acquired by the neonate either right before delivery or as it passed through the colonized birth canal.[6] As recently as 1972, 2 infants per 1000 live births were affected and there were 12,000 cases per year in the U.S. The fatality rate among infected infants was 50%. In fact, when I first arrived in Palo Alto to direct the clinical microbiology laboratories at Stanford in 1997, the Department of Obstetrics and Gynecology was still relying on risk-based prophylaxis for women arriving in labor rather than antenatal cultures, in contrast to the community laboratories for which I had been consulting in southern California.

In the risk-based scenario, antepartum screening for GBS colonization by vaginal/anal swab enriched culture at 35–37 weeks of gestation was optional. The second equally acceptable approach at that time, as practiced at Stanford and published in the MMWR recommendation of 1996,[12] indicated that women in labor should be given intrapartum antibiotic prophylaxis (IAP) if they had premature rupture of membranes (PROM) before 37 weeks of gestation, premature rupture of membranes lasting >18 hours, or temperature ≥38 °C. The term PROM is used when membranes rupture spontaneously at least 12 hours before uterine contractions begin, allowing the organisms colonizing the vagina plenty of time to move up into the birth canal and even into the remaining amniotic fluid surrounding the fetus. In addition, women who had previously delivered a baby who developed GBS disease, or who had "bacteriuria" with GBS, were also to be treated with intrapartum penicillin. These measures, by all accounts, appeared to be working very well. The National Health Objective of 0.5 EOGBS cases per 1000 live births was met in 1998, although the original expected date of meeting the goal had been at least a decade in the future.

Since then, we have learned a lot about identifying which women pose a risk to their babies. First of all, the most recent CDC recommendations[38] now define the relative amount of GBS in the mother's urine that contributes to a higher risk of acquisition by the neonate: it is 10,000 cfu/mL (Figure 1). This is good news for laboratories, who previously were either bound to subculture and rule out GBS for every suspicious colony on every urine culture from a woman of childbearing age, since laboratories cannot count on physicians relaying the information that their patient is pregnant, or face the prospect of a malpractice accusation if a urine culture from their laboratory was reported as "mixed gram-positive flora," and the patient gave birth to a baby who developed EOGBSD. Malpractice awards can be astronomically high, given that the healthcare costs for one injured baby are easily in

FIGURE 1. Urine culture from a pregnant woman yielding pure GBS in >10,000 cfu/ml, considered to be a risk factor for GBSEOD in the baby.

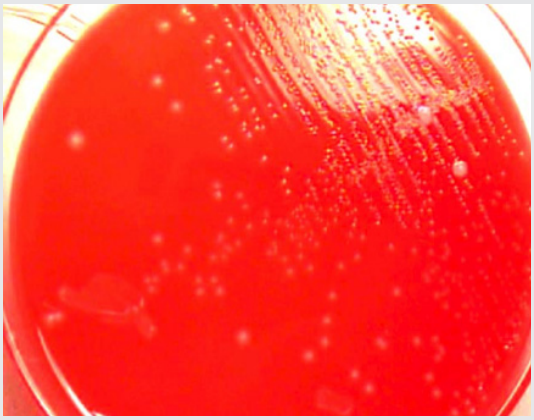


FIGURE 2. Arrow-shaped zone of enhanced hemolysis where enzymes from *S. aureus* (vertically streaked down the center of the sheep blood agar plate) and GBS (streaked horizontally to almost touch the staphylococcal inoculum line) synergistically lyse red blood cell membranes.

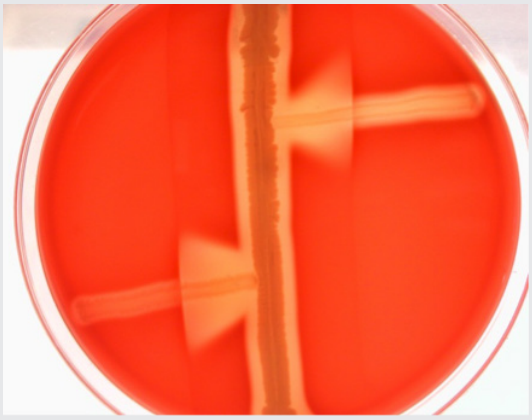


FIGURE 3. GBS D-test assay for inducible resistance to clindamycin. In this case, the organism is not resistant to clindamycin or erythromycin.

the millions over her lifetime. A parent often must stop working to care for the child, and other collateral damage to the family's well-being is not uncommon. A jury decision on one GBS case posted recently (accessed 2/13/13) online was $29 million.[A]

We also know now that lower vaginal secretions are more sensitive for detecting colonization than are samples collected from the endocervix.[11] In fact, because the natural habitat of the organism is actually in the gastrointestinal tract and it seems to migrate to the vagina only intermittently, we now know that collecting both vaginal and rectal swabs is necessary to detect all carriers.[4] Vaginal swabs alone will miss 52% % of colonized women and rectal swabs alone will miss another 11%.[16] One more important finding, however, is that based on enriched culture methods, a number of studies have shown that as many as 10% of women whose antenatal (35–37 weeks) screening results were negative will have become positive for GBS vaginal carriage at the time of delivery.[7,20,36] Without a test at the time of delivery, those women go untreated, so currently they are the cohort from which the most EOGBS babies are born.[30]

How does the neonate acquire the organism? It is thought that entry into the baby's system often occurs when the fetus is still in the uterus. The organisms traverse the membranes of the chorioamnion, begin to multiply in the amniotic fluid, and the baby aspirates this infected fluid, from which the organisms cause pneumonia, sepsis, and meningitis. Alternatively, the baby becomes colonized on the skin and mucous membranes during passage through the birth canal, and then develops systemic disease, although this pathogenesis is thought to be less common. To colonize tissue, the organism must adhere, mediated by adhesion factors called pili, and evade host antibodies and phagocytes, mediated by capsular polysaccharide. These are the major virulence factors of GBS. The hemolysin that causes diffuse beta-hemolysis under GBS colonies on blood agar is not thought to be an important virulence factor, but it does help identify the organisms in the historical CAMP test, in which the CAMP factor hemolytic protein of GBS combines with a sphingomyelinase produced by *Staphylococcus aureus* to make an intense hemolytic zone in the form of an arrow (Figure 2). Babies who develop GBS disease usually begin to show signs of illness within 24 hours, and, by definition, always within the first week of life. Because the organism lives asymptomatically in the gut and travels back and forth to the vagina, treatment of the colonized mother is not appropriate, nor is it effective.[29] The strategy developed by early researchers on the subject was to treat the baby so that the level of antibiotic in the baby's bloodstream would effectively thwart any GBS that managed to find their way into the circulation before or during labor.[11] And before the baby is born, the only way to treat him or her was to infuse antibiotics into the mother; those antibiotics effectively cross the placenta and enter the baby's bloodstream in utero.

Because GBS is still, luckily for us, susceptible to penicillin, that cheap and effective drug is the first choice, with ampicillin as an alternative. When women are known to be penicillin-allergic, cefazolin is recommended depending on the allergic status, and for

those who cannot take cefazolin, clindamycin or erythromycin is the next choice. At least one complication to the risk-factor based treatment system is that many women do not know their penicillin response, having never received it before becoming pregnant, and there have been reports of women developing anaphylaxis when first confronted with penicillin during labor. A recent survey showed that approximately half of 17 cases of anaphylaxis during labor were due to IAP.[33] The early screening strategy allows colonized women to be tested for penicillin sensitivity before they reach parturition. And although universal treatment of all women during labor, regardless of colonization status, has been shown to be the most cost-effective method, this level of antibiotic use is not considered to be desirable, and other strategies continue to be favored.[22]

At least one complication to the relative "ease" of IAP based on risk factors alone is that the levels of resistance to the secondary drugs erythromycin and clindamycin have been increasing. This factor places a new burden on microbiology laboratories to test those drugs against any GBS isolates they recover, especially when they are informed that the patient is penicillin-allergic. Most mechanisms of macrolide resistance are easy to detect using standard in vitro susceptibility methods and when both erythromycin and clindamycin are resistant, the results are reliable. But when erythromycin exhibits resistance and clindamycin remains susceptible, another possibility exists that requires additional laboratory confirmation. Erythromycin resistance due to a change in the ribosomal binding site target of the antibiotic based on a mutation in the *erm* gene is clearly revealed by disk diffusion testing. However, simple disk diffusion or MICs are not sufficient to detect all clindamycin resistance, as the organism may harbor an inducible macrolide resistance factor that is not apparent unless the isolate is growing in the presence of a macrolide to begin with. Thus, the D-test, so called because the zone of inhibition resembles the letter D, is necessary. By placing clindamycin and erythromycin disks close enough together on a blood containing agar plate, some of the erythromycin diffuses over to the region where the clindamycin is present in the agar surrounding the clindamycin disk and induces the colonies growing in that area to express their resistance and begin to grow where they previously would have been susceptible **(Figure 3)**. The test is completely described in the CLSI document M100-S23.[14] Allowing laboratories to have the time to perform such antibiotic susceptibility tests is another reason why antenatal screening for GBS colonization in pregnant women is a better approach to neonatal disease control.

The percent of women whose babies developed EOGBS disease was still quite low relative to the percent colonized with GBS, even before the advent of effective prophylactic therapy. It appears that the level of maternal colonization also affects whether the baby will become infected, as one might expect. Higher numbers of organisms are related to a higher chance of neonatal EOGBS disease.[39] At least one other major reason is thought to be the presence of maternal antibodies against the colonizing strain type in the mother. At least 9 serotypes of GBS exist, based on the capsular polysaccharide type of the strain. The capsule is probably the organism's major virulence factor, protecting it from phagocytic destruction. These serotypes, named Ia, Ib, and II-IX, have varying prevalence in different populations, but universally type III appears to predominate in EOGBS disease. In fact, one strain type (ST) of serotype III, called ST-17, has predominated in the most serious cases, including most meningitis cases.[28,37] The fact that babies of mothers with high levels of antibodies seem to escape disease raises hopes that a vaccine against the majority of serotypes predominating in GBS disease could be protective.[5,18] In fact, clinical trials of a glycoconjugate vaccine containing antigens Ia, Ib, and III are in progress (http://www.devaniproject.org). However, changing serotype distribution worldwide may render that design less desirable. The other major virulence factor, the pili, have been promoted as a vaccine target.[35] Due to its potential for more universal protection, pilus vaccine development is being contemplated.[32]

A related disease is late onset GBS (LOGBS) disease, again featuring serotype III as a major agent. In several studies a particular strain, again ST17, seems to be epidemiologically linked to LOGBS.[8,37] Strangely, this strain also is associated with macrolide (erythromycin) susceptibility, which, and this is conjecture on my part, may allow it some freedom (it does not carry the genetic burden of the resistance factors) to be more virulent.[26] Babies suffer septicemia, meningitis, and similar outcomes, but the numbers of milder disease presentation are higher with LOGBS than for EOGBSD. Numbers of babies with this syndrome have overtaken EOGBS in the U.S.[17] This invasive syndrome strikes anytime from 1 week to 3 months after birth, usually around 1 month after delivery, and so far no preventive measures have been successful. Here, a vaccine may prove to be the only option.[21] Not all of the possible means by which babies acquire the organism are known, but breast-feeding, horizontal transmission in the nursery, and transmission from other people are thought to be involved. At this time, there is no laboratory test for identifying babies at risk for developing LOGBS disease. An exciting new discovery is that low birth weight babies given lactoferrin (a white blood cell protein and a glycoprotein found in milk whey) orally for 4-6 weeks after birth had significantly lower rates of LOGBS.[24]

The need for a rapid and reliable test for GBS colonization has been recognized for years. Rapid antigen tests for group A beta streptococcal throat infections raised hopes for a similarly effective test for GBS, but early attempts fell short and confirmatory cultures for negative rapid tests were recommended.[12] One clever approach used a silicon wafer base to enhance the antigen-antibody binding and allow a stronger reaction, but rigorous testing against a good gold standard showed that even this assay platform lacked sufficient sensitivity.[3] The laboratory landscape changed radically, however, in 2000 when Bergeron, et al announced

FIGURE 4. Elizabeth Thonen-Kerr, Lead Molecular Technologist, holding a GBS cartridge (left) and Dr. Patricia Ferrieri, Medical Director, Infectious Disease Diagnostic Laboratory, University of Minnesota Medical Center, Minneapolis, MN (right).

development of a rapid PCR for vaginal swabs.[9] This test, soon acquired by GeneOhm and eventually by Becton Dickinson, transformed the situation. Although not rapid enough for intrapartum testing, the GeneOhm test was very sensitive.[31,34]

In 2006, Cepheid introduced the Xpert® GBS, which was cleared by the FDA for both antepartum and intrapartum testing. Xpert GBS was the first CLIA moderate complexity PCR-based test, and it could be used at time of delivery for women who would otherwise not be candidates for IAP because they lacked risk factors and either their antepartum culture results were negative for GBS, or they had no antepartum culture results available. In one study looking at outcomes based on the national recommendations, Davies et al. noted that for 20–30% of women who had prenatal cultures performed, the results were not available to the caregiver at the onset of labor.[15] The Xpert GBS was also the first Xpert format cartridge to accept a swab directly into the cartridge. It was so easy and rapid to perform, that a number of laboratories did a self-validation and began to use it instead of antepartum enrichment broth cultures as were recommended by the Centers for Disease Control and Prevention, among others (MMWR 2008). However the sensitivity of the test compared to enrichment culture was not ideal, hovering between 85–90%.[2,13,25] As a backup test for women without known status, it would identify those most at risk, since the limitation of detection is around 300 organisms/swab (Cepheid Xpert GBS Product Insert). As mentioned, the density of GBS in the vagina is directly correlated with colonization of the infant at delivery.[23] The time that antibiotics are circulating in the infant's blood (i.e., the duration of intravenous antibiotics that the mother receives before the baby is delivered) also seems to relate to colonization, with less time resulting in more colonized babies.[7] An earlier study actually quantified the cfu's of GBS in the vagina of colonized women during intrapartum prophylaxis, and showed that the numbers dropped precipitously to less than 20% of the original density within 2 hours of IAP.[27] These findings suggest that a test that is performed rapidly enough, especially if done right in the labor and delivery suite, would yield results fast enough to make a difference for women who would otherwise not receive prophylaxis.

The real-life experiment has now been done and the results are striking.[20] At Groupe Hospitalier Paris-Saint Joseph in Paris, Dr. Najoua El Helali enrolled 863 women into her study, all of whom had Xpert GBS performed intrapartum (in labor). Nine women with antepartum culture results negative for GBS delivered babies who were colonized with GBS. Because the protocol was experimental the results were not reported to the caregivers. Tragically, 4 infants developed EOGBS disease, which potentially could have been treated had the results been acted on as necessary. Her study proved that not only were 49% of women positive for GBS at delivery missed by the antenatal screening culture, but 42% of women with antenatal positive cultures had no GBS at the time of delivery and thus received unnecessary intravenous antibiotics.[20] Dr. El Helali followed up this landmark study with a second, looking at cost-effectiveness of intrapartum screening by PCR.[19] The results showed that in the prenatal screening strategy arm (>2800 patients) there were 3 proven (positive culture from blood or CSF along with clinical signs and symptoms) and 4 severe probable (positive gastric aspirate or ear canal cultures along with clinical signs and symptoms) EOGBS cases and 16 moderately severe probable EOGBS cases, whereas within the intrapartum PCR arm (also <2800 patients) there were 12 moderately severe probable EOGBS cases. With regard to overall costs of care for all deliveries and including cost of the ill babies, cost results were neutral, showing a large patient care outcomes advantage for intrapartum PCR without placing any additional cost burden on the healthcare system.[19]

Cost-effectiveness studies have been published on use of screening by culture vs. treatment by risk factors for many years, since the U.S. established its recommendations. European countries, whose national health services are the primary payers in many instances, were particularly interested, as cost-effectiveness and in some cases not individual patient lives saved, drives their national policies. In cost-effectiveness analyses time after time, the most cost-effective strategy is to treat every woman in labor with

intravenous penicillin, but fortunately, policy makers reject that idea due to the unacceptable nature of using antibiotics so widely.[22] So when considering the next best other strategies (stratified by least expensive for each quality-adjusted life year [QALY] gained), risk factors negative and PCR positive, or PCR positive alone are dominant (more cost-effective).[22] Thus is it highly surprising that after another round of studying the issue and considering the impressive progress made using antenatal screening as the cornerstone of policies in many other countries throughout Europe as well as the U.S., the United Kingdom health protection agency recently again rejected any strategy other than risk-based as the basis for reimbursing healthcare costs for women during labor and delivery in England (UK National Screening Committee Report; Screening for Group B Streptococcal infection in pregnancy. External review against programme appraisal criteria for the UK National Screening Committee available at http://www.screening.nhs.uk/policies), effectively maintaining the current policy of disallowing any tests for GBS as a basis for interventions to prevent EOGBSD.

Best of both worlds: PCR testing for both antepartum and intrapartum samples

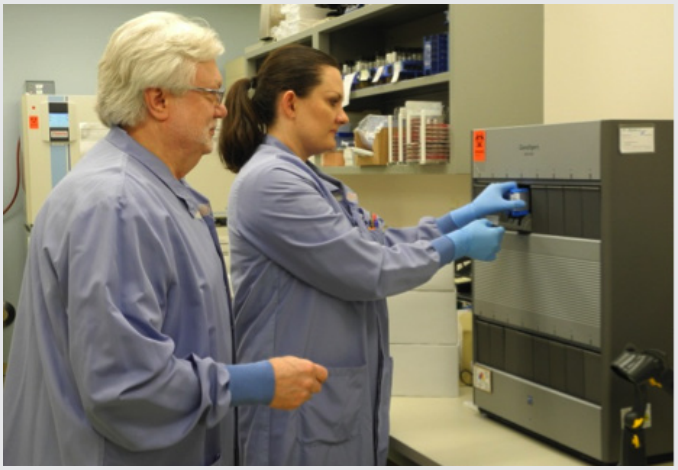
To be clear, using only rapid testing at delivery will not completely prevent EOGBSD. As many as 25% of women will deliver very quickly (<3.5 hours), not enough time to perform a rapid test and make a decision based on the results. And even with a very sensitive test, some patients with low organism counts may yield a negative result but the baby will still become colonized and develop disease. Meantime, others were harnessing the newly available PCR test to investigate whether this test could improve the sensitivity of the antenatal enrichment culture process. This would have the advantage of detecting GBS in a background of mixed flora, and could also pick up non-hemolytic strains. It is unclear whether the latter are virulent and contribute to EOGBS but some reports suggested that they might.[1] Several authors looked at existing commercial GBS tests using enrichment broth as the sample and found better sensitivities for GBS detection than culture.[10,34] So in the U.S., CDC reacted to these findings and modified their guidance recommendation with a revision that encouraged use of PCR on the enrichment broth, while still stating that direct PCR at time of delivery was acceptable if no other information about the mother was available.[38]

Cepheid responded by performing clinical trials with a redesigned product, which was cleared by the FDA for use on enrichment LIM broth this year. With a sensitivity near 100% and specificity of 92.4% before discrepant resolution, and closer to 100% after sequencing the samples that were discordant (Xpert® GBS LB product insert), this test serves the need for more sensitive results from antenatal cultures, and in the process, it also avoids the root cause of some invalid test results seen with the GBS direct product, probably due to cervical mucus on the swab. Dr. Patricia Ferrieri, M.D. Medical Director, Infectious Diseases Diagnostic Laboratory, University of Minnesota Medical Center, Fairview (Minneapolis, MN) (Figure 4), will present a poster on her study evaluating the utility of Xpert GBS LB at the American Society for Microbiology (ASM) General Meeting (GM) in Denver this May. Dr. Ferreiri said "My staff and I appreciate very much the efficiency of using the GBS-LB assay; work flow is improved compared to using our previous SMART-GBS."

Another microbiologist who had previously used other GeneXpert assays, Dr. Matt Bankowski, Ph.D., D(ABMM), HCLD/CC(ABB), Vice President and Technical Director, Clinical and Molecular Microbiology and Infectious Disease Diagnostic Laboratory Services, Inc. and The Queen's Medical Center, Honolulu, Hawaii, will also present a poster at the upcoming ASM GM. Dr. Bankowksi's group compared performance of two new molecular methods for identification of GBS from broth enrichment (Figure 5); his poster is entitled "Test Performance of the Xpert® GBS LB Assay Using LIM Broth Enrichment Compared to Illumigene® GBS." Dr. Bankowski stated "GeneXpert testing is the most favored molecular assay among all of our Microbiology staff. Even the technologists that were intimidated by molecular assays embrace it with vigor. In addition, the high test performance and turn-around-time have added significant value to our patient care."

The high sensitivity of the GBS-LB has the potential to reduce the number of patients whose status will change from negative to positive in the 4 weeks after antepartum screening, and for those patients with PROM or early onset of labor, the Xpert GBS test provides an excellent intrapartum testing option. With regard to GBS testing, Cepheid is proud to be able say "Mission Accomplished" in offering a complete portfolio of testing options which together may be able to help drive down the incidence of EOGBS infection even further.

FIGURE 5. Dr. Matt Bankowski looks on as Technologist Angela Hose performs a GBS-LB test on the GeneXpert at Diagnostic Laboratory Services laboratory in Honolulu.



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