

THE PREVENTION OF EARLY-ONSET NEONATAL GROUP B STREPTOCOCCAL DISEASE

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Abstract

Objective: To review the evidence in the literature and to provide recommendations on the management of pregnant women in labour for the prevention of early-onset neonatal group B streptococcal (GBS) disease.

Outcomes: Maternal outcomes evaluated included exposure to antibiotics in pregnancy and labour and complications related to antibiotic use. Neonatal outcomes of rates of early-onset group B streptococcal infections are evaluated.

Evidence: A review of the literature through MEDLINE from January 1980 to December 2003, relating to neonatal group B streptococcal infection and a review of the Centers for Disease Control and Prevention recommendations.

Values: The evidence obtained was reviewed and evaluated by the Infectious Diseases Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) under the leadership of the principal authors, and recommendations were made according to guidelines developed by the Canadian Task Force on the Periodic Health Exam.

Recommendations:

1. Offer all women screening for group B streptococcal disease at 35 to 37 weeks' gestation with culture done from one swab first to the vagina then to the rectal area. (II-1)

2. Treat the following women intrapartum at time of labour or rupture of membranes with IV antibiotics:
 - all women positive by GBS culture screening done at 35 to 37 weeks (II-2)
 - any women with an infant previously infected with GBS (II-3)
 - any women with documented GBS bacteriuria (regardless of level of colony-forming units per mL) in this pregnancy (II-2)
3. Treat women at less than 37 weeks' gestation with IV antibiotics unless there has been a negative GBS vaginal/rectal swab culture within 5 weeks. (II-3)
4. Treat women with intrapartum fever with IV antibiotics (i.e., chorioamnionitis must be treated, but broader spectrum antibiotics would be advised). (II-2)
5. If a woman is GBS-positive by culture screening or by history of bacteriuria, with prelabour rupture of membranes at term, treat with GBS antibiotic prophylaxis and initiate induction of labour with IV oxytocin (II-1)
6. If GBS culture result is unknown and the woman has ruptured membranes at term for greater than 18 hours, treat with GBS antibiotic prophylaxis. (II-2)

Validation: These guidelines have been reviewed and approved by the Infectious Diseases Committee of the SOGC, and approved by the Council of the SOGC.

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Key Words

Group B streptococcus, antibiotic therapy, infection, prevention

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INTRODUCTION

The purpose of this guideline is to review the literature and evidence for management of pregnant women in Canada in order to minimize the risk of early-onset neonatal group B streptococcal (GBS) disease. Since publication of the “National Consensus Statement on the Prevention of Early-Onset Group B Streptococcal Infections in the Newborn” in 1994, there have been many publications of new information to inform this management.¹ The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam.² (Table 1)

BACKGROUND

Group B streptococcal infection represents a very significant cause of neonatal morbidity and mortality.³ Neonatal GBS disease can be classified as early- or late-onset. Early-onset disease occurs less than 7 days after birth and comprises 80% of the disease in infants, and the mortality rate ranges from 5% to 20%.³ Davies *et al.* reviewed the distribution of disease in neonates and found 74% developed bacteremia, 14% meningitis, and 12% pneumonia. Twenty-five percent of cases occur in preterm infants (<37 weeks).⁴

Fortunately, the incidence of neonatal disease in Canada and the United States has decreased from 2 to 3 per 1000 to 0.5 per 1000 with introduction of intrapartum chemoprophylaxis.^{5,6} A Centers for Disease Control and Prevention (CDC) surveillance study estimated that the use of intrapartum chemoprophylaxis has prevented 4500 cases per year of GBS sepsis and 225 deaths per year in the United States.⁷ In a recent Canadian, population-based study, overall incidence was 0.64 per 1000 live births, with 57% early-onset disease. This study

demonstrated a case fatality rate of 9% with another 11% of all cases ending in stillbirth.⁴

Group B streptococcus is part of normal vaginal flora, and between 10% and 30% of women are colonized.⁸ A Canadian study published in 1998 showed an overall colonization rate of 11%,⁹ while another study in a different population showed a colonization rate of 19.5%.¹⁰ At birth, 50% of infants of colonized mothers will be colonized themselves. Of the 2% of infants who develop early-onset GBS infection, the case fatality is currently 5% to 9% compared with 70% three decades ago.^{3,7,11}

Women become colonized with GBS from the gastrointestinal tract, which is the natural reservoir. This explains why GBS rarely can be eliminated from the lower genital tract. Colonization can be transient and variable. Presence of GBS in clean-catch urine cultures shows evidence of heavy maternal colonization, which is associated with neonatal disease.^{12,13} Vaginal colonization in early pregnancy does not predict colonization at delivery,¹⁴ but vaginal colonization has been associated with young maternal age,¹⁵ sexual activity, tampon use, and infrequent handwashing.¹⁶ Most of these data are from small studies and require confirmation.

Risk factors for neonatal infection include less than 37 completed weeks of gestation, prolonged rupture of membranes (>12–18 hours), intra-amniotic infection, young maternal age, black race, Hispanic ethnicity, and low maternal levels of anti-capsular antigen.^{11,17–20} A UK study found the main risk factors to be prematurity, rupture of membranes for longer than 18 hours, and fever in labour.²¹ Of note, diabetes in pregnancy is associated with higher rates of GBS colonization.²² A recent study has implicated intrauterine monitoring as an independent risk factor for neonatal GBS disease.²³

GBS has been associated with adverse pregnancy outcomes.²⁴ The presence of heavy colonization with GBS has been

Table 1. Evaluation of Evidence Criteria

Quality of Evidence Assessment ²	Classification of Recommendations ²
The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam.	Recommendations included in these guidelines have been adapted from the ranking method described in the Classification of Recommendations found in the Report of the Canadian Task Force on the Periodic Health Exam.
I: Evidence obtained from at least one properly randomized controlled trial.	A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
II-1: Evidence from well-designed controlled trials without randomization.	B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one center or research group.	C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination, but recommendations may be made on other grounds.
II-3: Evidence obtained from comparisons between times or places with or without intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.	D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination.
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

associated with preterm labour and preterm premature rupture of membranes.^{24,25} Group B streptococcal bacteriuria occurs in 2% to 4% of pregnancies and is associated with maternal urinary tract disease as well as with an increased risk of neonatal disease.¹² Maternal colonization with GBS is associated with endometritis and wound infection.^{26,27}

STRATEGIES TO PREVENT NEONATAL GBS

Immunization strategies have been researched for many years, but the multivalent capsular coating of this bacteria has made development of a vaccine challenging.¹⁸ Chemoprophylaxis before the onset of labour or rupture of membranes has been shown to be ineffective.²⁸ Treatment of colonized women results in a 67% recurrence of GBS colonization.²⁹ Although treatment to the infant after delivery is useful, this strategy has only been demonstrated to decrease severity of disease but does not prevent disease.^{28,30} Intrapartum therapy has been found to be the most effective in preventing neonatal GBS disease.^{27,31}

The pivotal randomized controlled trial of Boyer and Gotoff in 1985 showed that use of intrapartum antibiotics decreased risk of early-onset disease in neonates and decreased perinatal febrile morbidity in colonized women.³² Since then, multiple approaches have been used and evaluated. Overall, the use of intrapartum antibiotic prophylaxis has been clearly demonstrated to significantly decrease maternal colonization and infant infection rates. This has been supported by a meta-analysis reporting a 30-times reduction in early-onset GBS disease with use of intrapartum antibiotics for GBS-colonized women.³³

This culminated in recommendations from the CDC in 1996.⁶ These recommendations advised 1 of 2 approaches: a universal screening or a risk-factor approach. The screening approach involved a week 35 to 37 vaginal/anal swab cultured in selective broth. All women colonized with GBS were to receive intrapartum antibiotics, and women with negative cultures were to receive antibiotics only if they became febrile. A risk-factor approach was considered an acceptable alternative. Risk factors included membrane rupture for longer than 18 hours or fever in labour. If women had GBS bacteriuria or a prior GBS-infected neonate, they would receive intrapartum chemoprophylaxis regardless of current colonization status.

In June 1997, the Society of Obstetricians and Gynaecologists of Canada presented guidelines which were similar.³⁴ The guidelines stated that 2 methods were acceptable, either universal screening at 35 to 37 weeks by singly combined vaginal/rectal swab and treatment of all colonized women. Alternatively, intrapartum chemoprophylaxis of women with risk factors was also a valid option. In summary, it was stated that no method prevents all GBS deaths, and that more research was required.

The impact of the 1996 and 1997 guidelines can be evaluated by the epidemiologic changes which have occurred since

the new guidelines were implemented. Since then, there has been a decline in perinatal GBS disease, with a 70% decrease in early-onset disease to 0.5 per 1000 live births.^{19,20} Maternal infection also declined by 21% from 0.29 to 0.23 per 1000 deliveries from 1993 to 1998.²⁰ Multiple studies have supported data indicating a general reduction of neonatal GBS rates with concomitant maternal benefits, but health-care providers' difficulties in complying with the complex protocol was often commented upon in the studies.^{4,7,35-39}

Despite a comment on the lack of quality of the studies reviewed, the Cochrane Review done in 2000 concluded that the use of intrapartum antibiotic treatment of women colonized with group B streptococcus reduces neonatal infection.³¹

RISK-BASED VERSUS SCREENING APPROACH

A number of studies have attempted to evaluate the merit of screening versus a risk-based approach. In most studies, the screening approach involved treating all women who were colonized at the time of delivery or rupture of membranes. In a study to evaluate screening-based versus risk-based outcomes, Gilson *et al.* compared 3164 screened versus 2684 unscreened mothers and found no cases of neonatal disease in the screened cohort and 4 cases in the unscreened ($p=0.04$).⁴⁰ A 2-time period study comparing a risk-factor approach in period A to a screening approach in period B resulted in a significant difference in disease with 20 cases in 3700 (5/1000) versus 5 cases in 3648 (1/1000) ($p=0.0024$).⁴¹

A single-centre study compared 13 270 women managed with the risk-factor approach versus 9304 women managed with the culture-based approach and found a difference in neonatal GBS rates of 1.1 per 1000 versus 0 per 1000 ($p=0.001$).⁴²

Another single-centre study was unable to show a statistically significant difference in neonatal disease, but reported reductions in maternal disease with clinical chorioamnionitis from 7.4% with the risk-based approach compared with 5.2% with universal screening (relative risk [RR], 0.7; 95% confidence interval [CI], 0.6–0.8). Endometritis rates were 4.0% with a risk-based approach and 2.8% with a screening approach (RR, 0.7; 95% CI, 0.6–0.8).⁴³

Mathematical projections show that universal screening would lead to greater disease declines than the risk-based approach, resulting in a 69% reduction in disease with 18% treated in a risk-based approach versus an 86% reduction of disease with 27% treated in a culture-based approach.²⁷

In a Canadian study involving 2 geographically separated regions, Davies *et al.* noted that physicians in Alberta were much more likely to use a screening-based approach compared to physicians in Toronto. They noted that associated with these practice patterns there were declines in the rates of neonatal GBS infections in both regions, but rates in Alberta were always significantly lower than rates in Toronto. The authors at the

time speculated that the difference in rates may be due at least in part to the differences in practice patterns.⁴⁴

The most compelling and largest study was a CDC multi-state study of a stratified random sample of 626 912 live births in 1998 and 1999. Of 5144 births, risk of early-onset disease was significantly lower among the infants of screened women compared to those in the risk-based approach (adjusted RR, 0.46; 95% CI, 0.36–0.60).⁴⁵ This has prompted the development of new guidelines by the CDC, as published in *Morbidity and Mortality Weekly Report* in August 2002.⁴⁶

Economic analyses of both approaches have also been conducted and essentially showed no significant difference if one considers the cost savings involved with reduction of morbidity and mortality. It has also been shown that a risk-based versus screening approach is essentially equivalent in cost and in the number of women treated with antibiotics.⁴⁷

RECOMMENDATION

- 1. Offer all women screening for group B streptococcus disease at 35 to 37 weeks' gestation with culture done from one swab first to the vagina then to the rectal area. (II-1)**

PRACTICAL ASPECTS OF THE SCREENING METHODS

The current gold standard for screening women and detecting GBS colonization of the genital tract is the use of a swab taken at 35 to 37 weeks' gestation. This is done using a single swab first in the vagina then into the rectal area and transported at room temperature to the laboratory in a non-nutritive transport medium; Amies or Stuart's is recommended.^{28,48} These specimens should be labelled clearly to inform the laboratory of the need to perform specific group B streptococcal culturing. In addition, if the woman is penicillin allergic, then this should be stated along with a request to perform sensitivity testing for clindamycin and erythromycin.^{49,50} The laboratory can then culture the organism in selective broth media to maximize the isolation of GBS.

Despite the acceptable predictive value of GBS cultures at 35 to 37 weeks for predicting colonization at delivery, a preferable method would be a rapid accurate test to detect presence of GBS at the actual time of delivery. As a result, rapid tests have been developed and evaluated for this. The utilization of a polymerase chain reaction (PCR) assessed by Bergeron *et al.* showed that these tests had a sensitivity of 97% and a negative predictive value of 98.8%.⁵¹ The negative PCR in the 33 women evaluated was in a woman with ruptured membranes prior to testing. With the development of accurate real-time PCR technology, this will likely permit evaluation of GBS status in labour. The advantage of the tool is the rapid, real-time result; the disadvantage is the lack of antibiotic sensitivity data, and potentially false-negative results related to rupture of membranes. This technique would be reserved for hospitals that had diagnostic laboratory capabilities of real-time PCR testing. A

cost-benefit analysis has been performed suggesting that, in a US setting, a screening strategy with real-time PCR testing would generate a cost benefit of US\$7.00 per birth when compared to the risk-factor strategy, and US \$6.00 per birth when compared to the culture-based strategy at 35 to 37 weeks.⁵² The authors conclude that there is a need for further study of these rapid tests, but the promise is in the ability to identify the woman and infant at risk in labour. A validated, accurate intrapartum test would certainly provide an excellent alternative to the current culture approach at 35 to 37 weeks.

ANTIBIOTIC CHOICES

Since group B streptococcus is uniformly sensitive to the penicillins, it is recommended that IV penicillin G be used instead of ampicillin IV (due to its narrow spectrum of action, which diminishes the risk of selective pressure on other organisms and decreases risk of ampicillin resistance development).^{53,54} If penicillin G is unavailable, ampicillin is acceptable. The neonatal recommendations have changed from prior guidelines to suggest that there is no need for a septic workup if the infant is well and antibiotics were given at least 4 hours prior to delivery. This is primarily based on data showing that the vaginal colonization rate dramatically falls off after 2 hours of therapy.⁵⁵ After a single 2 g dose of IV ampicillin, vaginal colonization rates are 46% in less than 1 hour, 29% between 1 and 2 hours, 2.9% between 2 and 4 hours, and 1.2% at greater than 4 hours.⁵⁵ Of note, the recommendations encourage use of cefazolin as the alternative for penicillin-allergic women who do not have a history of anaphylaxis (i.e., shortness of breath or evidence of airway edema rather than just rash or other allergic reaction). The risk of allergic or anaphylactic reaction to penicillins is between 4 per 10 000 and 4 per 100 000.⁴⁶ Of note, cephalosporins only have a 10% risk of cross-reaction allergy to penicillins.

The alternative antibiotics are erythromycin and clindamycin, which are demonstrating more in vitro resistance, particularly in the United States.^{49,56} In addition, a recent study from Alberta found GBS-resistance rates of 5.6% and 3% respectively for erythromycin and clindamycin.¹⁰ However, other studies of GBS resistance in North America range from 7% to 25% for erythromycin and 3% to 15% for clindamycin, suggesting an increasing problem with GBS resistance to these

Table 2. Recommended Antibiotics for Intrapartum Prophylaxis

1. Penicillin G 5 million units IV, then 2.5 million every 4 hours
or
2. If the woman is penicillin allergic but not at risk of anaphylaxis:
cefazolin 2 g IV then 1 g every 8 hours
or
3. If the woman is penicillin allergic and at risk of anaphylaxis:
clindamycin 900 mg IV every 8 hours or erythromycin 500 mg
IV every 6 hours

Note: If GBS resistance is demonstrated to clindamycin or erythromycin by culture and sensitivity, then give vancomycin 1 g IV every 12 hours.

2 antibiotics.^{14,57,58} Of note, no oral preparation is adequate, as it does not show satisfactory rates of clearance of GBS from the genital tract in the time frame of labour. (Table 2)

The implementation of a screening protocol will result in approximately 10% to 25% of women in labour receiving antibiotics for prevention of GBS neonatal disease. The worry that use of antibiotics for GBS prophylaxis may result in selection of other organisms such as *E. coli* is certainly a theoretical concern. However, a study of trends in neonatal sepsis has been reassuring, with no increase in the rate of neonatal sepsis overall in the post-GBS prophylaxis era, but some increase in *E. coli* sepsis in preterm or low-birth-weight infants.⁵⁹ It would be prudent to continue to be vigilant in tracking sepsis and antibiotic resistance trends as new antibiotic treatment regimens are implemented.

PREMATURE RUPTURE OF MEMBRANES (PROM) AT TERM (>37 WEEKS' GESTATION)

In the term PROM study, Hannah *et al.* reviewed their outcomes in GBS-colonized women versus GBS-negative women.⁶⁰ In this study, 4834 women were randomized to induction versus expectant management. Researchers found that 10.7% were GBS positive and 127 infants had neonatal infections, of which 10 were proven related to GBS — all in the expectant arm; there was 1 death due to GBS in the expectant group. The analysis revealed that for GBS-culture-positive women, induction decreased the risk of neonatal infection, with an odds ratio (OR) of 0.29 ($p=0.06$). In the expectant management group, GBS-positive women had a significantly greater risk of neonatal infection (OR 4.12, $p<0.001$). The conclusion of this study was that for GBS colonized women with PROM at term, immediate induction with oxytocin decreased risk of infection versus expectant management or induction with prostaglandin E2 (PGE2).

RECOMMENDATIONS

- 2. Treat the following women intrapartum at time of labour or rupture of membranes with IV antibiotics:**
 - all women positive by GBS culture screening done at 35 to 37 weeks (II-2)
 - any women with an infant previously infected with GBS (II-3)
 - any women with documented GBS bacteriuria (regardless of level of colony-forming units per mL) in this pregnancy (II-2)
- 3. Treat women at less than 37 weeks' gestation with IV antibiotics unless there has been a negative GBS vaginal/rectal swab culture within 5 weeks. (II-3)**
- 4. Treat women with intrapartum fever with IV antibiotics (i.e., chorioamnionitis must be treated, but broader spectrum antibiotics would be advised). (II-2)**
- 5. If a woman is GBS-positive by culture screening or by**

history of bacteriuria, with prelabour rupture of membranes at term, treat with GBS antibiotic prophylaxis and initiate induction of labour with IV oxytocin (II-1)

- 6. If GBS culture result is unknown and the woman has ruptured membranes at term for greater than 18 hours, treat with GBS antibiotic prophylaxis. (II-2)**

NEONATAL MANAGEMENT

Neonatal management has remained essentially unchanged from the prior Canadian guidelines; and on review of recent US guidelines, the committee did not see reason to alter Canadian recommendations.^{34,46} The current recommendations for infants are:

1. Infants delivered by women who have received intrapartum antibiotics at least 4 hours before delivery, do not need a septic workup. These infants should be observed in hospital for the first 24 hours for signs of infection, but do not need additional therapy or investigations.
2. Infants who appear well despite their mothers being GBS colonized and not receiving adequate antibiotics (<4 hours) should be observed for 48 hours and evaluated or treated if signs of sepsis develop.
3. Infants of mothers with chorioamnionitis should undergo a diagnostic evaluation for sepsis and be treated with antibiotics. (Sepsis workup includes a complete blood-cell count and differential, blood culture, and chest radiograph, including a lumbar puncture if feasible.)

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