

# The Prevention of Early-Onset Neonatal Group B Streptococcal Disease

This Clinical Practice Guideline has been prepared by the Infectious Disease Committee, reviewed by the Infectious Diseases and Immunization and the Fetus and Newborn Committees of the Canadian Paediatric Society, and the SOGC Family Practice Advisory Committee, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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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 disease. The key revisions in this updated guideline include changed recommendations for regimens for antibiotic prophylaxis, susceptibility testing, and management of women with pre-labour rupture of membranes.

**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:** Published literature was retrieved through searches of MEDLINE, CINAHL, and The Cochrane Library from January 1980 to July 2012 using appropriate controlled vocabulary and key words (group B streptococcus, antibiotic therapy, infection, prevention). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. There were no date or language restrictions. Searches were updated on a regular basis and incorporated in the guideline to May 2013. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

**Values:** The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

**Benefits, Harms, and Costs:** The recommendations in this guideline are designed to help clinicians identify and manage pregnancies at risk for neonatal group B streptococcal disease to optimize maternal and perinatal outcomes. No cost-benefit analysis is provided.

**Key Words:** Group B streptococcus, antibiotic therapy, infection, prevention

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**Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care**

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the 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 recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

\*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.<sup>73</sup>

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.<sup>73</sup>

### Summary Statement

There is good evidence based on randomized control trial data that in women with pre-labour rupture of membranes at term who are colonized with group B streptococcus, rates of neonatal infection are reduced with induction of labour (I). There is no evidence to support safe neonatal outcomes with expectant management in this clinical situation.

### Recommendations

- Offer all women screening for colonization with group B streptococcus at 35 to 37 weeks' gestation with culture taken from one swab first to the vagina and then to the rectum (through the anal sphincter). (II-1A) This includes women with planned Caesarean delivery because of their risk of labour or ruptured membranes earlier than the scheduled Caesarean delivery. (II-2B)
- Because of the association of heavy colonization with early onset neonatal disease, provide intravenous antibiotic prophylaxis for group B streptococcus at the onset of labour or rupture of the membranes to:
  - any woman positive for group B streptococcus by vaginal/rectal swab culture screening done at 35 to 37 weeks' gestation (II-2B);
  - any woman with an infant previously infected with group B streptococcus (II-3B);

- any woman with documented group B streptococcus bacteriuria (regardless of level of colony-forming units) in the current pregnancy. (II-2A)
- Manage all women who are < 37 weeks' gestation and in labour or with rupture of membranes with intravenous group B streptococcus antibiotic prophylaxis for a minimum of 48 hours, unless there has been a negative vaginal/rectal swab culture or rapid nucleic acid-based test within the previous 5 weeks. (II-3A)
  - Treat all women with intrapartum fever and signs of chorioamnionitis with broad spectrum intravenous antibiotics targeting chorioamnionitis and including coverage for group B streptococcus, regardless of group B streptococcus status and gestational age. (II-2A)
  - Request antibiotic susceptibility testing on group B streptococcus-positive urine and vaginal/rectal swab cultures in women who are thought to have a significant risk of anaphylaxis from penicillin. (II-1A)
  - If a woman with pre-labour rupture of membranes at ≥ 37 weeks' gestation is positive for group B streptococcus by vaginal/rectal swab culture screening, has had group B streptococcus bacteriuria in the current pregnancy, or has had an infant previously affected by group B streptococcus disease, administer intravenous group B streptococcus antibiotic prophylaxis. Immediate obstetrical delivery (such as induction of labour) is indicated, as described in the Induction of Labour guideline published by the Society of Obstetricians and Gynaecologist in September 2013. (II-2B)
  - At ≥ 37 weeks' gestation, if group B streptococcus colonization status is unknown and the 35- to 37-week culture was not performed or the result is unavailable and the membranes have been ruptured for greater than 18 hours, administer intravenous group B streptococcus antibiotic prophylaxis. (II-2B)
  - If a woman with pre-labour rupture of membranes at < 37 weeks' gestation has an unknown or positive group B streptococcus culture status, administer intravenous group B streptococcus prophylaxis for 48 hours, as well as other antibiotics if indicated, while awaiting spontaneous or obstetrically indicated labour. (II-3B)

### ABBREVIATIONS

CDC	Centers for Disease Control and Prevention
GBS	group B streptococcus
IV	intravenous
PCR	polymerase chain reaction
PPROM	preterm pre-labour rupture of membranes
PROM	pre-labour rupture of membranes

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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 disease due to group B streptococcus. Since publication of the 2004 SOGC guideline “The Prevention of Early-onset Neonatal Group B streptococcal Disease,”<sup>1</sup> there has been ongoing evaluation of screening, intrapartum antibiotic management, and neonatal outcomes.

## BACKGROUND

Group B streptococci (*streptococcus agalactiae*) are gram-positive, aerobic diplococci that typically produce a narrow zone of beta hemolysis on 5% sheep blood agar. These organisms are divided into 10 types on the basis of capsular polysaccharides (Ia, Ib, II, and III through IX). Types Ia, Ib, II, III, and V account for approximately 95% of cases in infants in the United States. Type III is the predominant cause of early-onset meningitis and the majority of late-onset infections in infants. Pilus-like structures are important virulence factors and potential vaccine candidates.<sup>2</sup>

Neonatal GBS disease can be classified as early- or late-onset. Early-onset disease occurs less than 7 days after birth and is associated with a mortality rate of 5% to 20%.<sup>3</sup> Davies et al. reviewed the distribution of early-onset disease in neonates in Canada and found 71% developed bacteremia, 11% meningitis, and 19% pneumonia.<sup>4</sup> The introduction of universal GBS screening in 2002 was associated with a reduction in rates of early-onset GBS disease to approach rates of late-onset disease.<sup>5,6</sup> Infection with GBS remains a significant cause of neonatal morbidity and mortality in North America.<sup>2,6</sup>

Associated with the introduction of systematic intrapartum chemoprophylaxis, the incidence of neonatal disease in Canada and the United States has decreased from 1 to 3 per 1000 in the early 1990s to 0.35 to 0.5 per 1000 since the adoption of universal screening.<sup>6-8</sup> A Centers for Disease Control and Prevention 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.<sup>9</sup> A Canadian population-based study demonstrated an overall incidence of neonatal GBS infections of 0.64 per 1000 live births, 57% of which were

early-onset disease. This study demonstrated a case fatality rate from early-onset GBS infection of 9%, with 11% of all cases of GBS disease ending in stillbirth.<sup>4</sup> Case fatality rates of 20% to 30% are seen in infants with GBS disease born preterm, compared with 2% to 3% among term infants.<sup>9</sup>

Group B streptococcus is part of the normal vaginal microbiome, and in North America 10% to 30% of women are colonized.<sup>10</sup> A Canadian study published in 1998 showed an overall colonization rate of 11%,<sup>11</sup> while a study in a different Canadian population showed a colonization rate of 30% at time of delivery.<sup>12</sup> An estimated 1% to 2% of infants born to colonized women develop early-onset GBS disease.<sup>13</sup> The overall case fatality rate is currently 5% to 9% compared with 70% three decades ago.<sup>3,11,14</sup> The prevalence of GBS colonization appears to differ among different populations. In the United Kingdom, the incidence of early-onset GBS disease, in the absence of systematic screening or wide-spread intrapartum antibiotic prophylaxis, is lower than in Canada, with a rate of 0.5 per 1000 births.<sup>15</sup> In addition, there was a comparable incidence of 0.4 per 1000 live births in Sweden,<sup>16</sup> supporting subsequent European clinical practice guidelines recommending a risk factor-based approach to prevention of GBS disease.

Lower urogenital tract colonization with GBS may be chronic, transient, or intermittent. The presence of GBS in clean-catch urine cultures reflects heavy genital tract maternal colonization, which is associated with neonatal disease.<sup>17,18</sup> Vaginal colonization in early pregnancy does not predict colonization at delivery,<sup>19</sup> but vaginal colonization has generally been associated with young maternal age,<sup>20</sup> sexual activity, tampon use, infrequent handwashing,<sup>21</sup> high temperatures, and humidity.<sup>22</sup> Most of these data are from small studies and require confirmation.

Risk factors for neonatal infection include < 37 completed weeks of gestation at birth, prolonged rupture of membranes (> 18 hours), intra-amniotic infection, low socioeconomic status, and low maternal levels of anticapsular antigen.<sup>14,23-27</sup> A UK study found the main risk factors to be prematurity, rupture of membranes for longer than 18 hours, and maternal fever in labour.<sup>28</sup> Of note, diabetes in pregnancy is associated with higher rates of GBS colonization.<sup>29,30</sup> One study using Canadian data has implicated intrauterine fetal monitoring (fetal scalp electrode) as an independent risk factor for neonatal GBS disease.<sup>27</sup> When birth weight is accounted for, maternal carriage of GBS has been shown to be independently associated with early-onset GBS disease (OR 6.9; 95% CI 2.8 to 17.1).<sup>31</sup> Recent information demonstrates that known antepartum or intrapartum predisposing risk factors for GBS disease are lacking in 30% to 50% of

women with infants with GBS disease.<sup>27,32–34</sup> The diagnosis of GBS sepsis in infants with risks for or signs of sepsis, therefore, should not be ruled out because of negative maternal GBS screening. This emerging information from European and Canadian populations was not available at the time of the Canadian Task Force on Preventative Health Care's 2001 report on the prevention of early-onset group B streptococcal infection in the newborn, which recommended that universal screening with selective intrapartum chemoprophylaxis be given to colonized women with risk factors.<sup>35</sup>

Heavy colonization with GBS has been associated with adverse pregnancy outcomes including preterm labour and preterm pre-labour rupture of membranes.<sup>36,37</sup> GBS bacteriuria occurs in 2% to 4% of pregnancies and is associated with both maternal urinary tract disease and an increased risk of neonatal disease.<sup>17</sup> Maternal colonization with GBS has been associated with endometritis and wound infection.<sup>38,39</sup> There is no convincing evidence that GBS bacteriuria with low colony counts ( $< 10^8$  CFU/L or  $< 10^5$  CFU/mL) is associated with increased risks for pyelonephritis, chorioamnionitis, or preterm birth, and antepartum treatment (prior to the onset of labour or rupture of membranes) for low colony counts is therefore not recommended. Intrapartum IV antibiotic prophylaxis is still recommended for GBS bacteriuria in the current pregnancy, regardless of colony count.<sup>40</sup> Laboratory reporting of any colony count of GBS in the urine in pregnancy is variable among centres in Canada.

## **STRATEGIES TO PREVENT NEONATAL GBS**

Chemoprophylaxis before the onset of labour or rupture of membranes has been shown to be ineffective;<sup>41</sup> antepartum antibiotic prophylaxis of colonized women results in a 67% recurrence of GBS colonization later in pregnancy.<sup>42</sup> Intrapartum therapy has been found to be effective in preventing neonatal GBS disease.<sup>39,43</sup> Immunization strategies have been proposed as a preferred prevention approach but vaccine development has been challenging, however, a multivalent capsular antigen based vaccine is in clinical trials at present.<sup>44</sup>

The pivotal randomized controlled trial of Boyer and Gotoff in 1985 showed that use of intrapartum antibiotics decreased the risk of early-onset disease in neonates and decreased perinatal febrile morbidity in colonized women.<sup>45</sup> An early meta-analysis of 7 studies (5 controlled trials and 2 cohort studies) demonstrated a 30-fold reduction in early-onset GBS disease with the use of intrapartum penicillin prophylaxis for GBS-colonized women.<sup>46</sup>

This culminated in screening and prophylaxis recommendations from the CDC in 1996.<sup>8</sup> These recommendations advised one of two approaches: a universal screening or a risk-factor approach. The screening approach involved performing a rectovaginal swab at 35 to 37 weeks and culturing 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 developed signs of chorioamnionitis. A risk-factor approach (onset of labour at  $< 37$  weeks' gestation, membrane rupture  $> 18$  hours, intrapartum temperature  $> 38.0^\circ\text{C}$ ) was considered an acceptable alternative. If women had GBS bacteriuria in the current pregnancy or a previous infant who had invasive GBS disease, they were to receive intrapartum chemoprophylaxis regardless of current colonization status, and would not require a vaginal/anal swab for GBS culture at 35 to 37 weeks' gestation.

In June 1997, the Society of Obstetricians and Gynaecologists of Canada presented guidelines which were congruent to those recommended by the CDC.<sup>47</sup> The Canadian guideline stated that two methods were acceptable, either universal screening at 35 to 37 weeks by combined vaginal/rectal swab and intrapartum chemoprophylaxis of all colonized women, or intrapartum chemoprophylaxis of women with risk factors. It was acknowledged that additional research was required to evaluate the prevention of neonatal GBS disease.

The influence of the 1996 CDC and 1997 SOGC guidelines can be evaluated by the epidemiologic changes which occurred following their implementation. There has been a decline in perinatal GBS disease, with a 70% decrease in early-onset disease to 0.5 per 1000 live births.<sup>25,26</sup> Maternal infection also declined by 21% from 0.29 to 0.23 per 1000 deliveries from 1993 to 1998.<sup>26</sup> While multiple studies have provided data demonstrating a general reduction of neonatal GBS rates with concomitant maternal benefits, health-care providers' difficulties in complying with the complex protocol was often commented upon in the studies.<sup>4,9,48–52</sup> Improved management of preterm deliveries and improved collection, processing, and reporting of culture results were recently identified as potential areas for improved prevention of early-onset GBS disease.<sup>53</sup>

Despite a comment on the lack of quality of the studies reviewed, a Cochrane Review performed in 2000 concluded that the use of intrapartum antibiotic prophylaxis of women colonized with GBS reduces neonatal infection.<sup>43</sup> A more recent Cochrane Review suggested that intrapartum antibiotic prophylaxis showed no statistically significant reduction in the risk for neonatal all-cause mortality, or

mortality from GBS and non-GBS organisms (primary outcome analyses).<sup>54</sup> However, analysis of secondary outcomes suggested a statistically significant reduction (80%) in the incidence of both confirmed early-onset GBS disease (RR 0.17, 95% CI 0.04 to 0.74, number needed to benefit 25) and probable early-onset GBS disease (RR 0.17, 95% CI 0.03 to 0.91, number needed to benefit 20) in neonates following intrapartum antibiotics compared to no prophylaxis. There was no reduction in the incidence of late-onset GBS neonatal disease. The trials included in this meta-analysis were of poor quality and had significant methodological biases.<sup>54</sup>

### **RISK-BASED VERSUS SCREENING APPROACH**

No randomized trials have evaluated intrapartum antibiotic prophylaxis based on risk factors versus universal screening approaches, although a number of non-randomized studies have attempted to evaluate the merits of screening versus a risk-based approach.<sup>55,56</sup> In most studies, the screening approach included intrapartum prophylaxis for all women who were colonized at the time of labour or rupture of membranes. A large CDC multistate study of a stratified random sample of 626 912 live births in 1998 and 1999 demonstrated that of 5144 births, the risk of early-onset disease was significantly lower among the infants of screened women compared to those born to mothers managed with the risk-based approach (adjusted RR 0.46; 95% CI 0.36 to 0.60).<sup>56</sup> This information prompted the development of revised guidelines by the CDC in 2002.<sup>57</sup> The most significant recommendation in the CDC guideline at that time included a change from a dual approach to universal prenatal culture-based screening for vaginal and rectal GBS colonization of all pregnant women at 35 to 37 weeks' gestation. Updated prophylaxis regimens for women with a penicillin allergy were provided, including cefazolin if not at high risk for anaphylaxis, clindamycin or erythromycin if high risk for anaphylaxis and GBS susceptible, or vancomycin if GBS resistant or susceptibility unknown. Clindamycin can only be utilized for erythromycin-resistant isolates if inducible clindamycin resistance has been excluded. Intrapartum antibiotic GBS prophylaxis for GBS-colonized women undergoing planned Caesarean delivery before the onset of labour with intact membranes was not recommended.<sup>57</sup>

A further update by the CDC in 2010 has included a change in the recommended dose for penicillin G for prophylaxis (acceptable dose range of 2.5 to 3.0 million units for doses subsequent to the initial dose), changes to prophylaxis regimens for women with penicillin allergy (removal of erythromycin as an acceptable alternative due

to an increase in resistance in GBS seen recently), and updated and separate algorithms for women with preterm labour (discontinue GBS prophylaxis if not in labour) and PPROM (provide GBS prophylaxis intravenously for 48 hours (or less if the swab for GBS culture is subsequently negative), as well as antibiotics for latency if other antibiotic regimens are usually used).<sup>13</sup>

Economic analyses of risk-based and universal culture-based approaches have been conducted and showed that universal culture-based is equivalent in cost to risk-based approach 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 receiving antibiotics prophylaxis.<sup>58</sup>

### **Recommendations**

1. Offer all women screening for colonization with group B streptococcus at 35 to 37 weeks' gestation with culture taken from one swab first to the vagina and then to the rectum (through the anal sphincter). (II-1A) This includes women with planned Caesarean delivery because of their risk of labour or ruptured membranes earlier than the scheduled Caesarean delivery. (II-2B)
2. Because of the association of heavy colonization with early onset neonatal disease, provide intravenous antibiotic prophylaxis for group B streptococcus at the onset of labour or rupture of the membranes to:
  - any woman positive for group B streptococcus by vaginal/rectal swab culture screening done at 35 to 37 weeks' gestation (II-2B);
  - any woman with an infant previously infected with group B streptococcus (II-3B);
  - any woman with documented group B streptococcus bacteriuria (regardless of level of colony-forming units) in the current pregnancy. (II-2A)
3. Manage all women who are < 37 weeks' gestation and in labour or with rupture of membranes with intravenous group B streptococcus antibiotic prophylaxis for a minimum of 48 hours, unless there has been a negative vaginal/rectal swab culture or rapid nucleic acid-based test within the previous 5 weeks. (II-3A)
4. Treat all women with intrapartum fever and signs of chorioamnionitis with broad spectrum intravenous antibiotics targeting chorioamnionitis and including coverage for group B streptococcus, regardless of group B streptococcus status and gestational age. (II-2A)

**Table 2. Recommended antibiotic regimens for intrapartum prophylaxis**

1.	Penicillin G 5 million units IV, then 2.5 to 3.0 million every 4 hours until delivery or
2.	If the woman is allergic to penicillin but has a low risk of anaphylaxis: cefazolin 2 g IV then 1 g every 8 hours until delivery or
3.	If the woman is allergic to penicillin and at risk of anaphylaxis: clindamycin 900 mg IV every 8 hours until delivery (if isolate is susceptible to clindamycin with no inducible resistance) or vancomycin 1 g IV every 12 hours until delivery

## **PRACTICAL ASPECTS OF THE SCREENING METHODS**

A vaginal/rectal (not vaginal/perianal) swab is taken at 35 to 37 weeks' gestation to screen women and detect GBS colonization of the genital tract. This is done by using a single swab first in the vagina then in the rectum and transporting it at room temperature to the laboratory in a non-nutritive transport medium; Amies or Stuart's medium is recommended.<sup>59</sup> These specimens should be labelled clearly to inform the laboratory of the need to perform specific GBS culturing. In addition, if the woman is allergic to penicillin and is at a high risk for anaphylaxis, this should be stated and a request made to perform susceptibility testing (see Table 2).<sup>60,61</sup> The laboratory can then culture the organism in selective broth media to maximize the isolation of GBS. Self-sampling for GBS at 35 to 37 weeks' gestation, with appropriate instruction in the clinical examination room or washroom, has been shown to be accurate and acceptable when compared with physician sampling in a Canadian population.<sup>62</sup>

### **Recommendation**

5. Request antibiotic susceptibility testing on group B streptococcus-positive urine and vaginal/rectal swab cultures in women who are thought to have a significant risk of anaphylaxis from penicillin. (II-1A)

Antenatal GBS cultures at 35 to 37 weeks' gestation have been shown in a recent systematic review to have acceptable positive and negative predictive values for colonization at delivery (mean PPV 69%, mean NPV 94%).<sup>63</sup> A preferable method may be a rapid accurate test to detect the presence of GBS at the actual time of delivery. The use of a polymerase chain reaction has been shown to have a sensitivity of 97% and a negative predictive value of 98.8%.<sup>64</sup> The one negative PCR in the 33 women evaluated was in a woman with ruptured membranes prior to testing. In a Canadian single-centre study evaluating the use of rapid PCR (IDI-Strep B assay) in the labour and delivery suite, 85% of the 190 women enrolled had results of the standard screen at

35 to 37 weeks available for comparison.<sup>12</sup> The sensitivity and specificity of the standard 35- to 37-week screen were 84.3% (95% CI 71.4% to 93.0%) and 93.2% (95% CI 86.5% to 97.2%), respectively, whereas the sensitivity and specificity of the rapid PCR were 90.7% (95% CI 79.7% to 96.9%) and 97.6% (95% CI 93.1% to 99.5%), respectively. The median reporting time for the rapid PCR test was 99 minutes (range 50 to 255). Results were available more than 4 hours before delivery in 81% of cases.<sup>12</sup>

The advantage of PCR screening is the rapid, real-time result; the disadvantages are the lack of antibiotic susceptibility data, potentially false-negative results related to rupture of membranes, and the fact that there is insufficient time for use of selective enrichment broth for at least 4 hours prior to PCR in the intrapartum setting. The 2010 CDC guideline suggests that a useful intrapartum screening test should be simple, have a turn-around time of < 30 minutes, and have a sensitivity and specificity of  $\geq 90\%$ .<sup>13</sup> This technique would be reserved for hospitals that had diagnostic laboratory capabilities of real-time PCR testing, validated PCR performance, and appropriate quality controls. A study comparing the estimated direct costs (including screening test costs and hospital costs) and consequences of intrapartum PCR screening for early-onset GBS disease (Xpert GBS test) with antenatal lower vagina culture screening demonstrated a higher detection rate of GBS colonization with PCR (16.7% versus 11.7%). The average total cost per delivery was US\$1759  $\pm$  1209 for antenatal screening in 2009 and \$1754  $\pm$  842 for intrapartum screening in 2010 ( $P = 0.9$ ).<sup>65</sup> With improved techniques, therefore, in some institutions GBS screening may be replaced by intrapartum PCR assessment.

## **ANTIBIOTIC CHOICES**

Since GBS appears to be uniformly susceptible to the penicillins, it is recommended that IV penicillin G be used instead of IV ampicillin because of penicillin G's narrow spectrum of action, which diminishes the risk of selective pressure on other organisms and decreases the

risk of ampicillin resistance.<sup>66,67</sup> The efficacy of alternatives to penicillin to prevent early-onset GBS disease (such as cephalosporins, clindamycin, or vancomycin) has not been evaluated in controlled trials.<sup>13</sup> Intravenous cefazolin is recommended as the alternative for penicillin-allergic women who are at low risk for anaphylaxis (do not have a history of anaphylaxis, angioedema, respiratory distress, or significant urticaria). It has a relatively narrow spectrum, with similar pharmacokinetics to penicillin, and achieves high intra-amniotic concentrations.<sup>13</sup> The risk of allergic or anaphylactic reaction to penicillins is between 4 per 10 000 and 4 per 100 000.<sup>56</sup> For first-generation cephalosporins, the risk of cross-reaction with penicillins is 0.5%; the risk with second- and third-generation cephalosporins appears to be even lower.<sup>68</sup>

Erythromycin and clindamycin were previously proposed as alternative antibiotics for women at high risk for anaphylaxis; however, the prevalence of resistance among invasive GBS isolates has increased over the last 20 years and ranges from 25% to 32% for erythromycin and from 13% to 20% for clindamycin.<sup>13,60,69</sup> Although efficacy data is limited, the 2010 CDC guidelines recommend intravenous vancomycin and clindamycin for women (if susceptible) at high risk for anaphylaxis from penicillin; clindamycin susceptibilities including a search for inducible clindamycin resistance should be performed if possible on prenatal GBS isolates from penicillin-allergic women.<sup>13</sup> If susceptibilities are not available for these women, intravenous vancomycin is the preferred intrapartum prophylaxis. Oral antibiotic preparations are not adequate for GBS prophylaxis, as they do not show satisfactory rates of clearance of GBS from the genital tract in the time frame of labour. Table 2 summarizes the recommended regimens for intravenous intrapartum antibiotic prophylaxis for the prevention of early-onset GBS disease.

The implementation of a screening protocol will result in approximately 10% to 25% of women in labour receiving antibiotics for the prevention of GBS neonatal disease. Concern that the use of antibiotics for GBS prophylaxis may result in the selection of other organisms such as *E. coli* is certainly an issue in theory; 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 only.<sup>70</sup> It would be prudent to continue to be vigilant in tracking trends in sepsis and antibiotic resistance as new prophylactic antibiotic regimens are implemented.

## **PRE-LABOUR RUPTURE OF MEMBRANES**

In the term PROM study, Hannah et al. reviewed their outcomes in GBS-colonized women versus GBS-negative women.<sup>71</sup> In that study, 4834 women were randomized to induction versus expectant management. Researchers found that 10.7% of women were GBS positive by vaginal/rectal swab culture and 127 infants had neonatal infections, of which 10 were due to GBS, all in the expectant arm; there was one death due to GBS in the expectant group. The analysis revealed that for GBS-positive women, induction of labour at term decreased the risk of neonatal infection (OR 0.29; 95% CI 0.08 to 1.05,  $P = 0.06$ ). In the expectant management group, GBS-positive women had a significantly greater risk of neonatal infection (OR 4.12; 95% CI 2.00 to 8.52,  $P < 0.001$ ). The conclusion of the study was that for GBS-colonized women with PROM at term, immediate induction with oxytocin results in a lower risk of infection than expectant management or induction with prostaglandin E2 (if there are no contraindications to vaginal delivery).

### **Summary Statement**

There is good evidence based on randomized control trial data that in women with pre-labour rupture of membranes at term who are colonized with group B streptococcus, rates of neonatal infection are reduced with induction of labour (I). There is no evidence to support safe neonatal outcomes with expectant management in this clinical situation.

### **Recommendations**

6. If a woman with pre-labour rupture of membranes at  $\geq 37$  weeks' gestation is positive for group B streptococcus by vaginal/rectal swab culture screening, has had group B streptococcus bacteriuria in the current pregnancy, or has had an infant previously affected by group B streptococcus disease, administer intravenous group B streptococcus antibiotic prophylaxis. Immediate obstetrical delivery (such as induction of labour) is indicated, as described in the Induction of Labour guideline published by the Society of Obstetricians and Gynaecologist in September 2013. (II-2B)
7. At  $\geq 37$  weeks' gestation, if group B streptococcus colonization status is unknown and the 35- to 37-week culture was not performed or the result is unavailable and the membranes have been ruptured for greater than 18 hours, administer intravenous group B streptococcus antibiotic prophylaxis. (II-2B)

The 2010 CDC guideline provides an updated and separate algorithm for women with PPRM. It recommends providing GBS prophylaxis intravenously for 48 hours (or less if the swab for GBS culture proves negative) and additional antibiotics to prolong the latency period when the standard of care would suggest that increased latency and expectant management might show improved maternal and fetal/neonatal outcomes over indicated obstetrical delivery (such as induction of labour).<sup>13</sup>

**Recommendation**

8. If a woman with pre-labour rupture of membranes at < 37 weeks' gestation has an unknown or positive group B streptococcus culture status, administer intravenous group B streptococcus prophylaxis for 48 hours, as well as other antibiotics if indicated, while awaiting spontaneous or obstetrically indicated labour. (II-3B)

**NEONATAL MANAGEMENT**

Information related to the current management of the infant at increased risk of sepsis, including risk of GBS disease, may be found on the website of the Canadian Paediatric Society (Fetus and Newborn Committee).<sup>72</sup>

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