The prevention of early-onset group B streptococcal infections in the newborn

GROUP B STREPTOCOCCI (GBS) ARE A MAJOR CAUSE OF morbidity and mortality among newborn infants. Various strategies to prevent infection in the newborn were reviewed by the Infectious Diseases and Immunization Committee and the Fetus and Newborn Committee of the Canadian Paediatric Society and by the Maternal/Fetal Medicine Committee of the Society of Obstetricians and Gynaecologists of Canada. The committees identified an urgent need for additional research to provide Canadian data upon which to base the selection of the optimal strategy. Until the results of these studies are available, this National Consensus Statement provides guidance for identification and management of women whose newborns may be at risk of group B streptococcal (GBS) disease.

BACKGROUND

GBS (Streptococcus agalactiae) continue to be a major cause of bacterial sepsis among newborns. The source of infection in the neonate is the colonized maternal birth canal; transmission occurs before or during the birth process. Estimates of GBS colonization rates among pregnant women range from 15 to 40% (1-4). GBS is transmitted to 40 to 70% of newborns of colonized mothers; however, only 1 to 2% of such infants develop
disease (5). Two types of GBS infections occur in the newborn. Early-onset disease (less than seven days of age) is more common and has a higher rate of mortality, and it is the subject of this statement. Late-onset disease (seven days to three months of age) is less common and has a lower associated mortality (6-8).

Factors that have been associated with increased risk of early-onset GBS disease include: maternal age less than 20 years; low socioeconomic status; gestation less than 37 weeks; prolonged rupture of membranes (greater than 12 h); maternal intrapartum pyrexia (temperature greater than 37.5°C); multiple pregnancy; GBS bacteriuria; and degree of maternal genital colonization (heavy versus light) (5,9,10). Colonization rates are relatively constant during pregnancy. Fewer than 10% of women who are culture-negative late in the second trimester are culture-positive at delivery (1,2).

**INTERVENTION STRATEGIES**

The high rates of morbidity and mortality associated with GBS infections and the rapidity of onset of postnatal disease have led to numerous strategies to prevent infection in the newborn. They include antenatal, intrapartum and postnatal chemoprophylaxis, and active and passive immunoprophylaxis. Controversy persists about the optimal strategy because of insufficient data or differing interpretations of existing data.

**Immunoprophylaxis – Active:** Serum antibody to GBS capsular polysaccharide correlates with protection against infection. Antibody levels to GBS in infected infants and their mothers are lower than in uninfected maternal-newborn pairs (11). This has led to efforts to develop GBS capsular polysaccharide vaccines for the active immunization of pregnant women to prevent early-onset and late-onset disease in the newborn (12). As with other bacterial vaccines, a substantial number of individuals do not respond to polysaccharide antigens either because of genetic influences such as immunoglobulin allotype or because of the T cell-independent nature of the antigen (13). Lack of significant placental transfer of immunoglobulin (Ig) G before 32 weeks of gestation also diminishes the usefulness of this intervention for protection of the very premature infant. However, efforts to develop an immunogenic vaccine that can be administered to all women, or during pregnancy, continue to be made. Although active immunization may be the ultimate solution, no vaccine is likely to be available in the foreseeable future.

**Passive:** The use of intravenous immunoglobulin (Ig-IV) has been proposed to increase antibody titres to GBS in newborns. Clinical studies using passive immunoprophylaxis have been disappointing (14). Variability in GBS-specific antibody in Ig-IV preparations may account for these poor results (15,16). Although recent efforts to produce a GBS hyperimmune Ig-IV preparation may make passive immunization a viable intervention in the future (17), at present, routine use of Ig-IV cannot be recommended for prevention or therapy of GBS infection in newborns (18).

**Chemoprophylaxis:** Several strategies have been employed using antibiotics for the prevention of GBS infections in the newborn. These can be categorized as neonatal, antepartum and intrapartum. However, no strategies prevent all cases of early-onset GBS disease. Fulminant GBS sepsis and neonatal demise can occur in spite of any planned intervention.

**Neonatal:** Although penicillin or ampicillin therapy of the neonate may prevent some cases of GBS in term infants (19), more than 60% of infants are already asymptomatic at, or shortly after, birth and are at high risk of GBS complications and poor outcome (7,9,20,21). Chemoprophylaxis of neonates appears to be an inferior strategy for prevention of GBS infections.

**Antepartum:** The efficacy of antibiotic therapy of GBS-colonized women during pregnancy for preventing neonatal infection has not been established. Studies using newborn infection as an outcome measure have been of insufficient size to demonstrate efficacy (22-24). Studies in which maternal GBS colonization was followed after a course of antibiotic therapy have demonstrated high rates of GBS recurrence (67%) by the time of delivery. This was true even when antibiotics were given to both pregnant women and their sexual partners (7,25). An exception to the lack of benefit of antepartum antibiotics is women with GBS bacteriuria, which increases the risk for premature rupture of membranes and preterm labour. Oral antibiotic therapy resolves GBS bacteriuria and decreases the risk of preterm labour, although genital colonization typically persists (2,10).

**Intrapartum:** Most experts agree that intrapartum maternal chemoprophylaxis is the best strategy available to prevent early-onset neonatal GBS disease (7,8,21,26). Several studies have assessed the benefit of intrapartum chemoprophylaxis (3,27-31): a meta-analysis of selected randomized controlled trials (5,29-31) showed benefit of intrapartum prophylaxis (32). The strategies used by the studies differ primarily in the methods used to select women for prophylaxis (including whether and when to screen pregnant women for colonization with GBS), laboratory methods to detect GBS colonization, and selective or nonselective chemoprophylaxis.

**Timing of GBS screening:** Anorectal and vaginal swabbing for GBS culture early in the third trimester (26 to 28 weeks) permits adequate time to identify GBS colonization. Problems with this approach include late acquisition of colonization and lack of prenatal care. A single culture has a predictive value of GBS colonization at delivery of only 67% (27). Screening late in the third trimester (36 weeks) decreases the likelihood of missing late acquisition of GBS but misses women with premature labour, and therefore, neonates who are at highest risk of GBS complications. A strategy that screens women presenting in premature labour (less than 37 weeks) and that treats GBS carriers or those
women in whom the test result is unavailable would result in the prophylaxis of as many as 7.5% of pregnant women (33), but it does not address term infants, who account for over two-thirds of early-onset GBS disease. Intrapartum screening suffers from the lack of rapid, sensitive laboratory tests, which would provide the opportunity to make decisions about chemoprophylaxis with sufficient time before delivery.

**Labo‌ratory tests:** Chemoprophylaxis strategies that involve identification of GBS-colonized women require tests with high sensitivity and specificity. The rate of isolation of GBS is improved through culture of the lower vagina and anorectum and through use of selective media for transport and culture (1,7). Bacterial isolation is time-consuming, and results are not rapidly available for the woman presenting in labour. Optimal use of chemoprophylaxis requires a sufficient interval (at least 4 h) between beginning antibiotics and delivery (34). Antigen detection tests provide results more quickly (5 h or less) but with loss of sensitivity relative to culture (29,35-39). The shortcomings of the laboratory tests have led to strategies for selective chemoprophylaxis based only on epidemiological risk factors without laboratory sampling (27,40).

**Selective versus nonselective prophylaxis:** Identification of risk factors that increase the likelihood of GBS infection in the newborn of a colonized woman has led to strategies for use of prophylaxis in high risk situations such as preterm labour (less than 37 weeks), prolonged rupture of membranes (greater than 12 h) and intrapartum maternal fever. This strategy has been shown to be efficacious (21,41,42) but is estimated to fail to prevent 25 to 30% of cases of early-onset GBS infection (9,21). Reasons for this failure are: infection in infants of mothers with rupture of membranes at less than 12 h; lack of maternal fever; and women receiving late prenatal care in whom GBS colonization is not recognized. Treatment based on risk factors alone without prior GBS screening has been reported in one selected population (9) but has similar limitations in prevention of neonatal GBS infection. Prophylaxis of all colonized women regardless of risk factors would decrease the number of undetected cases (except for the late prenatal care) but would dramatically increase the use of intrapartum antibiotics, with the associated risks of adverse reactions and, depending on the colonization rate of the population, possibly the loss of cost-effectiveness. Although identification of women with heavy GBS colonization predicted a higher risk of newborn GBS infection, 16% of infections occurred in newborns of lightly colonized women (28), suggesting that this stratification method was of limited benefit. More simply, increased sensitivity might be achieved by expanding the list of risk factors that would be indications for chemoprophylaxis (ie, GBS bacteriuria, multiple births in preterm labour).

**Cost-effectiveness:** Several strategies have been shown to be cost-effective in the United States, including screening at 26 to 28 weeks and selective intrapartum chemoprophylaxis (43). Intrapartum screening and chemoprophylaxis of all GBS-colonized women regardless of risk factors (44) and intrapartum prophylaxis based on risk factors only (43). The clinical outcomes and costs of 19 potential strategies were recently compared using decision analysis (45). Universal intrapartum chemoprophylaxis, intrapartum chemoprophylaxis based on risk factors, and universal screening at 36 weeks’ gestation plus intrapartum chemoprophylaxis of all GBS culture-positive women and women in preterm labour were identified as the optimal strategies. However, most of the strategies modelled are theoretical and need to be studied in practice before implementation. None of the cost analyses addressed the substantial implications or costs associated with the investigation and management of neonates whose mothers received intrapartum chemoprophylaxis, especially newborns without GBS disease.

**Management of infants of mothers who received intrapartum chemoprophylaxis:** No studies have been performed assessing the optimal management of newborns whose mothers received intrapartum chemoprophylaxis; therefore, recommendations are necessarily empirical (46). Management should take into account gestational age and clinical evaluation.
RECOMMENDATIONS

Although intrapartum chemoprophylaxis in high risk situations reduces the morbidity and mortality due to early onset of GAS infection, **no method prevents all GAS deaths**. Detailed review of this information indicates that specific Canadian data are required to determine the best strategy for chemoprophylaxis in the prevention of early-onset neonatal GAS infection (Table 1) and to test various methods of identifying women whose neonates may be at risk of GAS disease. Two widely recommended strategies are universal screening coupled with selective intrapartum chemoprophylaxis of colonized women at high risk or intrapartum chemoprophylaxis of all women at high risk. Currently available data favour the first approach; however, the cost implications of universal screening are considerable.

Until the results of Canadian studies are available, the Infectious Diseases and Immunization Committee and the Fetus and Newborn Committee of the Canadian Paediatric Society, and the Maternal/Fetal Medicine Committee of the Society of Obstetricians and Gynaecologists of Canada recommend the following:

1. The strategy for decreasing early-onset GAS infection in the neonate should be considered an area of urgently needed research in Canada (Table 1).

2. Until more specific information is available, identification and management of women whose newborns may be at increased risk of GAS disease are acceptable by either of two methods:
   a. Universal screening of all pregnant women at 26 to 28 weeks' gestation with a single combined vaginal-anorectal swab and selective intrapartum chemoprophylaxis of GAS-colonized women with identified risk factors (Table 2).
   b. No universal screening but intrapartum chemoprophylaxis for all women with identified risk factors (Table 2). This strategy should also be used in cases where universal screening is the policy but was either not done or the test results are not available.

3. Where GAS cultures are used, a single swab of the lower vagina and the anorectum should be
transported to the laboratory in selective broth medium and subcultured onto selective solid media. Standardized methods should be established in each facility for the collection, requisition, transport, testing and reporting of these specimens.

4. Antepartum oral antibiotic therapy should be used for women with GBS bacteriuria. These women should still be considered to be GBS-colonized at the time of going into labour. They do not need to be rescreened once they have been identified.

5. Use of intrapartum chemoprophylaxis of women who previously have given birth to an infant with GBS disease regardless of GBS colonization status.

6. The antibiotic regimen of choice for intrapartum chemoprophylaxis is intravenous ampicillin (2 g initially followed by 1 to 2 g every 4 to 6 h) or penicillin G (5 million U every 6 h) until delivery or until labour is stopped. Women who are allergic to penicillin may be given intravenous clindamycin (300 to 600 mg every 8 h until delivery).

7. Women with a culture positive for GBS at 26 to 28 weeks gestation do not require treatment unless they become high risk and are in labour.

8. Management of asymptomatic infants of mothers who received intrapartum chemoprophylaxis should be based on the infant's gestational age, results of investigations for sepsis and the adequacy of the maternal intrapartum chemoprophylaxis (Figure 1). Newborns with clinical signs of sepsis should be investigated and treated with antibiotics to cover GBS and other organisms regardless of maternal GBS colonization or chemoprophylaxis. Because of the concern that intrapartum antibiotics could interfere with the ability to obtain a positive blood culture, symptomatic infants in whom blood cultures are negative should receive a full course of antibiotics, the duration of which will depend on the clinical picture.

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