Review on Group B Streptococcal Infection

SHS Chan, KM Wan, WH Lee

Department of Paediatrics, Queen Elizabeth Hospital, 30 Gascoigne Road, Kowloon, Hong Kong, China

SHS Chan (陳凱珊/G20) MBBS(HK), MRCP(UK), FHKAM(Paed)
KM Wan (尹錦明/G20) MBBS(HK), MRCP(UK), FHKAM(Paed)
WH Lee (李偉航/G20) MBBS(HK), FRCP(Edin, Glas), FHKAM (Paed)

Correspondence to: Dr SHS Chan, Central Kowloon Child Assessment Centre, 147L Argyle Street, Kowloon, Hong Kong, China.

Received October 5, 1999

Abstract

Group B streptococcal (GBS) infections cause significant morbidity and mortality in the newborn population of the western countries. Since 1990, the focus of group B streptococcus (GBS) disease research has shifted to prevention. Intrapartum chemoprophylaxis is well proven to be cost-effective in the prevention of early onset GBS infection. In 1996, a consensus guideline on the "Prevention of Perinatal Group B Streptococcal Disease" was published in 1996, by the collaboration of the American College of Obstetricians and Gynecologists (ACOG), the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP). In recent 10 years, there are enormous ongoing studies leading to new insight in epidemiology, bacteriology, treatment and different preventive strategies of GBS infection. Vaccine development has yielded encouraging result on phase I human trial, demonstrating high immunogenicity and good tolerance when monovalent vaccine was given to women of reproductive age. Development of multivalent conjugated vaccine efficacious against major serotypes causing clinical disease, will be the next goal of effective prevention that may decrease use of antibiotic prophylaxis and to offer protection to a larger population including pregnant mothers and their babies, and also to the high risk elderly. Active research comparing the "universal cultures-based" vs "risks-based" screening strategies for intrapartum chemoprophylaxis is actively ongoing. These enormous upcoming data will lead to further refinement of current consensus guidelines.

Key words

Bacteriology; Colonization; Epidemiology; Group B streptococcal infection; Prevention; Treatment

Bacteriology

Streptococcus Agalactiae is a gram-positive group B beta-hemolytic streptococcus (GBS) that causes invasive disease, primarily in pregnant women and their newborn infants. In 1935, Lancefield and Hare reported on Group B Streptococcus as a cause of puerperal infection. However concern regarding GBS infection diminished, because of the greater pathogenicity of Group A Streptococcus that was described in the same studies. Clinical research regarding GBS infection only resumed during the 1960s. Streptococci are identified as group B because of their content of a rhamnose-containing "group-specific" polysaccharide. The capsule of the organism is composed primarily of a sialic acid containing type-specific polysaccharide, which is the basis for further classification into serotypes. In the past, serotypes Ia, Ib, II and III are recognized to cause most clinical infections. Serotypes III in neonates and type II in adults cause most meningitis. Strains of "non-typable" GBS have been recognized for years, and the recently described serotypes IV in Europe, V in the United States and VI and VIII in Japan account for most of these organisms. They are relatively infrequent causes of invasive infection. Recently, serotype VIII strain was also detected in the United States from the Boston area. In addition to these type-specific polysaccharides, two novel protein constituents have been recently described in GBS, the "C5a-ase" and protein "rib". These novel proteins may become potential carrier proteins for conjugate vaccine development in the future.

Invasive GBS disease in neonates is defined primarily by the presence of bacteremia, pneumonia, or meningitis. 80% of cases occur within the first seven days of life, and these are defined as early-onset infection. In the remaining
cases, the disease becomes apparent from seven days to three months of life; these are defined as late-onset infection. More than 90% of early-onset disease and almost all-fatal infections occur within the first day of life, with a median age of onset at 1 hour. The dominant feature of early-onset disease is sepsis with or without signs of respiratory distress. There is no change in the pattern of early-onset disease since its first description in 1983.\textsuperscript{10} Meningitis occurs in an estimated 5% to 10% of early-onset cases and 30% of late-onset disease cases. Disease localized to the soft tissues, bones, or joints is a feature found almost exclusively in late-onset cases. Fatal infections have been documented in both groups.

**Epidemiology and Risk Factors**

In recent years, two changes in epidemiological aspect of GBS disease in infants are noted. The first is the increasing frequency of the new type V serotype among colonizing or infected GBS isolates. Type V has been reported to cause 9% to 15% of bacteremic infections in neonates (both early and late onset) and pregnant women.\textsuperscript{5,7,11} This increasing prevalence of type V GBS strain, coupled with a proportionate decline in the prevalence of type II strains, represents the first shift in serotype distribution of strains in over 25 years.\textsuperscript{12,13} The second epidemiological shift is the occurrence of invasive infant GBS disease at an age exceeding three months, formerly considered the age limit of susceptibility. Many of these "late, late onset" disease occur among very-low-birth weight infants who remain hospitalized and susceptible, presumably through colonization at mucous membrane sites, and by virtue of immature immune status.\textsuperscript{14} Thus the extent of infant GBS disease to consider has expanded to include older infants with underlying immune compromise.

The incidence of neonatal sepsis and meningitis due to GBS is 0.5 to three cases per 1,000 live births, although there are substantial geographical and racial differences.\textsuperscript{11,15} Case-fatality ratios are now much lower than they were in the 1970s (>50%) and 1980 (15% to 25%). The decline is probably due to improved recognition and prompt treatment of babies with symptoms, since mortality has fallen in both term and preterm infants. During the 1990s in the USA, less than 10% of neonatal cases were fatal, with mortality being significantly more likely among preterm infants. Three quarters of neonatal GBS disease occurs in full term infants. However, the attack rates per 1,000 live births in preterm infants are much higher than in those born at full term.\textsuperscript{11} Recent surveillance in the United States revealed that the overall incidence of early-onset GBS disease remained relatively constant during 1991 to 1993,\textsuperscript{16} yet during 1993 to 1995 the incidence declined significantly in some areas.\textsuperscript{11} This finding is echoed by another population-based surveillance that showed significant decrease in the incidence of early-onset neonatal infection by 65%, from 1.7 per 1000 live births in 1993 to 0.6 per 1000 live births in 1998.\textsuperscript{17} Also among pregnant girls and women, the invasive group B streptococcal disease was observed to have declined by 21% from 1993 to 1998.\textsuperscript{17} This recent decline may reflect the impact of adopting measures to prevent early-onset neonatal GBS infections and coincide with the improved implementation of prophylactic intrapartum antibiotics and existing screening polices.

Three important risk factors were found to be consistently present in 90% of early-onset GBS disease cases: maternal GBS colonization, coincidental perinatal factors, and absence of antibody to GBS. Low levels of maternal antibody at delivery correlated with infants' susceptibility to invasive disease.\textsuperscript{18-20} A number of other risk factors were found to be associated with GBS disease, and these include preterm delivery, prolonged or premature rupture of membranes, delivery of a previous neonate with GBS disease and maternal GBS disease with bacteriuria. Multiple gestations was also found to be a significant risk factor, but this association might overlap to some extent with prematurity.\textsuperscript{21,22}

Pregnant mothers with GBS infection most commonly present as chorioamnionitis, endomyometritis, cystitis, pyelonephritis or post-partum wound infection. Potentially life-threatening complications such as endocarditis, meningitis or fatal septicemia with multiorgan failure have been described.\textsuperscript{23,24} During pregnancy, asymptomatic GBS bacteriuria correlates with adverse pregnancy outcome. Eradication of bacteriuria by antibiotic treatment reduces the risk of preterm delivery.\textsuperscript{25}

Invasive GBS disease does not only involve pregnant mothers and newborn babies. In fact, a population-based surveillance in North America has demonstrated that most cases of invasive GBS disease occur among non-pregnant adults, although rates of invasive disease are highest among infants. Among adults, incidence increases with age.\textsuperscript{26} Non-pregnant adults manifest sepsis, pneumonia, soft tissue infections such as arthritis and cellulitis, and urinary tract infections complicated by bacteraemia. Case-fatality rates for invasive disease are now higher among adults than in the newborn, and are highest among those older than 65 years of age.\textsuperscript{13,27}

**Colonization**

Although recent reports indicate that GBS colonization rates in pregnant women remain relatively constant at
around 15% to 30%. Contemporary assessment of vertical transmission or neonatal colonization rates have not been reported. Recently a prospective cross-sectional study revealed a maternal GBS colonization rate of 28%, with significantly diminished vertical transmission of GBS to neonates when their mothers had intrapartum antibiotics (0% vs 52%), rupture of membranes <12 hours before delivery (38.4% vs 73.3%) or delivery by cesarean section (25.9% vs 45.2%). Contemporary neonatal GBS colonization rate is 13.8%.

The rate of GBS isolation from pregnant women depends on the body site sampled and the specific media used to process cultures. Collection of specimens from two sites, the lower vagina and rectum, increases the likelihood of GBS isolation by 5% to 27% compared to sampling of only the lower vagina. Collection of cervical specimens rather than lower vaginal specimens decreases the yield of GBS. The use of broth media (not solid) that contain antimicrobial agents (selective broth) to inhibit competing organisms increases the yield of group B streptococci from cultures by 50%. The most sensitive method is culture of both vaginal and rectal swabs in selective broth. Direct plating will reliably detect only heavier colonization. Heavy colonization, defined as isolation of organism from direct plating, was associated with 1.5 times higher risk of preterm low-birth-weight after adjustment for other factors, and was present in 9.1% of the women.

The later in pregnancy that cultures are performed, the better the correlation with culture results at delivery. One study estimated that a single positive GBS culture at 26 to 28 weeks of gestation predicted carriage at delivery, with a sensitivity of 70% and a specificity of 90%. Among 26 women whose prenatal cultures were obtained within five weeks of delivery, concordance with intrapartum cultures results was 100%.

An attractive variation of detection method for GBS is the use of rapid antigen detection assay, avoiding the need for prenatal culturing. Unfortunately none of the available technologies - enzyme-linked immunosorbent assay and DNA probe - has sufficient sensitivity to be preferred as the optimal prenatal screening method. They lack adequate sensitivity for routine use but are of greater benefit in heavily colonized women, by which 65% to 88% of carriers can be identified. Their specificity is 98% to 99%, so a positive test is highly reliable.

To confirm neonatal colonization, cultures should be collected at 24 to 48 hours of age so that isolation of GBS would reflect active replication of the organisms (true colonization) rather than transient exposure to GBS in maternal genital secretions (contamination). Usually neonatal colonization is defined as isolation of the organism from one or more sites.

**Prevention**

From the epidemiological data of the western countries, GBS infection is associated with substantial perinatal mortality and morbidity. This makes preventive strategies imperative. Among different proposed strategies including chemoprophylaxis, immunoprophylaxis and local antiseptics, only intrapartum maternal chemoprophylaxis has been evaluated with proven efficacy.

**Chemoprophylaxis**

**Prenatal Chemoprophylaxis**

The approach of treating GBS carriers with oral antibiotics was first attempted almost two decades ago. The results were discouraging. In various attempts to eradicate maternal colonization, mothers were treated with oral antibiotics during the second or third trimester of pregnancy. Although treatment successfully eliminated colonization in the short term, relapse occurred commonly, and it was thought to have been reacquired via sexual contact. Subsequent studies therefore included treatment of partners as well, but the results were essentially the same. Recolonization was still observed in two-thirds of cases by the time of delivery.

**Intrapartum Chemoprophylaxis**

Several multi-center randomized controlled clinical trials of intrapartum chemoprophylaxis have demonstrated a significant reduction in vertical transmission of group B streptococcus and early-onset neonatal sepsis. Some trials have also reported an associated decrease in maternal febrile morbidity. The design and prophylactic agents used (ampicillin or penicillin) in these trials varied, but all used maternal GBS cultures to select candidates for prophylaxis.

Studies showed that 50% to 70% of the mothers of infected infants who develop early-onset GBS disease have at least one of three perinatal risk factors - premature labor, prolonged membrane rupture or intrapartum fever - during parturition. Those infected premature infants whose mothers have these risk factors are most likely to have fatal outcome. These form the strategy of "selective" or "risk-based approach".

Both the American Academy of Pediatrics (AAP) and American College of Obstetricians and Gynecologists (ACOG) agree that selective intrapartum antibiotics chemoprophylaxis is effective in the followings:

- Interrupting the transmission of GBS infection from a colonized mother to her neonate.
- Will prevent many, but not all cases, of early onset neonatal infection.
• Will decrease incidence of maternal GBS post-partum endometritis.

American Academy of Pediatrics (AAP) Guideline

The 1992 guidelines were based on controlled clinical trials demonstrating the efficacy of intrapartum chemoprophylaxis in GBS carriers (identified by anogenital cultures at 26 to 28 weeks of gestation) who had one or more of the following risk factors: (i) preterm labor at <37 weeks of gestation, (ii) preterm rupture of membranes at <37 weeks of gestation, (iii) fever during labor, (iv) rupture of membranes >=18 hours before delivery, (v) previous delivery of a sibling with invasive GBS disease. This recommendation would prevent 50.7% of early-onset GBS disease while administering antibiotics to <5% of all pregnancies.

Many unresolved questions arose with this "culture & risk-based approach". Obstetricians expressed the following concerns: (i) cultures at 26 to 28 weeks of gestation may not predict GBS colonization status at delivery, (ii) availability of prenatal GBS culture results to the delivery hospitals might be difficult, (iii) positive cultures may lead to inappropriate use of antenatal oral antibiotics, (iv) culture-based GBS screening is costly. (v) emergence of antibiotic-resistant bacteria. Pediatricians are also reserved about the 1992 AAP guidelines, especially concerning the newborn management that little information had been given. Also it does not address the 25% to 30% of GBS early-onset disease in term infants whose mothers had GBS colonization but no recognizable obstetrics risk factors.

Guidelines of the American College of Obstetricians and Gynecologists

At around the same time, the ACOG proposed their suggested guidelines with no culture screening for GBS. They suggested providing antibiotics for all pregnancies with intrapartum risk factors. This "risk-based approach" eliminates problems associated with determination of prenatal GBS culture status and estimates to prevent around 70% of cases of invasive GBS infection, similar to the "culture & risk-based method" proposed by AAP. However, the number of mothers who would receive prophylaxis would increase to ~20%.

New Recommendations: Consensus Guidelines by Both the ACOG and AAP

In collaboration with ACOG, AAP and American Academy of Family Physicians, the Centers for Disease Control and Prevention (CDC) has published a consensus guidelines on May 31, 1996 with the statement "Prevention of Perinatal Group B Streptococcal Disease: A Public Health Perspective." Two equally accepted strategies have developed (Universal culture screening with risk-based approach and risk-based non-screening approach) for preventing perinatal GBS disease.

The "universal culture screening with risk-based approach" specifies that all pregnant women should be screened at 35 to 37 weeks' gestation for GBS carriage, and all identified carriers should be offered intrapartum anti-microbial prophylaxis. Women who have previous delivery of infant with invasive GBS disease or GBS bacteriuria during the current pregnancy necessitate routine intrapartum chemoprophylaxis. Mothers with premature delivery, prolonged rupture of membrane (>18 hours) and intrapartum fever (>=100.4°F or 38.0°C) should be given intrapartum antimicrobial prophylaxis before availability of a culture result. With this approach, it is estimated that about 86% of early onset GBS infection can be prevented, with approximately 26.7% of women receiving intrapartum antibiotics.

The "risk-based non-screening approach" specifies that intrapartum antimicrobial agents should be offered to women with the following positive risk factors (those with elevated intrapartum temperature, membrane rupture >=18 hours, or premature onset of labor or rupture of membranes at <37 weeks).

In 1997, the AAP has formally adopted and published the revised guideline. Penicillin G is the preferred prophylactic agent (Table 1). An algorithm for the management of infants whose mothers receive prophylaxis has also been proposed. For asymptomatic

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Recommended Regimens for IAP for perinatal GBS disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No allergy to Penicillin</strong></td>
<td><strong>Recommended</strong></td>
</tr>
<tr>
<td>IV loading</td>
<td>Penicillin G</td>
</tr>
<tr>
<td>5 mU</td>
<td>2 g</td>
</tr>
<tr>
<td>Then IV every 4 hours until delivery</td>
<td>2.5 mU</td>
</tr>
<tr>
<td><strong>Allergic to Penicillin</strong></td>
<td>Clindamycin</td>
</tr>
<tr>
<td>900 mg IV every 8 hours until delivery</td>
<td>500 mg IV every 6 hours until delivery</td>
</tr>
</tbody>
</table>
infant, with gestational age <35 weeks should have a limited diagnostic workup (CBP & DC and blood culture) and be observed without treatment in the hospital for at least 48 hours. For asymptomatic infant, with gestational age >35 weeks, the duration of intrapartum prophylaxis before delivery determines subsequent management. If two or more doses of maternal prophylaxis were given before delivery, no investigation or antibiotic treatment is recommended. Observation in hospital for at least 48 hours is suggested. If only one dose of maternal prophylaxis was given before delivery, infants should have a limited evaluation and at least 48 hours observation. If during hospital observation signs of systemic infection develop, a complete diagnostic evaluation should be performed, and broad-spectrum antimicrobial therapy should be started. According to AAP, these guidelines regarding management of asymptomatic infants born to women given intrapartum chemoprophylaxis are empirical and can be modified in account of individual circumstances and preferences. The important point is routine use of prophylactic antimicrobial agents for infants born to mothers who have received intrapartum chemoprophylaxis is not advised.

Studies and trials to investigate these consensus strategies are ongoing. Outcomes including the incidence of neonatal and maternal GBS disease, occurrence of adverse reactions to antimicrobial prophylaxis and the emergence of penicillin-resistant perinatal infections, are compared among the two strategies. A population-based study adopting "risk-based approach" showed that 19.8% of the delivering population would potentially be candidates for intrapartum antibiotic chemoprophylaxis, agreeing with the previous statistical estimates. Another observational study, comparing the two strategies that were adopted over two different periods, revealed more effective reduction in the incidence of neonatal GBS infection with the culture-based approach as compared to the risk-based approach, and the rate of intrapartum antibiotic use was not much higher in the culture-based group. Although all GBS strains continue to be susceptible to penicillin, erythromycin and clindamycin resistance have been reported in 7.4% and 3.4% of invasive GBS isolates, respectively, and in 16% and 15% of genitourinary isolates. Alternatives such as a cephalosporin may be more appropriate than these two drugs in penicillin-allergic women. Also increasing episodes of resistant gram-negative neonatal sepsis after prophylactic antibiotics use have been reported, and this issue merits further attention.

Post-natal Chemoprophylaxis

In 1975, Dr. Steigman of Mount Sinai Hospital noted absence of GBS sepsis in infants who received the single dose of intramuscular injection of 50,000 units of aqueous penicillin G immediately after delivery, for the prevention of neonatal gonococcal ophthalmia. This initial observation stimulated subsequent investigations of various study designs in an attempt to test Dr. Steigman’s hypothesis.

Over the years, many different studies revealed contradictory results. It is difficult to compare these studies as the study protocols, enrollment criteria and designs are different. In one of the larger trial, 1187 high-risk premature neonates (<2 kg) were randomized to receive either Penicillin G (100,000 U/KG) or no treatment. These infants were given penicillin on delivery and then every 12 hours for 72 hours afterwards. At the same time, blood and surface swabs were cultured for GBS infection. It was found that treatment with penicillin did not prevent early-onset streptococcal disease, nor did it reduce the mortality associated with infection. The study also found that 21 of 24 infants in this study who developed early-onset disease had positive blood cultures at birth, suggesting that the disease was already well established in the immediate postpartum period. With about 70% of neonatal early-onset disease develops in utero during labor, prophylaxis of infant after birth appear to has value only for the minority of whom infectious inoculum is acquired at delivery.

Other researchers and individual hospitals continue to explore broader use of postnatal penicillin. Recently both a prospective study and a retrospective review had demonstrated reduced incidence of clinical sepsis with the use of postnatal penicillin prophylaxis as compare to the control non-treated group. No wide spread increase in the incidence of neonatal sepsis due to organisms other than GBS that are penicillin resistant has been identified in the context of postnatal prophylaxis programs.

Immunization

Active Immunization

It was observed that low level of maternal GBS antibody at delivery correlated with infants’ susceptibility, and antibodies to GBS capsular polysaccharide passively protected laboratory animals from bacterial challenge. These observations prompted research in vaccine development to induce active immune response.

The “first generation” vaccines consisted of purified polysaccharides of serotypes Ia, II, and III. Although these preparations were safe in healthy adults, immunogenicity was disappointing.

The “second generation” vaccines consisted of GBS-purified polysaccharides covalently coupled to tetanus toxoid, a carrier protein that is safe and with widespread international acceptance for use in pregnancy as a means of preventing neonatal tetanus. This strategy of vaccine has been effective and successful with the other two
encapsulated bacterial pathogens: Haemophilus Influenza type b and Streptococcus Pneumoniae. It was found that type III GBS-tetanus toxoid conjugate vaccine was highly immunogenic in both animal and human studies, and did not require pre-existing antibody for seroconversion.

The "third generation" vaccines are now under active investigations. There is considerable interest in the use of native proteins, including the α and β "C" proteins as well as the recently described "ribs" protein, as carriers. These are present in the majority of invasive strains regardless of serotype of GBS. Studies in animals models showed encouraging results. The role of these GBS surface proteins as immunogen or as carrier protein is still under investigation.

Several problems exist concerning the development of vaccination. First immunization of women during pregnancy will not protect infants less than 34 weeks gestation because of the inconsistent transplacental transfer of antibody before 32 to 34 weeks of gestation. Second, the emergence of new GBS serotypes in recent years means that frequent updating of vaccines against the prevalent strains is needed. Identification of a protein antigen that is universally present on all GBS could potentially solve this problem of shifting serotypes. Thirdly, demonstration of vaccine efficacy in pregnant women is very complicated and it involves a lot of future studies to prove its safety and effectiveness over other recommended strategies.

Administration of type III conjugated polysaccharide to women of reproductive age produced a fourfold or greater rise in antibody in 90%. These antibodies promoted opsonophagocytosis in an animal model and crossed the placenta to protect neonatal mice from lethal challenge with type III organisms. Sample sizes for trials to measure the clinical protective efficacy of vaccines against type-specific invasive GBS disease may be prohibitively large so research has focused on defining surrogates for clinical protection against invasive GBS disease through a variety of immunological assays. Vaccine development was at first targeted at women in the third trimester of pregnancy, in time for antibody production and placental transfer to the fetus. However, concerns about potential litigation groups (more than about teratogenesis) have expanded the proposed target to non-pregnant women or even adolescent girls. Measuring the impact of multivalent conjugate vaccines against vaginal GBS colonization may also provide surrogate information on clinical protection. Conjugate vaccines typically induce a T-cell-dependent response and promote immunological memory but the duration of protection afforded by the GBS conjugate vaccine is unknown, and the need to protect women over all their reproductive years may make booster doses necessary and complicate vaccination programs. A recent study showed that protein C, a potential component of GBS conjugate vaccine, only present in 8% of colonizing isolates. This suggested that although it might be a suitable carrier, induction of antibody to this antigen would not be expected to provide enhanced protection.

**Passive Immunization**

Animal studies have shown that passive transfer of antibody from intravenous immunoglobulin, hyperimmune serum or monoclonal antibody can prevent disease following bacterial challenge. No human trials of these products are available yet.

**Local Antiseptic Agents**

A novel approach to prevention of neonatal GBS sepsis is reduction of maternal vaginal colonization with anti-septic agents. Several studies outside the States have reported a beneficial effect of vaginal wash or wipe with chlorhexidine solutions or gel during labor. They found a reduction of admission to neonatal special care units for infants whose mothers received anti-septic agents. One of the recent study also included wiping of infants with chlorhexidine immediately after birth. None of these studies is sufficient to prove directly its effectiveness in the prevention of early onset invasive disease. These simple methods are of interest because they can provide a low risk and low cost alternative to systemic antibiotic treatment during labor. Yet they do not appear to be applicable in terms of prevention in the setting of chorioamnionitis or membrane rupture.

**Treatment**

For suspected GBS infection, the initial therapy should consist of ampicillin and gentamicin, which provide broad coverage for most neonatal pathogens and synergistic bacterial activity against GBS infection. Once GBS infection has been confirmed, penicillin G remains the treatment of choice. The recommended dosages and duration of treatment are based on clinical experience endorsing their safety and efficacy. Currently there is an upward "creep" in recommended dosages, up to daily doses of as much as 500,000 U/kg in meningitis. These changes in dosage recommendations are based on the theoretical consideration of "inoculum" effect, and not on comparative studies. The median minimal inhibitory concentration (MIC) of penicillin G for GBS is 0.1 µg/ml and the cerebrospinal fluid (CSF) inoculum may exceed 10³ colony-forming units/ml in GBS meningitis. The suggested high penicillin doses are to assure that there are adequate antibiotic levels to achieve rapid sterilization (within 24 hours) in the CSF (Table 2).

Study about the use of once-daily ceftriaxone appears to be safe and effective for infants with uncomplicated
### Table 2

<table>
<thead>
<tr>
<th>Infection</th>
<th>Antibiotic dose</th>
<th>Expected duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected meningitis</td>
<td>Ampicillin (300 mg/kg/d) &amp; Gentamicin (5-7 mg/kg/d)</td>
<td>Until CSF sterile &amp; Penicillin susceptibility documented</td>
</tr>
<tr>
<td>Suspected sepsis</td>
<td>Ampicillin (150 mg/kg/d) &amp; Gentamicin (5-7 mg/kg/d)</td>
<td>Until blood stream sterility documented</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>Ampicillin (150 mg/kg/d) or Penicillin G (200,000 U/kg/d)</td>
<td>10 days</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Penicillin G (400,000-500,000 U/kg/d)</td>
<td>Minimum 14 days</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Penicillin G (200,000-300,000 U/kg/d)</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>Penicillin G (200,000-300,000 U/kg/d)</td>
<td>3-4 weeks</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>Penicillin G (200,000-300,000 U/kg/d)</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

Monitor Peak and Trough level of aminoglycoside.

Sepsis and may be considered for the longer-term treatment of osteomyelitis and septic arthritis.59

In the presence of meningitis, a lumbar puncture is recommended to be repeated at 24 to 48 hours after initial therapy to assure sterility, and before discontinuing therapy after a minimum of 14 days of treatment, if indicated. If the CSF culture remains positive, this suggests the possibilities of antibiotic resistance, a purulent complications, or inappropriate agents or doses. If the CSF parameters suggest suboptimal resolution of the meningeal inflammation (protein >200 mg/dl or neutrophil counts exceed 30% of the total white cell count), an additional week of penicillin G is recommended. For infants with GBS meningitis, a contrast-enhanced CT brain is important before discontinuing antibiotic therapy. This serves the following three purposes: (1) identifying cerebritis which may need additional treatment; (2) recognizing any intracranial focus of infection; (3) identifying cerebral infarct which dictates close neurological follow-up.58

All infants recovering from invasive GBS disease should be closely monitored prospectively for developmental sequelae. For infants recovering from meningitis, this should include screening tests for auditory and visual function.

Other modalities of treatment are still under investigations. Intravenous immunoglobulin was not found to improve the overall survival of premature infants with suspected or proven sepsis in a large, multicenter trial.60

The cascade of cytokine activation that was seen in gram negative pathogenic septic shock with the production of tumor necrosis factor-α (TNF-α), was also observed in GBS type III exposure in vitro. Immunotherapy may therefore have a possible role. Dexamethasone administration in bacterial meningitis is thought to be beneficial. Clinical trials of steroids in neonatal GBS meningitis are underway, but a recommendation cannot be made yet.

One of the most lethal features of early onset GBS sepsis is the development of persistent pulmonary hypertension. Barefield et al.61 have demonstrated an elevated level of thromboxane A2, an eicoanoid that is a selective pulmonary vasoconstrictor, in animal models. Berger et al.62 found that inhaled nitric oxide (NO) reversed pulmonary hypertension and systemic oxygenation in a piglet model of GBS sepsis. Controlled clinical trials are awaited to confirm the role of NO to improve survival in early-onset GBS disease and reduce the indications for extracorporeal membrane oxygenation.

### Conclusion

A lot of data and information concerning GBS infection is available from the enormous ongoing studies in the United States. As additional experience accrues, it is likely that the 1996 consensus guidelines will be further refined. Development of a more sensitive and specific rapid screening test and effective vaccination could potentially eliminate the need for formal culture screening and/or chemoprophylaxis for gestations beyond 34 weeks as well as prevention of late-onset disease. Development of effective vaccination with mass scale immunization may bring the GBS control to a new millennium.

In HK, different hospitals adopted different strategies concerning preventive chemoprophylaxis. Meanwhile there is no available data to compare the effectiveness, safety and cost-benefit of different local strategies. Further local collaborative studies on our own GBS infections' prevalence, incidence, serotypes distribution, as well as maternal and contemporary neonatal colonization rates, with reference to the preventive strategies, are therefore helpful. Open communication and close collaboration with our obstetrics counterpart is essential to establish our own
optimal, practical and cost-effective management concerning prevention of early-onset GBS disease.

References

38. Tuppurainen N, Hallman M. Prevention of neonatal group B streptococcal disease: Intrapartum detection and chemoprophylaxis of heavily colonized parturient. Obstet...