Seminar

Group B streptococcus

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During the 1990s the focus of group B streptococcus (GBS) disease research has shifted to prevention. Increased use of intrapartum antimicrobial prophylaxis in North America and Australia has led to substantial declines in perinatal disease. Vaccine development (initiated two decades earlier) has yielded results—for example, polysaccharide-protein conjugate vaccines given to women of reproductive age proved to be highly immunogenic and well tolerated. Also economic evaluations have assessed the cost-effectiveness of prevention strategies in different populations. Although GBS has traditionally been considered a perinatal pathogen, the burden of invasive GBS disease among nonpregnant adults has been measured. Adverse outcomes of pregnancy attributable to GBS were addressed through a multicentre study which confirmed the important role of heavy colonisation with GBS in preterm low-birthweight deliveries. Finally, the pathogen itself has continued to evolve: new capsular serotypes described in the past decade are now causing an important proportion of clinical infections.

This seminar will highlight the spectrum of methods of preventing group B streptococcus (GBS) infection and examine their impact in research and field settings, including the clinical challenge posed by the broader use of intrapartum prophylaxis. Also covered are the expanded clinical spectrum of disease attributable to GBS and the role of GBS in nonindustrialised countries.

Perinatal disease burden

Many adults are colonised with GBS in the genital and gastrointestinal tracts but remain free of symptoms. However, women colonised with GBS during pregnancy are at increased risk of premature delivery[1] and perinatal transmission of the organism. Pregnancy-associated GBS disease is most often manifest during labour or within the first few days of an infant's life; it can affect the woman or her baby or both. Ascending spread leads to amniotic infection, which can result in maternal sepsis and, very rarely, meningitis. GBS is also a leading cause of chorioamnionitis and is one of several bacteria now thought to enhance the risk of preterm premature rupture of membranes. Newborn babies can acquire GBS by aspiration of infected amniotic fluid or during passage through the birth canal.

Since the 1970s, in many industrialised countries GBS has been the principal cause of sepsis and meningitis during the first week of life (ie, early-onset disease). GBS also causes late-onset infections (at more than 7 days of age but rarely after the third month). The incidence of neonatal sepsis and meningitis due to GBS is 0·5–3 cases per 1000 live births, although there are substantial geographical and racial differences.[2,3] During the 1990s in the USA less than 10% of neonatal cases were fatal, mortality being significantly more likely among preterm infants.[2] Case-fatality ratios are now much lower than they were in the 1970s (>50%) and 1980s (15–25%); 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. Three-quarters of neonatal GBS disease occurs in full-term infants, although attack rates per 1000 live births in preterm infants are much higher than in those born at 37 weeks' gestation or beyond.[2]

GBS amniotic infection can result in intrauterine death, although the proportion of all spontaneous abortions and stillbirths attributable to GBS is difficult to determine. Because vaginal colonisation with GBS occurs in about 20% of women, superficial contamination of the placenta is likely and this would give rise to false-positive results if surface swabs are relied upon for diagnosis. Careful pathological review and microbiological procedures must be followed to establish a causative role for GBS infection in stillbirths.

Prevention of perinatal infections

Antimicrobial prophylaxis

The intravenous or intramuscular injection of antimicrobial agents after the onset of labour or rupture of the membranes is highly effective in reducing neonatal colonisation with GBS.[4] Several clinical trials have demonstrated the efficacy of intrapartum antimicrobial prophylaxis in selected women (ie, GBS colonised, with or without obstetric complications such as preterm labour or rupture of the membranes, or prolonged rupture of the membranes) against laboratory-confirmed, early-onset GBS disease.[4] These methods are cost-saving, given rates of GBS disease found in North America and Australia.[5]

Clinical and public health authorities in the USA, Canada, and Australia have issued guidelines on intrapartum prophylaxis. The 1996 US consensus statement recommended one of two strategies[4]—a screening-based approach, in which vaginal-rectal swabs are collected at 35–37 weeks' gestation for culture in selective broth medium and GBS carriers and those delivering before 37 weeks with unknown GBS status are then offered intrapartum antimicrobial prophylaxis; or a risk-based strategy in which women of unknown GBS status receive intrapartum prophylaxis based on threatened delivery at <37 weeks' gestation, rupture of the membrane 18 hours or more, or intrapartum fever

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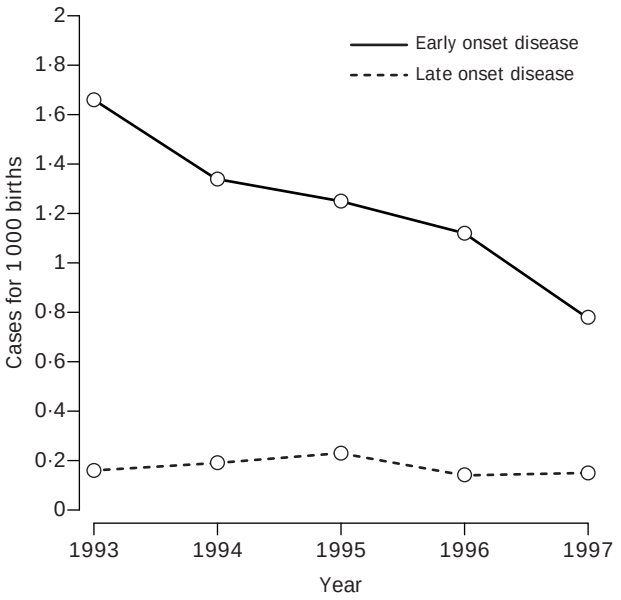
Panel 1: **Methods for prevention of perinatal GBS**

Method	Current status	Advantages	Disadvantages
Intrapartum antimicrobial prophylaxis to at-risk mothers	Recommended in USA, Canada Australia	Efficacy shown in clinical trials; led to significant decline in early-onset GBS sepsis	No impact on late-onset disease, stillbirths, or GBS-related prematurity; increases antibiotic use in women
Postnatal penicillin prophylaxis to newborn babies	Used in some hospitals	Led to decrease in early-onset GBS disease among term infants; avoids risk of maternal anaphylaxis	Did not reduce GBS disease among low birthweight infants; no impact on late-onset disease, stillbirths or GBS-related prematurity; increases antibiotic use in newborns
Vaginal disinfectants	Used in research trials in Europe, Africa, USA	No impact on antibiotic resistance; inexpensive and simple; applicable to poorly equipped delivery sites	Efficacy against confirmed GBS sepsis not documented; no impact on stillbirths, GBS-related prematurity
GBS polysaccharide-protein conjugate vaccines	Phase II clinical trials	Expected to prevent both early and late-onset GBS sepsis; no impact on antibiotic resistance	Efficacy against confirmed GBS sepsis not documented; legal aspects of vaccinating during pregnancy are obstacles in industrialised countries; other schedules less efficient

(≥38°C). Penicillin was the agent of choice because its antimicrobial spectrum, narrower than that of ampicillin, would reduce the likelihood of resistance developing in other organisms.

A review of early-onset GBS during 1995 in four areas in North America suggests that these strategies would reduce early-onset disease by 41% (risk-based) or 78% (screening-based).[6] As predicted, substantial decreases in early-onset GBS disease have been reported in individual hospitals where policies were implemented and in larger geographical areas.[3] The US Centers for Disease Control and Prevention's surveillance data indicate that early-onset disease declined by 53% between 1993 and 1997 in areas with continuous data (unpublished) (figure). The incidence of late-onset disease remained stable. This decline in early-onset disease in a multistate population in the USA was accompanied by a significant increase in the proportion of hospitals adopting prevention policies.[7] Only 14% of hospitals had a written GBS policy in 1994 compared with 46% in 1997.



Incidence of early-onset and late-onset GBS disease
Source: CDC Active Bacterial Core Surveillance in United States, 1993–97. Data reflect aggregate disease rates from three counties in California, eight in Georgia and five in Tennessee and the state of Maryland; annual births about 190 000.

Complex issues regarding management of babies whose mothers have received prophylactic antibiotics remain. For example, the extended observation (eg, 48 h or more) of these newborns has important economic consequences, and more data are needed to clarify whether this is necessary. Also guidelines for evaluating infants born to women who have received prophylaxis consider less than two antibiotic doses or an interval of less than 4 hours from initiating antibiotics until delivery to be inadequate—ie, in such situations additional evaluation of the baby is deemed necessary. More research is needed to refine recommendations on what is adequate maternal antibiotic prophylaxis and appropriate neonatal management.

GBS prevention significantly increases the use of intrapartum antimicrobial agents. 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,[8] and in 16% and 15% of genitourinary isolates.[9] Alternatives such as a cephalosporin may be more appropriate than these two drugs for prophylaxis in penicillin-allergic women. No widespread increase in the incidence of neonatal sepsis due to organisms other than GBS that are penicillin resistant has been identified in the context of either intrapartum or postnatal prophylaxis programmes.[10] However, episodes of resistant infection after prophylactic antibiotic use have been reported,[11] and this issue merits further attention. Because there is substantial variation in the incidence of neonatal sepsis between hospitals and over time, long-term monitoring in large populations is needed to characterise the adverse effects of antimicrobial prophylaxis.[12]

Although consensus guidelines in some countries have recommended prevention programmes incorporating intrapartum antimicrobial agents, researchers and individual hospitals continue to explore broader use of

postnatal penicillin, administered either to all infants[10] or to infants born to colonised mothers who did not have fever, prolonged rupture of the membranes, or preterm delivery.[13] Prenatal detection of GBS via culture in a selective broth remains the gold standard, and late gestation cultures are the best way to improve accuracy of the prenatal screening test.[4] Rapid detection tests are under investigation. The ones available are less sensitive than selective broth medium,[14] but some are sensitive for heavy colonisation and this feature might justify their use in certain circumstances when GBS carriage status is unknown at the time of delivery.

Vaginal disinfectants

A less invasive approach to the interruption of perinatal transmission of GBS is the use of vaginal disinfectants when labour begins. Chlorhexidine was investigated in a randomised trial in Sweden.[15] Transfers to neonatal intensive care were fewer among infants born to chlorhexidine-treated mothers than in the controls, but the study was too small to identify the impact of vaginal disinfectants on laboratory-confirmed GBS sepsis or meningitis. Although vaginal disinfection is likely to be less effective than systemic antibiotic prophylaxis, topical microbicides should not lead to increases in resistant pathogens. A vaginal chlorhexidine intervention study in Malawi found a significant decline in admissions for clinically defined neonatal sepsis and for mortality attributed to infectious causes during the intervention period compared with the period of no intervention.[16]

Vaccines

Antibodies to capsular polysaccharide passively protect laboratory animals from bacterial challenge,[17] and infants with early-onset GBS disease are more likely than healthy infants born to GBS-colonised mothers to have low levels of antibody to the GBS capsular polysaccharide of the infecting organism.[18] These observations prompted research on GBS polysaccharide antigens and resulted in production of purified polysaccharides and, more recently, conjugated vaccines against the major serotypes causing disease. Administration of type III conjugated polysaccharide to women of reproductive age produced a fourfold or greater rise in antibody in 90%.[19] These antibodies promoted opsonophagocytosis in an animal assay and crossed the placenta to protect neonatal mice from lethal challenge with type III organisms.[19]

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. Measuring the impact of multivalent conjugate vaccines against vaginal GBS colonisation may also provide surrogate information on clinical protection. 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. A routine healthcare visit in adolescence for provision of vaccines—especially, booster doses of antigens used in the childhood series—makes this addition to the schedule feasible, although the coverage that is achievable in adolescence remains to be determined. Nor do many countries have the infrastructure for immunisation at this age. 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 programmes.

A challenge to GBS vaccine development has been the shift in serotypes of strains causing disease. First recognised in the USA in 1993, serotype V now accounts for 10% or so of neonatal disease and 30% of invasive disease in non-pregnant adults in the USA. The serotype V polysaccharide has been purified and conjugated, and clinical trials are in progress. Newer serotypes (VI and VIII) may be increasingly common in parts of Asia.

Prematurity and GBS

The relation between GBS and prematurity is complex. The incidence of invasive disease (ie, sepsis and meningitis) is higher among preterm infants than among those born at term, although 74% of early-onset GBS and 56% of late-onset cases occur in full-term infants. Antibody transport across the placenta is reduced early in gestation. Preterm infants born to colonised mothers may have a higher risk of disease because lower amounts of protective maternal antibodies were transported across the placenta. Premature rupture of membranes (ie, rupture before spontaneous onset of labour) is strongly associated with early-onset GBS disease. Premature rupture of membranes earlier than 37 weeks occurs in 30–40% of preterm deliveries.[20] GBS, and several other bacteria, may cause preterm premature rupture through a variety of mechanisms, including

Panel 2: **Published large studies of effect of GBS on preterm delivery and/or low birthweight**

Ref	Number of women (% GBS+)	Specimen and methods	Outcome(s) measured	GBS + with outcome	GBS – with outcome	OR	Adjustment for other factors?
Regan[1]	13 646 (21·1)	C, V, SBM, plates	PTD + LBW	6·6% (heavy)	4·7%	1·5 (p<0·05)	Yes
Regan[27]	6706 (13·4)	C; rapid test	PTD <32 w	5·4%	1·8%	4·4 (p<0·005)	No
Thomsen[28]	4122 (1·6)	Urine culture	PTD	38%	4·7%	p<0·001	No
Sweet[29]	3293 (14·3)	V; broth, plates	PTD LBW	7·3%	6·0%	1·2 (p=0·33) 1·5 (p<0·05)	Yes
Moller[30]	2745 (2·5)	Urine culture	PTD	20%	8·5%	2·8 (p<0·001)	No
McKenzie[31]	2043 (4·1)	Urine culture	PTD	3·5%	7·2%	0·47 (p=0·22)	No
Hastings[32]	1457 (28·4)	V, R; SBM	PTD	6·5%	6·4%	1·0 (p=0·97)	Results also NS for heavy GBS +
Matorras[33]	1050 (11·5)	V, R; SBM	PTD	21·4%	23·1%	NA	No

OR=odds ratio; C=cervical swab; V=vaginal swab; R=rectal swab; SBM=selective broth media; PTD=preterm delivery at <37 weeks unless otherwise specified; LBW=low birthweight (<2500 g); NS=not significant.

secretion of proteases that degrade collagen and weaken fetal membranes.[20]

The pathways involved in preterm rupture of the membranes are complex. This new understanding has revealed the multifactorial nature of prematurity, and earlier work, looking at single causes of prematurity in isolation, may have failed to take into account important interactions—so critical review of the evidence relating GBS to prematurity and/or preterm low birthweight is appropriate. Panel 2 summarises reports of published investigations involving at least 1000 pregnancies. Establishing causality in preterm delivery is difficult, and many reports which have linked GBS colonisation with prematurity did not distinguish whether GBS infection directly contributed to preterm labour, to onset of membrane rupture before 37 weeks, or both. Data on other infections and prematurity have identified varying risks in different populations. Conflicting results of investigations of the role of GBS in prematurity could reflect differences in the populations studied.

GBS was detected by a variety of techniques in these studies. The most sensitive method is culture of both vaginal and rectal swabs in selective broth.[4] Direct plating will reliably detect only heavier colonisation, as will most of the rapid antigen-detection methods. GBS bacteriuria is probably an indicator of heavy colonisation too. Regan and colleagues recently reported an investigation involving 13 646 women in several centres in the USA.[1] Heavy colonisation, defined as isolation of the organism from direct plating, was associated with 1·5 times higher risk of preterm low birthweight, after adjustment for other factors, and was present in 9·1% of the women. The same multicentre study group reported that bacterial vaginosis was associated with a 1·4 times increased risk of preterm low birthweight and was present in 16% of the cohort.[21] Antibiotic treatment trials for bacterial vaginosis have reduced preterm low birthweight in some populations but an erythromycin trial among women with GBS colonisation failed to reduce premature delivery,[22] even though the relative risks in these two groups are similar. The erythromycin trial had limited power to identify an impact among heavily colonised women, and the agent used did not significantly reduce GBS carriage. Larger studies that focus on heavily colonised women and use other antimicrobial agents (or vaccines, if these prove to reduce genital colonisation) are needed to determine whether interventions aimed at GBS colonisation can affect preterm and/or low-birthweight deliveries.

Disease in non-pregnant adults

Population-based surveillance in North America has demonstrated that most cases of invasive GBS disease, defined as isolation of GBS from a normally sterile site, occur among non-pregnant adults, although rates of invasive GBS disease are highest among infants. Among adults, incidence increases with age. Non-pregnant adults manifest sepsis, pneumonia, soft-tissue infections such as cellulitis and arthritis, and urinary-tract infections complicated by bacteraemia.[23] Case-fatality rates for invasive GBS disease are now higher among adults than in the newborn and are significantly higher among those aged 65 plus than in younger adults.[2,24]

Independent risk factors associated with GBS disease in non-pregnant adults include diabetes mellitus, cirrhosis, renal failure, stroke, and breast cancer.[24] A substantial proportion of these infections are polymicrobial (26%) and/or nosocomially (22%) acquired.[24] Older age, independent of underlying medical condition, increases the risk of invasive GBS disease.

Although our understanding of the immune mechanisms responsible for protection against invasive GBS disease in adults is limited, vaccines developed for prevention of perinatal infections might also protect at-risk adults, and further exploration of the immunology of GBS disease and protection in adults is appropriate.

GBS in non-industrialised countries

The apparent lack of significant clinical disease due to GBS in less developed countries is puzzling. Birth practices differ substantially around the world, and home births and less invasive procedures during hospital births might limit the risk of GBS sepsis in the newborn. However, detection of early-onset infections may be obscured by the large proportion of deliveries that take place outside health centres and the probability that infants who develop GBS sepsis on the day of birth will not survive. Even for infants born in hospital, bacteriological procedures are not routine in many developing countries. Other clinical presentations of GBS morbidity may predominate in some areas. For example, a case-control study comparing women with spontaneous abortions and gestation-matched controls in Nairobi, Kenya, found that vaginal colonisation with GBS was strongly associated with miscarriages independently of other factors.[25]

Published data on GBS colonisation among women in developing countries suggests geographical variation in GBS carriage but the range (12% in India and Pakistan to 22% in North Africa and the Middle East) is consistent with the range found in industrialised populations.[26] Characterisation of isolates from The Gambia and Peru suggests that the serotypes carried by women in those countries are similar to those carried by women in the USA.

Since exposure to the organism seems to be similar in pregnant women in developing and industrialised countries, the failure to recognise GBS as an important cause of neonatal sepsis in developing countries could reflect either insufficient surveillance or true population differences in clinical disease. One hypothesis is that GBS-related morbidity among women in developing countries may more often manifest through preterm delivery, in which case infants may not survive to develop confirmed sepsis. By contrast, in industrialised countries more extensive interventions available for complicated deliveries could permit infants at risk of GBS disease to survive and develop full clinical sepsis. These matters require further investigation.

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