Early Onset Group B Streptococcal Disease (EOGBSD)

Introduction

- Perinatal infection with group B streptococcus (GBS) is a worldwide public health problem.\(^1,2\)
- It is the commonest serious bacterial pathogen affecting neonates, varying in incidence between 1-4 cases per 1000 livebirths for the most serious form, early-onset infection (<48 hours).\(^1,2\)
- Mortality varies between 6-15% and morbidity is significant for mother and infant.\(^1,2\)
- Transmission is vertical and occurs before or during labour since >70% of neonates with early onset disease are bacteraemic at birth.\(^3\)
- Rapid, accurate, "bedside" tests to identify carriers in early labour are not yet readily available.\(^4\)
- Maternal carriage varies between 10-40% resulting in a 50-70% neonatal colonisation rate and 1-2% disease rate.\(^1,2\)
- Maternal and thus neonatal, absence of GBS-specific immunoglobulin G is one of the most significant risk factors.\(^5,6\)
- Until the development of a safe, immunogenic vaccine, prevention by intrapartum chemoprophylaxis of at-risk mothers should be introduced. This practice is justified from the cumulative evidence concerning efficacy, safety and cost effectiveness. The evidence is presented below.
- Audit of public hospitals in Victoria in 1997/8 found 97% hospitals identified and treated pregnant women at risk of EOGBSD\(^7\) and audit of ACOG fellows in the US found >95% do so.\(^8\)
- The outcomes of intervention for RPA Hospital are described below. Universal screening and treatment of carriers in labour was chosen as this intervention will prevent a greater number of cases than risk factor intervention in labour.\(^9,10\)
- **Following intervention in 1988 at RPA, the rate of EOGBSD fell from 1.4 to 0.2/1000.** *Successive audits have shown the following low rates:*
  - 5 years, 1988 to 1993 was 0.37 per 1000 livebirths\(^11\)
  - 8 years, 1988 to 1996 was 0.20 per 1000 livebirths\(^12\)
  - 5 years, 1996 to 2001 was 0.26 per 1000 livebirths (HJ unpublished)

Incidence of EOGBSD

Estimates of early-onset (EOGBSD) before widespread intervention, have varied between 1 and 4/1000 livebirths, in Australia\(^11,13,14,15\), the United States\(^16,17,18,19\), and Western Europe.\(^20,21\)

Limited reports from the United Kingdom suggest a lower incidence of 0.3-1/1000\(^22,23,24,25\).
although recent data indicate rates similar to the US\textsuperscript{26, 27, 28, 29, 30} Currently, public health information is being collected to inform best practice in the UK\textsuperscript{31} and in Europe there is a plea for a consensus.\textsuperscript{32}

Following intrapartum chemoprophylaxis, the incidence has decreased to 0.5 and 0.6 per 1000 livebirths in Australia\textsuperscript{33} and the US \textsuperscript{34, 35} respectively. Where compliance is high (> 90%) the figures for units in Australia \textsuperscript{12} and the US \textsuperscript{36} are 0.2 and 0.14 per 1000 respectively.

Late-onset disease occurs at a rate of 0.5/1000 and is limited to the first 3 months of life.

### Risk factors

#### Maternal carriage

The maternal genital and gastro-intestinal tract are the principal source of GBS organisms leading to both maternal and neonatal infection. Vaginal colonisation occurs in about 20% of women of childbearing age, range 10-40% and 50-75% of their infants become colonised but only about 2% acquire EOGBSD.\textsuperscript{37, 38} At RPA hospital, carriage rate is 12-15% using low vaginal swabs and non-selective media.

**Factors which increase the prevalence of maternal carriage** include age <20 years, parity <4, ethnic background, all of which may reflect socioeconomic status or sexual activity. However sexual intercourse is not the major mode of transmission among humans.\textsuperscript{38} Evidence suggests that the gut is the primary reservoir of GBS carriage. The organisms are recovered more often from rectal than genital cultures and from external compared with internal genital cultures. (Hence low not high vaginal swabs ± anal swabs will give the highest yield). Similar to other enteric bacteria, GBS, although sensitive to penicillin, is refractory to penicillin therapy of vaginal carriage. Women can be either continuous vaginal carriers of GBS, or more often, transient or intermittent carriers.

**Carriage rate** then, will depend on

- sampling site (vagina alone or vagina and anorectal area)
- the exact site of sampling (low vagina/vulva or high vagina/cervix)
- the number of times each woman is sampled during pregnancy\textsuperscript{39}
- use of broth enrichment techniques.

Sampling from both low vaginal and anorectal sites at 28 weeks gestation and the use of selective broth media, to inhibit competing organisms, enabled prediction of intrapartum GBS carriage with >90% accuracy.\textsuperscript{39}

The most sensitive and specific tool for identification of infants at risk of EOGBSD is a maternal vaginal culture at time of delivery. This test identifies <15% of all parturients, only 2% of whom have neonatal infection, yet accounts for >97% of all infants with disease.\textsuperscript{40} Benitz et al\textsuperscript{40} classified clinical risk factors into two groups:

1. **Risk factors with high attack rates > 50/1000 livebirths but relatively rare**
   - Preterm premature rupture of membranes in a GBS-colonized mother
   - Clinical chorioamnionitis
2. Risk factors with lower attack rates 10-25/1000 but more prevalent
   - Light (10/1000) or heavy (24/1000) GBS vaginal culture at delivery
   - Birth weight <2500g (16/1000)
   - Preterm <37 weeks (10/1000) with a gradient of <28 weeks (45/1000), 28-30 (21/1000), 31-33 (10/1000), 34-36 (5/1000)
   - Prolonged rupture of membranes >18hours (12/1000)
   - Intrapartum fever >37.5 (10/1000)
   - One or more of Intrapartum fever, PROM or preterm (12/1000)
   - Intrapartum fever or PROM in term infants (14/1000)
   - Positive rectovaginal culture for GBS at 28 weeks (9/1000)
   - Positive rectovaginal culture for GBS at 36 weeks (9/1000)

Clinical Features

Fetal and Neonatal infection

Ascending infection, with resulting amniotic fluid and fetal infection occurs most often during labour, sometimes with intact membranes, and can lead to stillbirth but usually results in a symptomatic neonate at birth. Both early fetal death, weight <500 grams, and late deaths have been documented but the incidence is not known.

The EOGBSD accounts for up to 80% of infant cases of sepsis and usually presents with respiratory distress (grunting, tachypnoea, retractions, cyanosis, apnoea) or with non-specific signs of sepsis, such as tachycardia (heart rate >160/min) and hypotension (mean BP < 30 mm Hg). Meningitis occurs in 6-15% with estimates of long term neurologic sequelae in 15-30% of survivors. Mortality is inversely related to birthweight.

Late-onset GBS disease is less fulminant and most commonly presents in the first month with meningitis, bacteraemia or both, with sequelae in about 20% (also see Lin Feng-Ying C.2002 Abstract SPR). Perinatal and nosocomial transmission of GBS to the infant has been documented.

Maternal infection

GBS bacteruria is usually asymptomatic and is therefore detected by screening the urine of pregnant women, most commonly in the first trimester. Peripartum maternal infection usually presents as fever >37.5°C, secondary to chorioamnionitis, endometritis or post-caesarean wound infection. Independent risk factors for clinical chorioamnionitis include GBS colonization, membrane rupture for > six hours, internal fetal monitoring for > twelve hours and the number of vaginal examinations. Evaluation includes physical examination, differential white cell count, gram stain and culture from swabs of the lower vagina and cervix and possibly cultures of amniotic fluid, blood and urine.
Diagnosis

Rapid diagnosis of the disease by clinical or laboratory methods is difficult. The clinical history and examination of the mother and neonate may indicate a risk of sepsis but are not diagnostic. Neither laboratory tests nor chest X-rays provide a rapid and accurate diagnosis of GBS sepsis. Management should be based on maternal and fetal risk factors and neonatal assessment

- **Chest X-ray** may be non-specific, consistent with pneumonia or indistinguishable from respiratory distress syndrome. Surfactant dysfunction has been documented in EOSBD, and should be treated with exogenous surfactant.

- **Blood cultures** may be negative in up to 50% of neonates with pneumonia and following intrapartum antibiotics. False positive cultures result usually from contamination of a colonized neonate and may explain the asymptomatic neonate with a positive blood culture. The additional limitation is the delay in bacterial growth, 96% of positive blood cultures being identified by 48 hours of incubation and 98% by 72 hours.

- **CSF cultures.** Lumbar puncture may be restricted to neonates with a positive blood culture, abnormal neurological signs, GBS bacterial antigen in the urine, in a symptomatic baby exposed to antibiotics in labour or suspected late onset GBS disease.

- **Urine latex particle agglutination (LPA) test for GBS antigen** is useful, especially if intrapartum antibiotics inhibit growth of the blood culture. Most neonates pass urine within 24 hours of birth. A false positive LPA test may occasionally be due to cross-reacting antigens but is caused most commonly by contamination of urine from a heavily colonized neonate. The urine LPA test has a documented sensitivity of 88-100% and specificity of 81-100% for detecting infection, as defined by a positive blood culture. Alternatively, if a symptomatic neonate colonized with GBS is used as the gold standard for EOSBD, we found the sensitivity to be 88%, specificity 98%, positive predictive value 79%, and negative predictive value 99%. A negative test thus reliably excludes GBS disease.

- **Haematologic tests**, especially the total and differential WBC and tests for acute phase reactants such as C-reactive protein (CRP), are additional but imperfect screening tests for sepsis. The WBC values, if used in scoring systems to predict sepsis such as the Manroe and Rodwell scores performed at 12-24 hours of age, can predict EOSBD with 100% sensitivity. The interpretation of the values for CRP, which is synthesised in the liver 6-24 hours after an inflammatory stimulus, is most valuable with serial tests. Uninfected neonates have normal CRP values, in general <0.8-1.0 mg/dL.

- **Superficial swabs.** Ear swab is the most sensitive of superficial skin swabs to detect colonisation.

- **Cytokines** on cord blood, such as IL6, may suggest early onset infection although the organism cannot be defined.

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Treatment

1. **Antibiotic therapy**

- **Intrapartum penicillin or ampicillin** have been used most widely in controlled clinical trials of chemoprophylaxis.

- Penicillin G is the drug of choice as no resistance to GBS has been demonstrated and it is less likely to lead to selection of resistant organisms. Gentamycin is added if clinical chorioamnionitis is suspected. Alternatively, ampicillin crosses the placenta more rapidly
than penicillin G and achieves higher concentrations in the fetal compartment. Bactericidal levels have been documented as early as 5 minutes after administration.\textsuperscript{62}

- **Clindamycin and erythromycin are suggested alternatives** if there is a convincing history of penicillin allergy.\textsuperscript{63} However resistance to clindamycin (6.9\%) and erythromycin (20.2\%) has been reported recently in the US.\textsuperscript{64} Cephalosporins are thus the recommended alternative drug eg cephalothin.

- **Penicillin or ampicillin together with gentamycin** have been most commonly used for presumed or proven neonatal sepsis with GBS. These regimes are based on evidence that GBS are uniformly sensitive to the penicillins but killing is enhanced by an aminoglycoside, at least in vitro.\textsuperscript{65}

- **Asymptomatic neonates**, born following intrapartum chemoprophylaxis to GBS-colonised mothers at or near term gestation (>34 weeks), do not need postnatal antibiotic therapy, Fig 1.\textsuperscript{11} The more preterm the neonate the less chance of passive immunisation with IgG specific GBS antibodies.\textsuperscript{66} Therefore, such neonates need assessment as to whether empirical treatment with antibiotics is commenced while awaiting laboratory results. Antibiotics should be ceased at 48-72 hours if all cultures and tests are negative and the infant asymptomatic, so as to prevent the development of bacterial resistance.

2. Biochemical and immunological approaches to therapy

The mortality associated with EOGBSD is due to septic shock. The clinical findings are similar to gram negative endotoxaemia. The pathogenesis includes, damage from bacteraemia and tissue invasion by live bacteria as well as cell-free GBS antigens, and sequestration of neutrophils in the lung.\textsuperscript{67} Infusion of GBS in lambs produces an early-phase response, within the first hour, characterised by pulmonary hypertension and alteration of lung mechanics, followed 2-4 hours later by evidence of increased endothelial vascular permability, the late-phase response.\textsuperscript{68}

Selective immunotherapy with GBS specific immunoglobulin and selective cytokine therapy with recombinant, human granulocyte colony-stimulating factor (rh G-CSF) or tumour necrosis factor alpha offer potential in the future, if non-preventable infection occurs. The efficacy and safety of each of these modes of therapy will need evaluation in large randomised control trials. Their application may be most valuable as an adjunct to treatment, especially in preterm infants of <35 weeks where the benefit of active maternal immunisation and transplacental transfer is limited and there is impaired phagocytosis and opsonisation towards group B streptococci.
**Flowchart**

Recommendations for universal screening and intrapartum chemoprophylaxis for GBS carriers and their neonates.

**IF:** (Known Carrier)
- Low vaginal swab is GBS positive at 28 weeks
  - Or
- MSU* positive for GBS at any antenatal visit
  - Or
- Previous history of GBS perinatal infection.

**OR:** (High risk)
- Preterm labour Or PPROM
  - And
carrier status unknown.

**TREAT:**
Ampicillin, 1g intravenously every 6 hours, as soon as labour starts or membranes rupture.
(Cephazolin 1g every 8 hours IV if allergic to penicillin)

**WELL NEONATE**
To ward with mother record temperature and respiratory rate for 24 hours

**SYMPTOMATIC NEONATE**
- Or <35 weeks gestation
  - Admit to neonatal unit, consider evaluation and treatment

* MSU Mid stream urine
Adapted: Jeffery and McIntosh 14
Prevention

The acquisition of GBS occurs largely during labour, since up to two thirds of infants are bacteraemic at birth. This limits a curative approach. Disease is already established and morbidity and sometimes death unavoidable, even with appropriate treatment. Prevention rather than cure is needed, whether by chemoprophylaxis or immunoprophylaxis.

Preventive strategies have either (i) focused on interrupting vertical transmission from mother to baby by intrapartum antibiotics - chemoprophylaxis or (ii) targeted the most important risk factor, absence of type-specific maternal IgG antibody to GBS capsular antigen, by active immunisation of the mother and passive transplacental transfer to the fetus – immunoprophylaxis.

Chemoprophylaxis

Three approaches have been variably evaluated:

(i) **Eradication of maternal GBS colonisation during pregnancy.** Oral antibiotics to treat colonised mothers during pregnancy and their partners have been unsuccessful. Recolonisation occurred in up to 60% prior to labour.

(ii) **Treatment of all or high-risk neonates.** The only randomised control trial which evaluated intramuscular penicillin G in high-risk neonates (<2000 grams), showed that EOGBSD and mortality were neither prevented nor reduced. Rather the results emphasised the need for intrapartum prophylaxis as 21 of 24 neonates with GBS disease had positive blood cultures at birth.

(iii) **Intrapartum antibiotics to reduce vertical transmission**

   a. **Neonatal colonisation.** Intrapartum administration of intravenous ampicillin or penicillin to GBS colonised mothers is effective in interrupting vertical transmission of GBS from a mother to her baby. Epidemiological reviews unanimously support this observation. The overview of the trials by Smaill indicates that the effect is large, with between 80 to 90% of neonates free of GBS colonisation after maternal treatment (pooled OR and 95% CI, 0.10 and 0.07-0.14). This unequivocal finding should predict a reduction in EOGBSD, since Dillon found no infection in 10,967 neonates if there was no evidence of colonisation. This was determined following culture in selective media from four sites at birth and is consistent with the pathogenesis as an infection acquired in-utero.

   b. **Neonatal infection.** Authors of several randomised control trials have reported a decrease in EOGBSD in both heavily and lightly colonised mothers and high and low-risk neonates following intrapartum chemoprophylaxis. However reviewers disagree as to the conclusive evidence that EOGBSD is significantly reduced. The effect on LOGBSD has not been evaluated.

      o **Smaill** included four trials that met the inclusion criteria for analysis of infection.

      o The studies showed a significant reduction in EOGBSD, with a pooled OR of 0.17 and 95% CI of 0.07-0.39 and although she comments that blinding of randomisation and of observer was not adequately assured, the outcome variables, namely colonisation and sepsis were unambiguous.
Allen, Navas and King\textsuperscript{74} concluded from the examination and meta-analyses of control trials and cohort studies,\textsuperscript{46, 59, 60, 61, 76, 77} that there was a beneficial effect of intrapartum penicillin prophylaxis, with a pooled OR of 0.03 (95% CI 0.0013 to 0.17) indicating an overall 30-fold reduction in the incidence of EOGBSD.

Ohlsson and Myhr\textsuperscript{75} suggest that the poor quality of the randomised control trial methodology limits meta-analysis of the trials. They conclude that of the four acceptable trials\textsuperscript{46, 58, 60, 61} there was individually insufficient power to show a statistically significant difference, although there was a trend towards reduction in early neonatal infection.

Australia and the US have concluded that intrapartum antimicrobial prophylaxis is efficacious (GBS colonised, with or without risk factors) and have written defined guidelines that have been shown to be cost saving, given the baseline rates.\textsuperscript{2, 78} UK and Europe have not yet reached a consensus.\textsuperscript{31, 32}

c. **Detection of carriers.** Further controversy surrounds the optimum timing and methods of detecting maternal colonisation.

- Ideally this would be at the commencement of labour with a rapid test readily available throughout 24 hours that was inexpensive and accurate. This implies maternal recognition and presentation in early labour.
- Currently, rapid tests detect heavy but not light colonisation, require laboratory expertise which limits availability and are not sufficiently rapid.\textsuperscript{4, 37, 79}
- A recent pilot study of PCR detection of GBS, within 30-45 minutes, in 112 pregnant women at delivery is encouraging. Predictive values compared with the ideal conventional culture were sensitivity 97%, specificity 100% and positive and negative predictive values of 100%.\textsuperscript{80}
- As the time between screening and delivery decreases, the predictive value of a culture for GBS increases but the number of high-risk, preterm fetuses identified decreases.
- Thus at present antenatal screening, from swabs of the lower vagina and anorectum cultured in selective media, is recommended by authors at 26-28 weeks, 32 weeks and 35-36 weeks gestation.\textsuperscript{46, 63, 79} If cultured at 26-28 weeks, between 60-75% of women with positive tests for GBS will still be colonised at delivery\textsuperscript{79, 81, 82} and between 0-13%\textsuperscript{79, 81, 82} of those with negative cultures will be colonised at term. At RPA Sydney, mothers are screened at 28 weeks gestation. In the US, screening is advised at 35-37 weeks gestation.\textsuperscript{83}

d. **Universal or selective prophylaxis.**

- **Universal prophylaxis** includes swabbing all pregnant women at a defined time and treating positive GBS carriers in labour
- **Selective prophylaxis** is limited to those carrier mothers with factors which increase the risk of disease and death in their neonate or mothers with risk factors alone, namely:
  - labour before 37 weeks
  - prolonged rupture of membranes for >12 or > 18 hours
  - intrapartum fever of >37.5°C or >38°C\textsuperscript{46}

In some studies, between 23-70% of infected neonates did not have such risk factors.\textsuperscript{11, 37, 61, 84} Withholding prophylaxis from known carriers may thus impose ethical and medico-legal difficulties\textsuperscript{71, 84, 85} especially as the risk of early infection is significantly higher than for non-carriers.\textsuperscript{86} This approach will capture < 50% term neonates who have 75% of the EOGBSD.\textsuperscript{10}

- In addition, there is maternal benefit from a non-selective policy in that postpartum febrile morbidity in treated mothers is significantly reduced from 21% to 8%\textsuperscript{46} and both clinical chorioamnionitis (intraamniotic infection) estimated at
2.9% and post partum endometritis estimated at 2.0% in GBS colonized, are also significantly reduced. The reduction is similar to that achieved by antibiotic prophylaxis for caesarian section to prevent wound infection, for which there is a consensus. The number of mothers exposed to antibiotics would be similar for prophylactic caesarian section and universal chemoprophylaxis for GBS carriers, about 15-20% in Australia.

- The principal concerns of a non-selective policy have been the risk of serious reaction to ampicillin or penicillin, bacterial resistance and cost

since only 1-2% of neonates of carrier mothers are infected. The true population incidence of penicillin-induced anaphylaxis in pregnancy is unclear. The most important practical assurance is an adequate history from the mother and if significant an alternative antibiotic should be used. In practice, neither serious side effects nor selection of resistant nursery flora in treated neonates have been a problem in Australia. In 2002, Stoll et al reported both increased resistance and an increased rate of early onset E coli infections in the US.

- In instituting antepartum screening and non-selective intrapartum chemoprophylaxis for GBS we considered the principal risk of treatment, anaphylaxis, was far less than the risk of not treating, that is death and serious neonatal morbidity and maternal morbidity due to GBS.

In summary: At RPA Hospital in Sydney

- Universal screening and selective intrapartum chemoprophylaxis is used as this is more effective than a strategy based solely on treatment of risk factors.
- Outcome data in 36342 livebirths (1988-1996) indicate reduction in EOGBSD from 1.4 to < 0.2/1000 livebirths even when only low vaginal swabs (not rectovaginal) and non selective media were used. Further auditing of the 5 years, 1997-2001, demonstrate the same low rate of EOGBSD of 0.26/1000 livebirths.
- This approach may change with further evidence of a suitable rapid test in labour to target chemoprophylaxis and/or immunoprophylaxis.

Immunoprophylaxis

- Immunisation offers the most effective way of preventing GBS infection, both early onset GBS disease and late onset GBS disease, maternal peripartum infection and adult GBS disease.
- An estimated 90% of GBS infections in infancy are potentially preventable with a vaccine.
- The relative importance of vaccination can be seen from the comparative significance of GBS with Haemophilus influenzae group B. In Australia, there were an estimated 500 bacteraemic cases per year of EOGBSD alone, compared with 700 cases (0-5 years) of Haemophilus infection, for which there is an effective vaccine.
- Neonatal protection is afforded by transplacental passage of antibodies and probably by increased breast milk antibodies, which would potentially protect the neonate from
gastrointestinal colonisation and invasive disease.\textsuperscript{94} Susceptibility correlates with low levels of opsonically-active antibodies\textsuperscript{5}, either because the mother is deficient or the baby is born preterm and <35 weeks gestation, prior to the major transplacental passage of IgG antibodies\textsuperscript{66}

- Boyer et al\textsuperscript{95} provide evidence that the marked decline in GBS infections after 3-4 months is due to the acquisition of IgM specific antibodies by 3 months of age, which were undetectable at birth. Both IgG and IgM are functionally comparable in in-vitro studies of opsonopagocytosis of GBS.\textsuperscript{96}

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**Assisting women with information**

**Web sites for further information:**

- http://www.cdc.gov/ncidod/dbmd/gbs
- http://www.gbss.org.uk

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**Key Points**

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<th>Key Points</th>
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<td>Intrapartum chemoprophylaxis reduces EOGBSD</td>
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<td>Screening for maternal GBS at 26 weeks will result in ~ 30% women negative for GBS at term and ~ 6% women will acquire GBS by term</td>
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<td>Vaginal and rectal composite swabs cultured in selective media will provide maximal recovery of GBS colonization</td>
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<td>EOGBSD is characterized by a 95% incidence of culture positive and clinical signs of infection within 24 hours</td>
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<td>An asymptomatic neonate of 35 weeks or greater whose carrier mother is adequately treated does not require treatment</td>
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A neonate of a carrier mother who is not adequately treated in labour requires evaluation for clinical signs and treatment with IV penicillin and gentamycin until cultures are negative (48 hours) and the infant remains well

Carrier mothers should be informed, given a written explanation and advised to present to hospital for IV antibiotics when labour starts or membranes rupture

References


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