Royal College of Obstetricians & Gynaecologists

The Prevention of Early-onset Neonatal Group B Streptococcal Disease

Green–top Guideline No. 36

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The Prevention of Early-onset Neonatal Group B Streptococcal Disease

This is the second edition of this guideline. The first edition was published in 2003 under the same title.

1. Purpose and scope

The purpose of this guideline is to provide guidance for obstetricians, midwives and neonatologists on the prevention of early-onset neonatal group B streptococcal (EOGBS) disease. Prevention of late-onset GBS and treatment of established GBS disease is not considered beyond initial antibiotic therapy.

2. Background

Group B streptococcus *(Streptococcus agalactiae)* is recognised as the most frequent cause of severe early-onset (at less than 7 days of age) infection in newborn infants. However, there is still controversy about its prevention. Surveys in 2001 and 2008 demonstrated that less than 1% of UK maternity units were performing systematic screening for GBS[1,2] and, to date, UK clinicians have not generally adopted the US and Canadian practice of routine screening for GBS carriage.[3,4] Extrapolation of practice from the USA to the UK may, however, be inappropriate. The incidence of EOGBS disease in the UK in the absence of systematic screening or widespread intrapartum antibiotic prophylaxis (IAP) is 0.5/1000 births,[5] which is similar to that seen in the USA after universal screening and IAP, despite comparable vaginal carriage rates.[6] The incidence of culture-confirmed early-onset disease in the USA has fallen in association with the introduction of screening pregnant women for GBS.[3] The current US guidelines[7] advise that all women colonised with GBS at 35–37 weeks of gestation (or labouring before this time) should be offered IAP, usually in the form of high-dose intravenous benzylpenicillin or ampicillin. IAP has been shown to significantly reduce the risk of culture-positive early-onset but not late-onset disease (occurring 7 or more days after birth). There is also indirect evidence of an impact on neonatal deaths. A review of sepsis-related neonatal mortality in the USA showed a decline in mortality in the first week after birth, coinciding with the introduction of IAP.[8] However, a Cochrane review concluded that, while IAP for colonised mothers reduced the incidence of EOGBS disease, it has not been shown to reduce all causes of mortality or GBS-related mortality.[9] There have been no studies addressing whether routine screening has had any impact on all-cause mortality. Antenatal screening and treatment may carry disadvantages for the mother and baby. These include anaphylaxis,[10] increased medicalisation of labour and the neonatal period, and possible infection with antibiotic-resistant organisms, particularly when broad-spectrum antibiotics such as amoxicillin are used for prophylaxis.[11,12] The UK National Screening Committee examined the issue of strategies for the prevention of EOGBS disease in November 2008 and recommended that routine screening using bacteriological culture or near-patient testing techniques should not be introduced into UK practice.[13]

3. Identification and assessment of evidence

This RCOG guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines.[14–16] The Cochrane Database of Systematic Reviews, DARE, EMBASE, Medline and PubMed (electronic databases) were searched for relevant randomised controlled trials, systematic reviews and meta-analyses. The search was restricted to articles published between 2003 and August 2011. Search terms included: 'group B streptococcus', '*Streptococcus agalactiae*', 'group B streptococcus and pregnancy', 'beta haemolytic streptococcus and pregnancy', and 'beta haemolytic streptococcus and neonatal', 'beta hemolytic streptococcus and neonatal', 'GBS bacteriuria', and was limited to humans and the English language. The National Library for Health and the National Guidelines Clearing House were also searched for relevant guidelines and reviews. Studies relevant to the scope of the guideline were selected by the members of the guideline development group. Where possible, recommendations are based on available evidence. Areas lacking evidence are highlighted and annotated as 'good practice points.'

4. Antenatal screening

4.1 Should all pregnant women be offered bacteriological screening for GBS?

Routine bacteriological screening of all pregnant women for antenatal GBS carriage is not recommended. **D**

Until it is clear that antenatal screening for GBS carriage does more good than harm and that the benefits are cost-effective, the National Screening Committee does not recommend routine screening in the UK.[13] Initiating national swab-based screening for antenatal GBS carriage would have a substantial impact on the provision of antenatal care within the UK. Major organisational changes and new funding would be required to ensure an equitable and quality-assured service.

Evidence level 4

4.2 If GBS is detected incidentally earlier in the pregnancy, should women be treated before the onset of labour?

Antenatal treatment with benzylpenicillin is not recommended. **C**

Antenatal prophylaxis with oral benzylpenicillin for vaginal/rectal colonisation does not reduce the likelihood of GBS colonisation at the time of delivery[17] and so is not indicated in this situation. IAP should be offered to GBS-colonised women (see section 5.2).

Evidence level 2+

4.3 Should women be screened for GBS or receive IAP if GBS was detected in a previous pregnancy?

Current evidence does not support screening for GBS or the administration of IAP to women in whom GBS carriage was detected in a previous pregnancy. **D**

If GBS was detected in a previous pregnancy, the likelihood of carriage in a subsequent pregnancy is around 38%.[18] This gives a risk estimate of neonatal EOGBS disease of approximately 0.9 cases/1000 births versus a background risk of 0.5 cases/1000 births or 2.3 cases/1000 births in women with GBS detected in the current pregnancy. The time interval between the two pregnancies and the intensity of colonisation in the previous pregnancy are predictive of recurrent GBS colonisation.[18]

Evidence level 3

5. Reducing the risk of neonatal GBS disease in women known to be colonised with GBS.

5.1 How should GBS bacteriuria in the current pregnancy be managed?

Clinicians should offer IAP to women with GBS bacteriuria identified during the current pregnancy. **C**

GBS bacteriuria is associated with a higher risk of chorioamnionitis[19] and neonatal disease.[20] It is not possible to accurately quantify these increased risks. These women should be offered IAP. Women with GBS urinary tract infection (growth of greater than 10^5 cfu/ml) during pregnancy should receive appropriate treatment at the time of diagnosis as well as IAP.

Evidence level 3

5.2 Should women receive IAP if GBS is detected in the current pregnancy?

IAP should be offered if GBS is detected on a vaginal swab in the current pregnancy. **C**

Vaginal swabs should not be taken during pregnancy unless there is a clinical indication to do so. ✓

If GBS is present in a vaginal swab, it is likely that the risk of neonatal disease is increased. A risk of disease of 2.3/1000 may be assumed (overall UK incidence 0.5/1000; approximately 21% women are carriers).[21]

Evidence level 3

5.3 How should women with known GBS colonisation undergoing planned caesarean section be managed?

Antibiotic prophylaxis specific for GBS is not required for women undergoing planned caesarean section in the absence of labour and with intact membranes. **C**

All women having caesarean section should receive antibiotic prophylaxis according to NICE guideline no. 132.[22]

Women undergoing planned caesarean delivery in the absence of labour or membrane rupture do not require antibiotic prophylaxis for GBS, regardless of GBS colonisation status. The risk of neonatal EOGBS disease is extremely low in this circumstance.[23] Evidence level 3

5.4 How should women known to be colonised with GBS who experience spontaneous rupture of membranes at term be managed?

Immediate induction of labour and IAP should be offered to all women with prelabour rupture of membranes at 37^{+0} weeks of gestation or more. **D**

The NICE guideline on induction of labour [24] recommends that all women with prelabour rupture of membranes at term (37 weeks + 0 days of gestation or greater) should be offered immediate induction of labour, or induction after 24 hours. If GBS colonisation was identified earlier in the pregnancy (by a swab taken for other reasons), immediate induction of labour and IAP should be offered. Evidence level 3

5.5 How should women with GBS colonisation and suspected chorioamnionitis be managed?

If chorioamnionitis is suspected, broad-spectrum antibiotic therapy including an agent active against GBS should replace GBS-specific IAP and induction of labour should be considered. **A**

Chorioamnionitis is known to be associated with maternal and neonatal morbidity including sepsis,neonatal lung and brain injury and cerebral palsy.The risk of these complications is reduced by broad-spectrum antibiotic therapy.[25] Evidence level 1+

6. Management of labour (including rupture of membranes) to reduce the risk of neonatal GBS disease in women without known GBS colonisation

6.1 Should women presenting in preterm labour with intact membranes be offered IAP?

Women presenting in established preterm labour with intact membranes with no other risk factors for GBS should not routinely be offered IAP unless they are known to be colonised with GBS. **C**

Although the risk of EOGBS infection is higher in preterm than in term infants (see Appendix I), there are reasons to be cautious about widespread prescription of antibiotics for these women. Approximately 50% of all women thought to be in preterm labour will not deliver preterm. Women presenting in uncomplicated spontaneous preterm labour with intact membranes are the same group of women as those recruited to the ORACLE trial, where there was evidence of harm in terms of adverse neurodevelopmental outcome including cerebral palsy in their infants at 7 years of age in the absence of any demonstrable benefit in the short term.[26] Although the antibiotics used in ORACLE are different from those used for IAP for GBS, there is no evidence from long-term follow-up studies that other antibiotics, including penicillin, are safe. As the risk of EOGBS infection in this group of infants is still low, prompt management of early-onset sepsis, if it occurs, is preferable to IAP for large numbers of women.

There is currently no evidence to show that the subgroup of women in preterm labour with ruptured membranes have greater benefit from IAP.The difficulty in balancing risks and benefits of IAP for women in preterm labour could be resolved by a randomised controlled trial.

6.2 How should women with clinical risk factors such as a pyrexia (>38°C) in labour be managed?

IAP should be offered to women who are pyrexial in labour (>38°C). C

Women who are pyrexial in labour should be offered broad-spectrum antibiotics including an antibiotic for prevention of neonatal EOGBS disease. ✓

Intrapartum pyrexia (>38°C) is associated with a risk of EOGBS disease of 5.3/1000 (versus a background risk of 0.5/1000).[5,27] In view of this increased risk, IAP should be offered in the presence of maternal pyrexia.

Evidence level 3

6.3 How should women with term prelabour rupture of membranes be managed?

The evidence for IAP for women with term prelabour rupture of membranes is unclear and NICE recommends that it is not given, unless there are other risk factors. C

Women with prelabour rupture of membranes at term should be offered immediate induction of labour or induction after 24 hours (in line with the NICE guideline on induction of labour[24]).

6.4 How should women with preterm prelabour rupture of membranes be managed to reduce the risk of neonatal GBS disease?

Antibiotic prophylaxis for GBS is unnecessary for women with preterm rupture of membranes. C

Women who experience preterm rupture of membranes should be managed according to the RCOG Green-top Guideline *Preterm Prelabour Rupture of Membranes.*[28] Antibiotic administration specifically for GBS colonisation is not necessary prior to labour and should not be given 'just in case'.[18,29] If these women are known to be colonised with GBS, IAP should be offered. Induction of labour should be considered if there is suspicion of chorioamnionitis.

Evidence level 3

6.5 Should women with a previous baby with neonatal GBS disease be offered IAP?

IAP should be offered to women with a previous baby with neonatal GBS disease. D

Subsequent infants born to these women are likely to be at increased risk of GBS disease, although this has not been accurately quantified. The probable increase in risk may be attributable to persistence of low levels of maternal anti-GBS antibodies.[30] Vaginal or rectal swabs are not helpful, as IAP would be recommended even if these swabs were negative for GBS.

Evidence level 3

7. Which antibiotics should be given to prevent early-onset neonatal GBS disease?

For women who have accepted IAP, benzylpenicillin should be administered as soon as possible after the onset of labour and given regularly until delivery. B

Clindamycin should be administered to those women allergic to benzylpenicillin. D

It is recommended that 3 g intravenous benzylpenicillin be given as soon as possible after the onset of labour and 1.5 g 4-hourly until delivery. Clindamycin 900 mg should be given intravenously 8-hourly to those allergic to benzylpenicillin. Current clindamycin resistance rates in England and Wales stand at 10%;[31] thus, there is a chance that clindamycin might be less effective. An alternative agent in this situation is vancomycin. It should be noted that dosage regimens are based on tradition rather than evidence and the British National Formulary should be consulted for specific dose recommendations. Broad-spectrum antibiotics such as ampicillin should be avoided if possible, as concerns have been raised regarding increased rates of Gram-negative neonatal sepsis.[11] To optimise

Evidence level 3

the efficacy of IAP, the first dose should be given at least 2 hours prior to delivery.[32,33] There is evidence that benzylpenicillin levels in cord blood exceed the minimum inhibitory concentration for GBS as early as 1 hour after maternal administration,[34] but it is not known how this relates to neonatal colonisation or disease. Oral antibiotics for IAP are not recommended because of variable absorption in labour.

Evidence level 3

8. Should vaginal cleansing be performed in labour?

There is no evidence that intrapartum vaginal cleansing will reduce the risk of neonatal GBS disease. C

Although vaginal cleansing with chlorhexidine has been shown to reduce the risk of neonatal GBS colonisation,[35] a recent large randomised controlled trial showed no impact on EOGBS disease.[36]

Evidence level 3

9. How should the newborn infant be managed?

The evidence base upon which to make treatment decisions for newborn infants is weak. Few randomised controlled trials have been performed.[37–39] Previous guidelines have largely been based on consensus rather than evidence. Published data permit risk estimates to be made which can be used to inform decision making regarding the need for enhanced observation or investigation and initial treatment. There is no good evidence to support routine blood tests to aid decision making about the management of these infants.[40]

The continuing management of infants with established disease is not within the scope of this guideline.

In a UK study of invasive GBS disease, 89% of early-onset cases were identified on day 1.[41] Of those developing clinical features on day 1, 97.6% were noted by 12 hours of age (where hour of onset was given).[41] More recent UK data from an infection surveillance network showed that 94% of early-onset cases occurred on day 1.[42] Most cases (65–67%) have one or more risk factors prior to or during labour.[41,42] A significant number will also have had signs of fetal distress, an emergency delivery and low Apgar scores. The majority of early-onset cases in these studies presented with sepsis (79.4%), 11.8% had meningitis, 7.8% had pneumonia and 1% focal infection.[41]

9.1 How should well infants at risk of EOGBS disease be monitored?

Well infants at risk of EOGBS should be observed for the first 12–24 hours after birth with regular assessments of general wellbeing, feeding, heart rate, respiratory rate and temperature. ✓

The great majority of infants (89–94%) who develop EOGBS infection develop signs within the first 24 hours after birth and the majority of such infants (65–67%) will have had one or more 'conventional' risk factors evident in or before labour. A significant number will also have had signs of fetal distress, an emergency delivery and low Apgar scores. Clearly, any baby with clinical signs and symptoms compatible with sepsis should be evaluated and commenced on antibiotics. Other infants without clinical signs but with other risk factors should be observed closely for such signs over the first 24 hours after birth.

9.2 Should postnatal antibiotic prophylaxis be given to low-risk term infants?

Postnatal antibiotic prophylaxis is not recommended for asymptomatic term infants without known antenatal risk factors. C

The incidence of EOGBS disease in asymptomatic term infants without known antenatal risk factors in the UK is estimated at 0.2 cases/1000 births.[5] No randomised controlled trial has investigated treatment in this group. If postnatal antibiotic treatment were completely effective and there were no adverse effects, 5000 infants would need to be treated to prevent a single case and at least 80 000 infants would have to be treated to prevent a single death from EOGBS disease.

Routine postnatal antibiotic prophylaxis is not recommended. Evidence level 3

9.3 How should the well infant with one or more risk factors be treated?

Randomised controlled trials have not provided a sufficient evidence base for clear treatment recommendations in well newborn infants. C

Estimates of the risk of EOGBS disease in the presence of individual antenatal risk factors, before and after IAP, are shown in Appendix I.

Some clinicians will recommend intravenous antibiotic treatment of well infants with risk factors (and stop therapy when cultures are negative or after a defined period if IAP was given), while others will prefer to observe infants because the balance of risks and benefits of treatment is uncertain. Around 90% of cases present clinically before 24 hours of age,[41,42] so the risk of disease in infants who remain well without treatment beyond this time may not be substantially elevated above that of the infant with no risk factors. Prolonged observation of well infants is therefore not indicated. The argument for using prophylactic treatment in well infants is stronger in the presence of multiple maternal risk factors but is still unproven. However, in well infants whose mothers had risk factors and received appropriate IAP, the risk of EOGBS is significantly lower and these infants can be observed for 24 hours without treatment.

9.4 How should the neonate with clinical signs of EOGBS disease be managed?

Infants with clinical signs of EOGBS should be treated promptly with appropriate antibiotics. C

Many infants with EOGBS disease have signs at or soon after birth.[41] Neonatal sepsis may present with subtle signs initially but can progress rapidly to death. Whether they received intrapartum antibiotics or not, any newborn infant with clinical signs compatible with infection should be investigated and treated promptly with antibiotics which are narrow spectrum but provide cover against GBS and other common pathogens such as *Escherichia coli*[43] (for example, benzylpenicillin and gentamicin). Blood cultures should always be obtained before antibiotic treatment is commenced, and cerebrospinal fluid cultures should be considered unless the clinical condition precludes a lumbar puncture. A lumbar puncture should be obtained at the earliest opportunity once the clinical condition has stabilised. Evidence level 3

9.5 How should the infant of a mother with a previous infant with GBS disease be managed?

For a well infant whose mother has had a previous infant with GBS disease, either clinical evaluation after birth and observation for around 24 hours are necessary, or blood cultures need to be obtained and the infant treated with benzylpenicillin until the culture results are available. It is unclear whether further action is necessary for the well infant. C

The risk of GBS disease is unquantified but is probably significantly increased.[27] The infant should be evaluated clinically soon after birth and observed for at least 24 hours. It is unclear whether further action is necessary, but an alternative approach would be to obtain blood cultures and treat with benzylpenicillin until the culture results are available. There is insufficient evidence to suggest that neonatal treatment should be given if IAP has been administered. Evidence level 3

9.6 Are routine neonatal surveillance cultures of value?

It is not necessary to perform routine surface cultures or blood cultures on well infants. ✓

Most infants who develop EOGBS disease present with illness soon after birth and 90% have presented clinically by 24 hours of age, before culture results become available.[41,43] Postnatal antibiotic treatment has not been shown to eradicate carriage of GBS or to influence the risk of Evidence level 3

late-onset GBS disease. It is therefore unnecessary to perform routine surface cultures or blood cultures on well infants, whether they received IAP or not. Evidence level 3

9.7 Is there any need for breastfeeding to be avoided?

There is no evidence to discourage breastfeeding where there are concerns regarding the possible risk of transmission of GBS disease.

10. Suggested audit topics

- Percentage of eligible women with various risk factors receiving IAP.
- Percentage of women receiving IAP for at least 2 hours prior to delivery.
- Percentage of women with pyrexia receiving broad-spectrum antibiotics.
- Percentage of infants with risk factors being observed for 12–24 hours.
- Percentage of infants with signs of possible GBS disease receiving appropriate investigation and treatment.

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APPENDIX I

Estimates of the risk of EOGBS disease in the presence of individual antenatal risk factors, with and without IAP.

These estimates are based on an incidence of EOGBS disease in the UK of 0.5/1000,[5] which is likely to be the minimum incidence.

Risk factor	Risk of EOGBS disease if IAP not given	Risk of EOGBS disease if full IAP given	Risk of death from EOGBS disease if IAP not given	Risk of death from EOGBS disease if full IAP given
Intrapartum fever (>38°C)	1:189	1:943	1:1783	1:8915
Prolonged rupture of membranes (>18 hours) at term	1:556	1:2777	1:9754	1:48 772
Prematurity (<37+0 weeks of gestation)	1:435	1:2173	1:2377	1:11 885
Prematurity (<35+0 weeks of gestation)	1:357	1:1786	1:1566	1:7829
Positive GBS swab in a previous pregnancy	1:1105	1:5525	1:10 424	1:52 122
Positive GBS swab in current pregnancy	1:434	1:2170	1:4094	1:20 471

EOGBS = early-onset group B streptococcus; IAP = intrapartum antibiotic prophylaxis.

The assumptions on which the figures in the table above are based are as follows:

- Live birth rate in the UK in 2008: 793 388[44]
  - 1.9% intrapartum fever >38°C[45]
  - 9.4% PROM at term[45]
  - 7.9% <37 weeks of gestation[46]
  - 4.0% <35 weeks of gestation[46]
- Prevalence of maternal risk factors in infants with EOGBS disease:
  - 19.9% intrapartum fever >38°C[41,45]
  - 34% PROM at term[5]
  - 37% <37 weeks of gestation[5]
  - 22% <35 weeks of gestation[5]
- Incidence of EOGBS in the UK: 0.5/1000[5]
- Mortality of EOGBS in the UK is:
  - 10.6% overall[5]
  - 18.3% <37 weeks of gestation
  - 22.8% <35 weeks of gestation
  - 5.7% >37 weeks of gestation
- 80% effectiveness of IAP in preventing EOGBS[12]

It should be noted that GBS bacteriuria is a risk factor for neonatal disease but the magnitude of risk cannot be quantified.

APPENDIX II

Indications for offering GBS-specific IAP:

- Previous baby with invasive GBS infection.
- GBS bacteriuria in the current pregnancy.
- Vaginal swab positive for GBS in current pregnancy.
- Pyrexia (>38°C) in labour (give broad-spectrum antibiotics to include GBS cover).
- Chorioamnionitis (give broad-spectrum antibiotics to include GBS cover).

IAP for GBS is not necessary if delivering by pre-labour lower segment caesarean section with intact membranes.

APPENDIX III

Clinical guidelines are 'systematically developed statements which assist clinicians and women in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No.1: *Development of RCOG Green-top Guidelines* (available on the RCOG website at **http://www.rcog.org.uk/guidelines**). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research might be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendations

A	At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group

This guideline was produced on behalf of the Guidelines Committee of the Royal College of Obstetricians and Gynaecologists by:
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Conflicts of interest: none declared.

The final version is the responsibility of the Guidelines Committee of the RCOG.

The guidelines review process will commence in 2015 unless evidence requires an earlier review.

