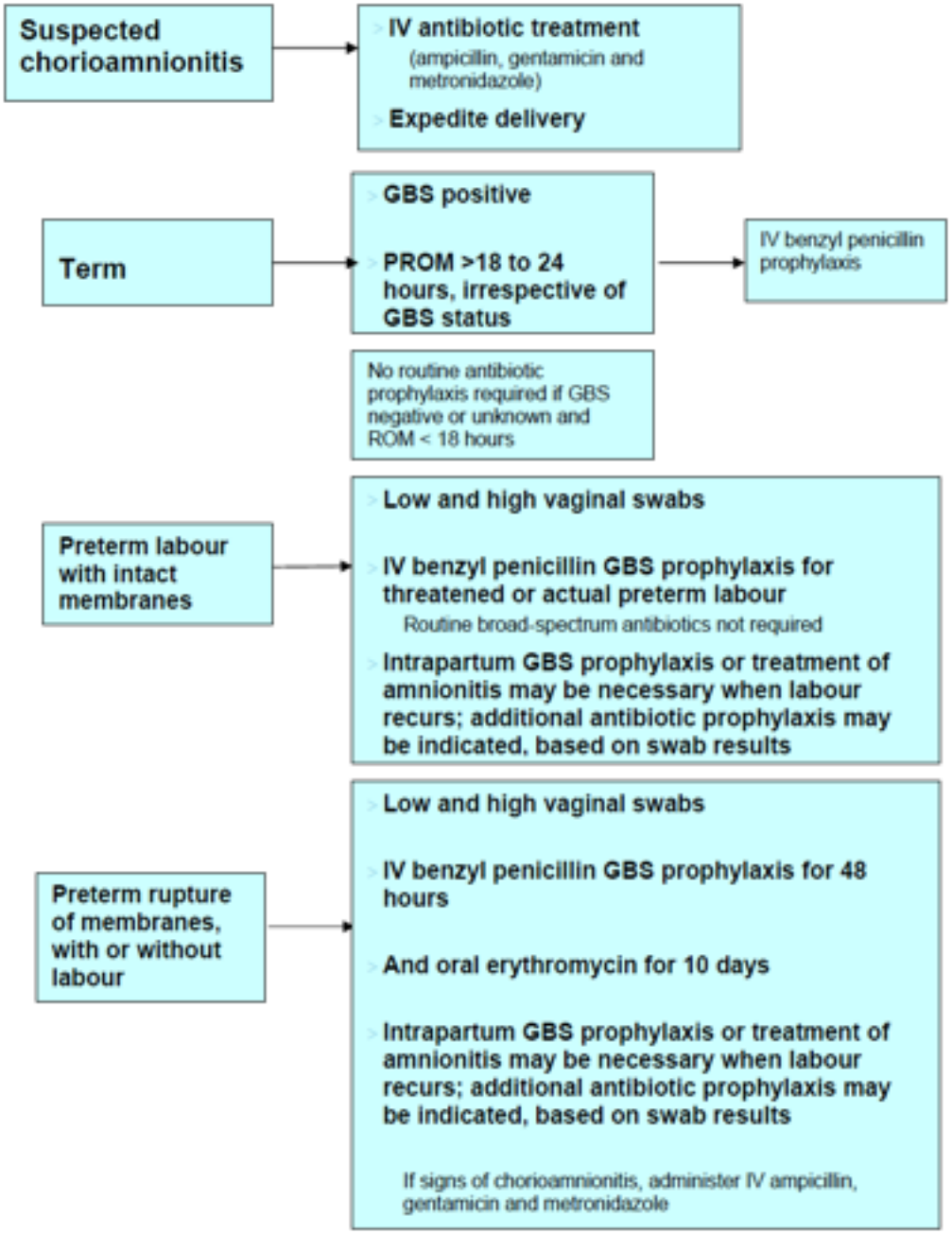
Neonatal Sepsis

Obstetric management for treatment of chorioamnionitis and prevention of early onset neonatal sepsis



NOTE: GBS positive = positive swab or bacteriuria this pregnancy, or previous infant with early onset GBS sepsis

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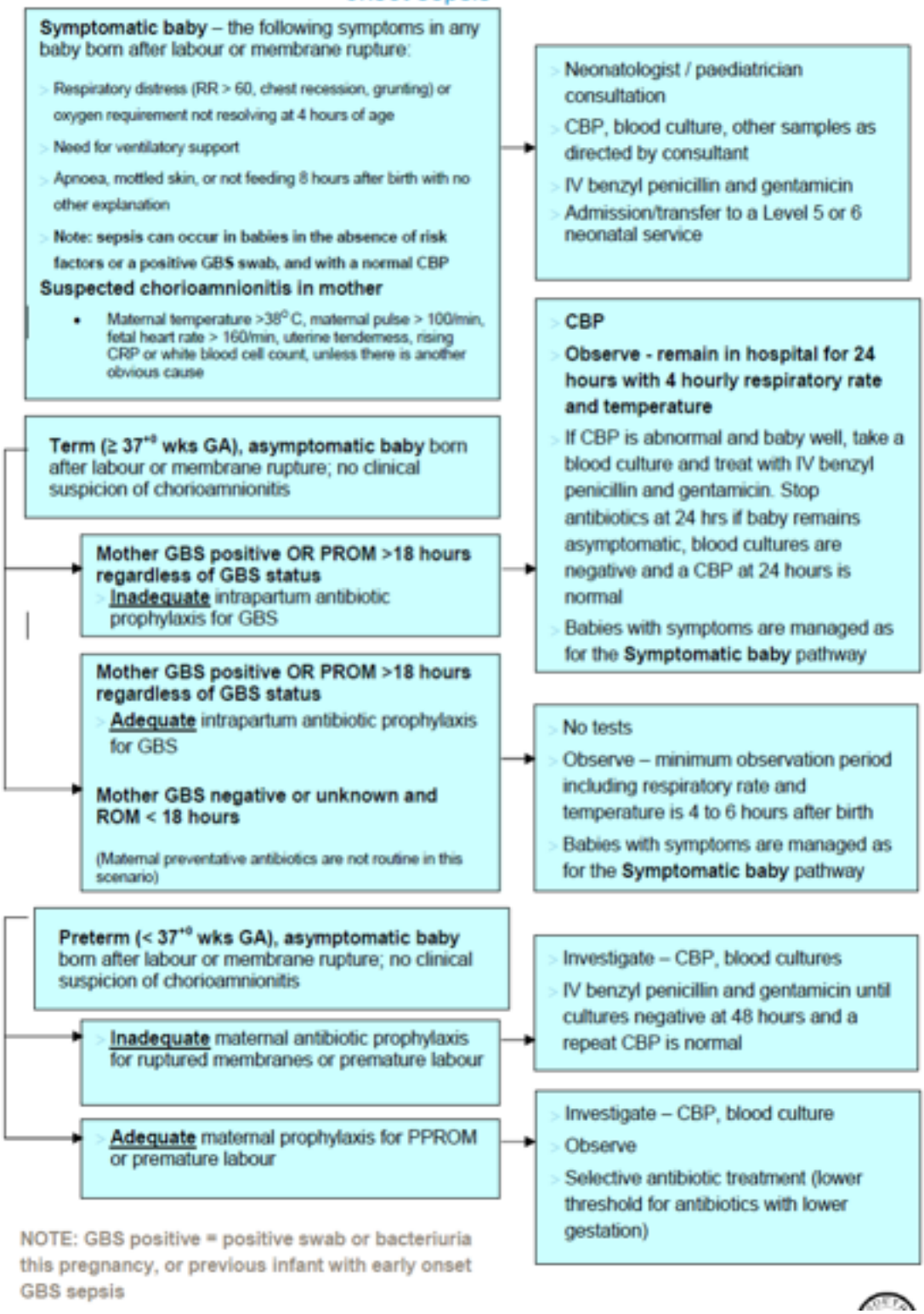
Neonatal management for prevention and treatment of early onset sepsis



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Important points

- The following guidelines represent a combination of
  - Established consensus guidelines for the prevention of neonatal Group B Streptococcal (GBS) infection using antenatal screening and intrapartum antibiotic prophylaxis
  - Evidence derived from trials of antibiotics in various prenatal scenarios
  - Suggested management strategy for chorioamnionitis
  - Suggested guidelines for the management of the newborn
- Early onset neonatal bacterial sepsis is associated with significant morbidity and mortality. The vast majority of infections are due to Group B Streptococcus (GBS) or Escherichia coli, with other organisms seen less frequently. Other micro-organisms that may be constituents of the normal vaginal flora are potential neonatal pathogens. These include Streptococcus pneumoniae, Haemophilus influenza, Staphylococcus aureus, Clostridia sp., and other Enterobacteriaceae such as Klebsiella.
- In 2002 the CDC published detailed consensus guidelines that form the basis for the management of GBS prophylaxis.[1] No published consensus guidelines or evidence based recommendations exist for intrapartum prophylaxis against the other pathogens listed above.
- Antibiotic prophylaxis during labour for women with risk factors for GBS has been shown to be effective in preventing GBS transmission to the neonate, and to reduce early onset GBS sepsis.[1] Antibiotic prophylaxis during labour has no effect on late onset neonatal sepsis due to GBS or other organisms.[1]
- A policy of screening for GBS and giving intrapartum antibiotic prophylaxis to carrier mothers is the most effective means of preventing early onset GBS.[2] Prospective surveillance for cases of early onset GBS has shown a reduction from 0.47 cases/ 1,000 livebirths to 0.34 cases/1,000 livebirths following the publication of the 2002 CDC guidelines and widespread implementation of universal GBS screening and intrapartum chemoprophylaxis.[3]
- A retrospective cohort study evaluating universal GBS screening has shown that for 116/189 (61.4 %) term infants with early onset GBS the antenatal screen, as a to GBS status at birth, was falsely negative.[4] This emphasises the importance of not relying solely on a negative maternal swab. Thus maternal antibiotic prophylaxis should be provided in the context of preterm labour and prolonged rupture of membranes even if maternal GBS status is negative. The treatment of symptomatic babies with antibiotics is also emphasised regardless of maternal GBS status.
- Antibiotic prophylaxis for GBS should be given as soon as possible in labour. Adequate GBS prophylaxis is considered to have been achieved if at least 1 dose of antibiotics is given 4 hours before birth.[1] However, antibiotic prophylaxis should still be given even if predicted time to delivery is short. GBS colonisation of the newborn is reduced where antibiotics are given at least 1 hour before birth.[5] Where fetal infection is established maternal antibiotics will pass quickly into the fetal blood-stream and commence early treatment of sepsis.
- Benzylpenicillin IV is the drug of choice for GBS prophylaxis.[1] Ampicillin (or amoxycillin) is an acceptable alternative but may result in higher levels of antibiotic resistance due to its broader spectrum of activity. If the mother is known to be allergic to penicillin, then lincomycin, azithromycin or erythromycin are alternative antibiotics
- Erythromycin oral has been shown to be of benefit in preterm prelabour rupture of membranes without evidence of clinical chorioamnionitis.[6] Amoxycillin / clavulanic acid should be avoided because of an association with neonatal necrotising enterocolitis.[6,7] Systematic reviews of antibiotic prophylaxis for preterm prelabour rupture of the membranes and preterm labour with intact membranes do not address intrapartum GBS prophylaxis

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- For prolonged preterm prelabour rupture of the membranes, serial cultures may help to define vaginal colonisation; this information may help to rationalise subsequent intrapartum antibiotic therapy or treatment of chorioamnionitis, but treatment of colonisation in the absence of labour or signs of chorioamnionitis is not advised
- There are few data on the safety of maternal gentamicin for the fetus. Ototoxicity and nephrotoxicity are described.[8] Gentamicin should therefore be reserved for cases where there is proven or suspected chorioamnionitis
- The recognition of symptoms of neonatal sepsis and treatment on clinical grounds is critical. Respiratory distress due to congenital pneumonia is the most common presentation of early onset sepsis. Any respiratory distress in a preterm infant, or respiratory distress not settling by 4 hours of age in a term infant should be investigated and treated as possible sepsis, unless the baby has been delivered from a sterile uterus by elective caesarean section. Other clinical findings that should raise suspicion of sepsis include apnoea, poor skin perfusion and abnormal feeding behaviour (not interested in feeding for 8 hours after birth or the last feed) where another cause is not immediately apparent. Neonatologist or paediatrician consultation and transfer/retrieval to a Level 5 or 6 neonatal service (previously Level 3) are necessary where symptomatic early onset sepsis is suspected
- For a baby with respiratory distress there is a narrow window for withholding antibiotics based on clinical judgment, restricted to babies born by caesarean section without labour or membrane rupture and where respiratory distress is improving with time. Neonatal practitioners should pay careful regard to all risk factors and the clinical condition of babies before withholding antibiotics
- Reported normal ranges for neonatal CBPs vary with population, gestation and postnatal age.[9,10] The immature:total neutrophil ratio is the most sensitive indicator of sepsis.[11] An I:T ratio of > 0.2 is a suggested cut-off for abnormality[12]
- The CBP can be normal if taken early after birth in a colonised baby who subsequently becomes unwell. Sensitivity is higher at 4-6 hours after birth. Where symptoms of sepsis develop the baby should be treated regardless of the CBP result
- The CBP has a high false positive rate in asymptomatic term babies at risk of sepsis. Asymptomatic term at-risk babies who are treated with antibiotics based on a CBP and who remain well at 24 hours can reasonably have antibiotics ceased at 24 hours where blood cultures are also negative and the CBP has normalised

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Antenatal screening

Antenatal screening for GBS at 36 weeks:

- The CDC and RANZCOG recommend that a combined low vaginal swab and rectal swab be taken for GBS culture in all women at 36 weeks' gestation, unless GBS bacteriuria has been demonstrated in the current pregnancy or the mother has had a previous infant infected with GBS in which case screening is unnecessary. The rate of detection of GBS colonisation can be increased from 22 % to 27 % by sampling the lower vagina and rectum rather than only the lower vagina[13]
- Discuss the benefits of performing both low vaginal and rectum sampling with the woman. If the woman declines rectal sampling, advise low vaginal sampling only and document this on the pathology form
- If the woman agrees to both low vaginal and rectal sampling, offer to collect the swab or advise her she may collect her own swab by inserting a single swab firstly into the vaginal introitus and then the same swab through the anal sphincter
- The swab must be cultured using a GBS selective medium (Stuart's or Amies). Results are valid for a period of 5 weeks
- It is unnecessary to give prophylactic antibiotics for GBS in the case of elective caesarean section. Women planning elective caesarean birth still need screening at 36 weeks in case of labour or membrane rupture
- If recent antibiotic treatment, swabs should be postponed and taken at least one week after the cessation of antibiotics
- If mother is allergic to penicillins, request susceptibility testing of the isolate on the pathology form to guide intrapartum antibiotic use of macrolides (azithromycin, erythromycin) or lincomycin

NB: All women with spontaneous preterm labour, or preterm prelabour rupture of membranes should have a low vaginal swab sent for GBS *and* high vaginal swab for other pathogens at the time of initial assessment

Risk factors for neonatal sepsis

An infant is considered at risk for early onset neonatal sepsis (GBS or other organisms) if any of the following apply

- Evidence of maternal chorioamnionitis. Assume chorioamnionitis if maternal temperature above 38^{O} C, maternal pulse > 100 / min, fetal heart rate > 160 bpm, uterine tenderness, rising CRP or white blood cell count, unless there is another obvious cause
- Preterm labour at less than 37^{+0} weeks gestation
- Preterm prelabour rupture of membranes
- Prolonged rupture of membranes greater than 18 hours at term (greater than 36 completed weeks gestation) with or without labour, irrespective of GBS status
- Mother is GBS positive, defined as:
    - Maternal GBS vaginal colonisation during this pregnancy based on a swab taken less than 5 weeks before labour
    - Maternal GBS bacteriuria in the current pregnancy
    - Early onset neonatal GBS sepsis in a previous pregnancy

Management of intrapartum antibiotic prophylaxis and treatment

1. Women in labour where there is evidence of chorioamnionitis

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- Perform a low and high vaginal swab for culture
- Treat mother with IV antibiotics (ampicillin [or amoxycillin] 2 g IV initial dose then 1g IV every 4 hours, gentamicin 5 mg / kg IV as a single daily dose, metronidazole 500 mg IV every 12 hours)
- Delivery should be expedited

2. Women at term who are GBS positive, in labour or with pre-labour rupture of membranes

- *Give IV benzylpenicillin 3 g loading dose as soon as possible, then 1.2 g IV every 4 hours until delivery*
- If allergic to penicillin, lincomycin 600 mg IV every 8 hours, or azithromycin 500 mg IV once daily are alternatives, preferably prescribed based on sensitivity results from antenatal swabs
- Consider advising induction / augmentation of labour for women with pre-labour rupture of membranes and involve the woman and her partner in the decision making process

3. Women at term with prolonged rupture of membranes > 18 hours, irrespective of GBS status

- *Give IV benzylpenicillin 3 g loading dose as soon as possible, then 1.2 g IV every 4 hours until delivery*
- There is insufficient data to make a recommendation regarding the use of broad spectrum antibiotics in cases of PROM > 18 hours[14]
- If allergic to penicillin, lincomycin 600 mg IV every 8 hours, or azithromycin 500 mg IV once daily are alternatives, preferably prescribed based on sensitivity results from antenatal swabs
- Consider advising induction / augmentation of labour and involve the woman and her partner in the decision making process

4. Women at term who are GBS negative or unknown, and with pre-labour rupture of membranes less than 18 hours

- Consider advising induction / augmentation of labour and involve the woman and her partner in the decision making process

5. Preterm labour with intact membranes

- Perform a low and a high vaginal swab for culture
- Give IV benzylpenicillin 3 g loading dose as soon as possible, then 1.2 g IV every 4 hours for threatened or actual preterm labour, unless GBS status is documented to be negative at presentation
- If delivery does not occur, further benzylpenicillin prophylaxis is indicated when labour recurs if the mother is GBS positive
- If other potentially significant pathogens are found on the high vaginal swab,. consult a neonatologist to discuss antibiotic prophylaxis/treatment of the mother in labour and the postnatal management of the infant

6. Preterm rupture of membranes, with or without labour

- Perform a low and a high vaginal swab for culture
- Give IV benzylpenicillin 3 g loading dose as soon as possible, then 1.2 g IV every 4 hours for 48 hours or until delivery if this occurs before 48 hours
- Commence oral erythromycin as soon as possible 250 mg 4 times a day for 10 days or until delivery if this occurs before 10 days

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- If delivery does not occur, further benzylpenicillin prophylaxis is indicated when labour recurs, unless chorioamnionitis supervenes in which case manage as per 1. above
- Repeat high vaginal swab at weekly intervals; results may guide use of antibiotics in any subsequent labour
- As with point 5, consult a neonatologist if other potentially significant pathogens are found on the high vaginal swab

Postnatal maternal antibiotics

Intravenous

- If chorioamnionitis, consider treatment with continued ampicillin [or amoxycillin] 1g IV every 4 hours, gentamicin IV 5 mg / kg as a single daily dose and metronidazole 500 mg IV every 12 hours for 5 days

Oral

- May change to oral antibiotics once the woman is afebrile and tolerating oral medication

  e.g. amoxycillin 500 mg every 8 hours and metronidazole 400 mg every 12 hours **OR** amoxycillin/ clavulanic acid (Augmentin Duo Forte x 1 every 12 hours) for the rest of the 5 days

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Management of the neonate in the postnatal period

1. **Baby with symptoms possibly due to early onset sepsis, or born after suspected chorioamnionitis**
   - Routine investigations are a blood culture, and complete blood picture with immature / total neutrophil ratio
   - Benzylpenicillin: 60 mg (100,000 units) / kg IV every 12 hours plus Gentamicin

Gentamicin is given according to the following regimen:

For Neonates < 33 weeks Corrected Age

The dosing schedule for gentamicin in neonates < 33 weeks corrected age depends upon the type of monitoring that is available at your institution. Both schedules provide the same dose over a 48-hour period

Dosing Schedule A applies if your institution measures gentamicin by performing a single **trough level** (i.e. prior to the next dose)

Dosing Schedule B applies if your institution measures gentamicin by performing two post dose levels and estimates the Area-Under-The-Curve (AUC) for gentamici

Corrected Age (weeks) [Gestational Age PLUS Postnatal Age]	Dosing Schedule A (trough levels)		Dosing Schedule B (AUC estimation)	
	Dose (mg/kg)	Dosing Frequency	Dose (mg/kg)	Dosing Frequency
< 33 weeks	3mg/kg	every 24 hours	6mg/kg	every 48 hours

For Neonates ≥33 weeks Corrected Age

Corrected Age (weeks) [Gestational Age PLUS Postnatal Age]	Dose (mg/kg)	Dosing Frequency
33 to 35 weeks	4.5mg/kg	every 24 hours
36 to 41 weeks	5mg/kg	every 24 hours
42 to 44 weeks	7.5mg/kg	every 24 hours

- Duration of treatment depends on clinical circumstances but is at least 48 hours
- If maternal gentamicin is given < 12 hours before delivery, consider neonatal gentamicin serum levels to determine timing of first dose
- Admit / transfer to level 5 or 6 neonatal service

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- There should be a low threshold for lumbar puncture in symptomatic babies. However, a lumbar puncture should never delay initiation of antibiotics, nor cardio-respiratory stabilisation where this is required. A lumbar puncture is always required where there are neurological symptoms or if a blood culture returns positive after commencement of antibiotics
- An endotracheal aspirate for culture should be taken if intubated
- Gastric aspirate or surface swabs (e.g. ear) may be useful to determine colonising flora if taken soon after birth, but have a poor correlation with invasive sepsis
- The urine latex test for GBS is no longer recommended as a screening test for the evaluation of suspected sepsis in babies

2. **Term baby, asymptomatic, mother GBS positive, or ROM > 18 hours and GBS negative or unknown; mother received inadequate intrapartum antibiotic prophylaxis**
   - Investigate with a complete blood picture
   - Observe closely (usually postnatal ward respiratory rate and temperature 4 hourly for 24 hours)

3. **Term baby, asymptomatic, mother GBS positive, or ROM > 18 hours and GBS negative or unknown; mother received adequate intrapartum antibiotic prophylaxis**
   - No investigations
   - Observe closely (minimum period of observations including respiratory rate and temperature is 4 to 6 hours after birth)

4. **Term baby, asymptomatic, mother GBS negative or unknown with ROM < 18 hours**
   - No investigations
   - Observe closely (minimum period of observations including respiratory rate and temperature is 4 to 6 hours after birth)

5. **Preterm baby, asymptomatic, mother received inadequate intrapartum antibiotics**
   - Investigate as for 1. and treat with penicillin and gentamicin (or other antibiotics based on results of preterm cultures)

6. **Preterm baby, asymptomatic, mother received adequate intrapartum antibiotics**
   - Investigate as for 1., observe closely, consider selective antibiotics (e.g. based on results of preterm cultures or degree of prematurity)

Management of early discharge home (< 48 hours after birth) of the term asymptomatic infant with risk factors

- Term, asymptomatic infants at risk for sepsis and with inadequate intrapartum antibiotic prophylaxis and a normal CBP should be observed in hospital for at least 24 hours. Clinical circumstances may indicate a longer period of observation
- Term asymptomatic babies at risk for sepsis but with adequate intrapartum antibiotic prophylaxis, and those where mother is GBS unknown but with no other risk factors, may be discharged after a minimum observation period of 4-6 hours. If discharged,

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parents should be advised to seek immediate medical attention is their baby develops breathing difficulty or poor feeding over the following 24 hours

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Useful web sites

Courts Administration Authority South Australia

http://www.courts.sa.gov.au/index.html

South Australia Coroners findings for 2009

http://www.courts.sa.gov.au/courts/coroner/findings/findings_2009/content_2009.html

http://www.courts.sa.gov.au/courts/coroner/findings/findings_2009/linnell_sienna_jools.pdf

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South Australia Coroner's findings 2012

http://www.courts.sa.gov.au/CoronersFindings/Lists/Coroners%20Findings/Attachments/469/KISON%20Trinity%20Isabel.pdf

Centers for Disease Control and Prevention (CDC). Group B Strep (GBS). For pregnant women. Available from URL:

http://www.cdc.gov/groupbstrep/index.html

Royal Women's Hospital Victoria: Instructions for the collection of a genital swab for Group B Streptococcus Available from URL: http://www.thewomens.org.au/uploads/images/HealthProfessionals/CPGs/rwhcpg/GBS_Genital_Swab_Diagram_Final_Version3.gif

Abbreviations

AUC	Area under the curve
bpm	Beats per minute
CBP	Complete blood picture
CDC	Centers for Disease Control and Prevention
CRP	C-reactive protein
GA	Gestational age
g	Gram(s)
≥	Greater than or equal to
GBS	Group B streptococcus
I:T ratio	Immature:total neutrophil ratio
IV	Intravenous
≤	Less than or equal to
%	Percentage
mg	Milligram(s)
PROM	Pre-labour rupture of the membranes
PPROM	Premature pre-labour rupture of the membranes
RANZCOG	Royal Australian and New Zealand College of Obstetrics and Gynaecology
RR	Respiratory rate
ROM	Rupture of membranes

Version control and change history

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1.0	04 Aug 04	30 April 07	Original version
2.0	30 April 07	20 Oct 09	Reviewed
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