Clinical Guideline for Management of Neonates with Suspected or Proven Early-Onset Bacterial Sepsis

1. Background

- Early-onset bacterial sepsis (EOS) defined by the National Institute of Child Health and Human Development and Vermont Oxford Networks as sepsis with onset at ≤72 hr of age.

- EOS is a significant cause of mortality and morbidity in newborn babies. The great majority of babies do not experience EOS but critical illness can develop quickly in affected babies.

- Organisms responsible for neonatal EOS come from the maternal genital tract. The predominant pathogens causing EOS are GBS, Listeria monocytogenes and E coli. Group B Streptococcus (GBS, Streptococcus agalactiae) is the most frequent cause of severe neonatal EOS.

- The clinical diagnosis of sepsis in the neonate is difficult, because many of the signs of sepsis are nonspecific and are observed with other noninfectious conditions. Although a normal physical examination is evidence that sepsis is not present, bacteremia can occur in the absence of clinical signs.

2. Risk Factors for EOS including red flag

1. Parenteral antibiotic treatment given to the woman for confirmed or suspected invasive bacterial infection (such as septicaemia) at any time during labour, or in the 24-hour periods before and after the birth (Red Flag)

2. Suspected or confirmed infection in another baby in the case of a multiple pregnancy (Red Flag)

3. Invasive group B streptococcal infection in a previous baby

4. Maternal group B streptococcal colonisation, bacteriuria or infection in the current pregnancy (Not received Adequate IPA)

5. Prolonged rupture of membranes more than 18 hours

6. Preterm birth following spontaneous labour (before 37 weeks' gestation)

7. Suspected or confirmed rupture of membranes for more than 18 hours in a preterm birth

8. Intrapartum fever higher than 38°C, or confirmed or suspected chorioamnionitis
3. Clinical Indicators Suggestive of EOS including red flag

1. Respiratory distress starting more than 4 hours after birth (Red Flag)
2. Need for mechanical ventilation (Red Flag)
3. Signs of shock (Red Flag)
4. Seizures (Red Flag)
5. Altered behaviour or responsiveness
6. Altered muscle tone
7. Feeding difficulties (e.g. feed refusal)
8. Feed intolerance (e.g. abdominal distension, vomiting, gastric aspirate)
9. Abnormal heart rate (bradycardia or tachycardia)
10. Apnea
11. Hypoxia (central cyanosis or reduced oxygen saturation level)
12. Jaundice within 24 hours of birth
13. Signs of neonatal encephalopathy
14. Need for cardio–pulmonary resuscitation
15. PPHN
16. Temperature instability not explained by environment
17. Unexplained bleeding disorder (e.g. thrombocytopenia or impaired coagulation profile)
18. Oliguria persisting beyond 24 hours after birth
19. Altered glucose homeostasis
20. Metabolic acidosis ((base deficit of 10 mmol/litre or greater)
21. Local signs of infection e.g. skin, eyes
4. Management of the Neonate:

4.1 Identifying infants with possible EOS

- Management of the newborn infant within the first 72 hours of life should be based on an assessment of risk factors and clinical indicators. Certain risk factors and clinical indicators are “red flags” which signify a high likelihood of early-onset neonatal infection.

- Any risk factor or clinical indicator identified by maternity staff before or following delivery should prompt a careful clinical assessment of the baby without delay. This should include a review of the maternal and neonatal history and a physical examination of the baby including an assessment of vital sign.

4.2 Neonatal care-pathways based on risk factors and clinical indicators

4.2.1. Infant with any red flag: Investigate and treat

4.2.2. No red flags, but two or more non-red flag risk factors or clinical indicators: Investigate and treat

4.2.3. No red flags, and only one non-red flag risk factor or clinical indicator:

- Observe and Monitor

- If one or more further clinical indicator develops: Investigate and Treat

- If no further concerns arise during observation and monitoring period baby can be discharge home after 24 hr and parent should be instruct regarding signs and symptoms of sepsis and baby should be reevaluated after 3 days from discharge.

Note: Monitoring should include documentation of clinical condition and vital signs (temperature, pulse and respiratory rate) at 0, 1, and 2 hours, and then 2-hourly for at least a further 10 hours.

4.2.4. No risk factors or clinical indicators: Continue routine postnatal care.

Note: If maternal GBS colonisation is first identified after birth but within the first 72 hours of life, the baby should be assessed for any other risk factors and any clinical indicators of infection.
4.3 Neonatal investigations for suspected EOS

- Blood Culture (at birth) and sample for CBC, CRP (at 6-12 hr after birth) should always be taken before administering the first dose of antibiotic. Data suggest that 1ml of blood should be minimum volume drawn for culture

- Routine urine / culture are not recommended

- A second CRP should be measured 18-24 hours after presentation

- Surface skin swabs for culture are not recommended in either well or unwell babies, in the absence of clinical signs of a localized infection

- A lumbar puncture should be performed before starting antibiotics if it is safe to do so and there is a strong clinical suspicion of infection. If performing lumbar puncture would delay starting antibiotics beyond a safe duration (maximum 1 hour), perform the LP as soon as possible after starting antibiotics

- If an LP was not done at presentation, an LP should be considered if:
  - the baby whose clinical course or laboratory data strongly suggest bacterial sepsis
  - blood culture is positive, or
  - there is an unsatisfactory response to antibiotic treatment

- For any baby who is critically ill and likely to have cardiovascular or respiratory compromise from procedure, LP can be deferred until the baby is more stable

- A chest X-Ray should be performed if there are clinical signs of respiratory disease

- Cultures and Gram stains of tracheal aspirate specimens may be of value if obtained immediately after endotracheal tube placement. Once an infant has been intubated for several days, tracheal aspirates are of no value in the evaluation of sepsis

- If infants show signs consistent with impaired coagulation (eg, gastric blood, bleeding from puncture sites, or other bleeding), coagulation profile should be evaluated

4.4 Empirical antibiotic therapy for suspected EOS

- Babies commenced on antibiotic treatment should receive the first dose as soon as possible and always within 1 hour of the decision to treat

- Babies commenced on antibiotics for suspected early-onset neonatal infection should receive: IV penicillin and IV Gentamicin
Babies commenced on antibiotics should be assessed regularly and the antibiotic regimen reviewed on the basis of the baby’s clinical condition and culture results.

If baby’s clinical condition deteriorated repeat septic work up and add cefotaxime.

Babies with purulent umbilical discharge or peri-umbilical cellulitis should have full sepsis evaluation and umbilical swab for Gram stain and culture. Start IV Flucloxacillin and Gentamicin.

Babies with a significant purulent eye discharge within first 72 hours should have full sepsis evaluation and standard eye swabs sent urgently for gram stain and culture, and Chlamydia eye swab for PCR. Treat for possible gonococcal infection. Start on topical gentamycin and single dose of ceftriaxone 25-50mg/kg IV/IM (not to exceed 125 mg) if infant not jaundiced, if jaundiced start on IV Cefotaxime 100 mg/kg IV/IM and to consult ophthalmologist. Specific therapy should be guided by microbiology results.

### 4.5 Care of babies receiving antibiotics for suspected EOS

- If baby stable should be admitted and receive antibiotics in pediatric ward (if mother discharged) and if mother not discharged to be admitted to SCBU.

- If baby not stable should be admitted and receive antibiotics in the NICU and should remain in NICU until considered fit to be nursed with mother in pediatric ward.

### 4.6 Duration of treatment in babies with negative cultures

- The usual duration of antibiotic treatment for babies with a negative blood culture but in whom there has been strong suspicion of sepsis should be 7 days.

- Consider stopping antibiotics 36 hours after starting antibiotics if:
  - The blood culture is negative, and
  - The initial suspicion of infection was not strong, and
  - The baby's clinical condition is reassuring with no clinical indicators of possible infection, and
  - The levels and trend of CRP are reassuring

- If blood culture is negative but it is decided to continue beyond 36 hours, the baby should have a clinical review once every 24 hours. At each review, consider whether to stop or continue antibiotic treatment, taking account of:
  - the level of initial clinical suspicion of infection
  - the baby's clinical progress and current condition
  - the levels and trends of C-reactive protein concentration
Note: if the mother received antibiotic therapy before delivery, especially if she received the therapy within several hours of delivery. This may result in negative culture results in an infant who actually has bacteremia or sepsis. With this in mind, the need for continued therapy (consider 10 days) should be based not on a single test, but on a review of all diagnostic data

4.7 Targeted antibiotic therapy for culture-positive EOS and duration of therapy

4.7.1 Neonatal early-onset bacteraemia:

- Gram-negative organism grown on blood culture:
  - Add Cefotaxime
  - If gram-negative infection is confirmed, stop the penicillin.
  - Treat for 14 days from first negative culture

- GBS or Listeria grown on blood culture:
  - Continue penicillin and Gentamicin.
  - Treat for 10 days

Note: Repeat blood cultures should be obtained, usually within 24 h of presumed effective therapy, to document clearance, as persistent positive cultures could mean failure of antimicrobial therapy or evidence of intravascular site infection, and antibiotic coverage and duration may need to be adjusted

4.7.2 Neonatal early-onset meningitis:

- Empirical treatment pending CSF culture: Penicillin and Cefotaxime

- To determine whether the CSF is sterile, a follow-up lumbar puncture is recommended within 48-72 hours after initiation of antibiotic therapy

- Uncomplicated meningitis attributable to GBS is treated for minimum of 2 weeks. Gram negative meningitis is treated for minimum of 3 weeks or 2 weeks after obtaining negative culture, whichever is longer

- Treatment of gram negative meningitis should include cefotaxime and aminoglycoside (Gentamicin) until the results of susceptibility are known

5. Consultations:

- An infectious disease consultation is useful, especially if the infant is not responding to treatment, is infected with an unusual organism, or has had a complicated clinical course

- A pediatric surgical consultation may be necessary if sepsis is complicated by abscess, or if the differential diagnosis includes necrotizing enterocolitis
6. Discharge after stopping antibiotic therapy:

- It is not necessary to keep a well baby in hospital for observation after stopping antibiotics

7. Prevention Strategies for EOS:

- The only intervention proven to decrease the incidence of early-onset neonatal sepsis is maternal treatment with intrapartum intravenous antimicrobial agents for the prevention of GBS infections.

- Adequate prophylaxis is defined as penicillin (the preferred agent), ampicillin, or cefazolin given for ≥4 hours before delivery. Erythromycin is no longer recommended for prophylaxis because of high resistance rates.

- For parturients with a history of serious penicillin allergy (anaphylaxis, angioedema, respiratory compromise, or urticaria), clindamycin is an acceptable alternative agent.

- Intrapartum antimicrobial agents are indicated for the following situations:
  
  1. Positive antenatal cultures at admission for GBS (except for women who have a cesarean delivery without labor or membrane rupture)
  
  2. Unknown maternal colonization status with gestation <37 weeks, prolonged rupture of membranes or temperature >38°C
  
  3. GBS bacteriuria during the current pregnancy
  
  4. Previous infant with invasive GBS disease
References:

1. CDC guideline for secondary prevention of early onset neonatal sepsis. 2010

2. Management of Neonates with Suspected or Proven Early-Onset Bacterial Sepsis. Clinical report. AAP 2012


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