CHAPTER

24

Neonatal Sepsis

Sepsis is one of the most common causes of neonatal mortality globally.[1] Most infection-related neonatal deaths occur in low and middle-income countries due to poor hygiene and suboptimal infection control practices. Sepsis-related mortality is largely preventable with the prevention of sepsis itself, timely recognition, rational antimicrobial therapy, and aggressive supportive care.

EPIDEMIOLOGY: INDIAN DATA

The Delhi Neonatal Infection Study (DeNIS) collaboration reported a 6.2% and 14.3% incidence of culture-positive sepsis and total (culture-positive or culture-negative) sepsis among all NICU admis-sions.[2] Nearly two-thirds of sepsis episodes occurred at or before 72 hours of life (early-onset sepsis). Two-thirds of the isolates were gram-negative, including, *Acinetobacter* spp. (22%), *Klebsiella* spp. (17%), and *Escherichia coli* (14%), with high rates of multi-drug resistance among these isolates. The common gram-positive pathogens were coagulase-negative *Staphylococcus* (15%), *Staphylococcus aureus* (12%), and *Enterococcus* spp. (6%). The profile of organisms responsible for early-onset and late-onset sepsis (i.e. after 72 hours) was not different. Nearly a quarter of neonatal deaths were attributable to sepsis.

Neonatal sepsis is a clinical syndrome of a dysregulated host response to bloodstream infection in the first 28 days of life. It encompasses various systemic infections such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis, and urinary tract infections. Superficial infections (umbilical infections, conjunctivitis, and oral thrush) are not usually included under neonatal sepsis.

CLASSIFICATION

Neonatal sepsis can be classified into two major categories depending on the onset of symptoms.

Early-onset sepsis (EOS) presents at or before 72 hours of life. In severe cases, the neonate may be symptomatic at birth. Infants with EOS usually manifest with respiratory distress and pneumonia. The source of infection has been traditionally believed to be the maternal genital tract.

Based on the literature, the following risk factors seem to be associated with EOS:[3–5]

1. Spontaneous preterm labor in absence of PROM
2. Foul-smelling liquor
3. Prelabor rupture of membranes >24 hours (PROM)
4. Confirmed or suspected intrauterine inflammation, infection, or both (*Triple I*[6])
5. Single unclean vaginal examination during labor
6. Prolonged labor (sum of 1st and 2nd stage of labor >24 hours)
7. Severe perinatal asphyxia (Apgar score <4 at 1 minute).

Late-onset sepsis (LOS): It presents after 72 hours of life. LOS can be either healthcare-associated (HAI) or community-acquired infection. The neonates usually present with septicemia, pneumonia, or meningitis. Various factors predispose to an increased risk of HAI, includingprematurity, low birth weight, admission to the intensive care unit, mechanical ventilation, presence of invasive lines, administration of parenteral fluids, and use of stock solutions. Factors that might increase the risk of community-acquired LOS include poor hygiene, poor cord care, bottle feeding, and prelacteal feeds.

CLINICAL FEATURES

Nonspecific features: The earliest signs of sepsis are often subtle and nonspecific. Indeed, a high index of suspicion is needed for early diagnosis. Neonates with sepsis may present with one or more of the following symptoms or signs:

a. Hypothermia or fever (the former being more common in preterm neonates).
b. Lethargy, poor cry or refusal to suck.
c. Poor perfusion, prolonged capillary refill time.
d. Hypotonia, absent neonatal reflexes.
e. Bradycardia/tachycardia.
f. Respiratory distress, apnea and gasping respiration.
g. Hypo/hyperglycemia.
h. Metabolic acidosis.

Clinical features specific to various systems:

- **Central nervous system:** Bulging anterior fontanelle, vacant stare, high-pitched cry, excess irritability, stupor/coma, seizures, neck retraction/retrocollis.

  The presence of these features should raise clinical suspicion of meningitis.
- **Cardiovascular:** Hypotension, cyanosis, shock.
- **Gastrointestinal:** Increased gastric residuals, vomiting, diarrhea, abdominal distension, paralytic ileus.
- **Hepatic:** Direct hyperbilirubinemia (especially with urinary tract infections).
- **Renal:** Acute renal failure.
- **Hematological:** Bleeding, petechiae, purpura.
- **Skin changes:** Multiple pustules, abscess, sclerema, mottling, umbilical redness and discharge.

INVESTIGATIONS

Treatment should be initiated in a neonate suspected to have sepsis without any delay—only minimal and rapid investigations should be undertaken.

1. **Blood culture:** It is the gold standard for the diagnosis of sepsis and must be performed in all neonates with suspected sepsis. A positive blood culture with a known sensitivity pattern of the isolated organism is the best guide to antimicrobial therapy. Therefore, following the proper procedure for collecting the blood culture is essential. One ml of blood is adequate for a blood culture bottle containing 5–10 ml of culture broth. The samples from indwelling catheters should be avoided because of the risk of the growth of contaminants.

   Blood cultures should be observed for at least 72 hours before they are reported as sterile. It is now possible to detect bacterial growth within 12–24 hours using improved bacteriological techniques such as BACTEC and BACT/ALERT culture systems. These systems are based on using carbohydrate substrates in culture media and subsequent production of CO_2 by growing microorganisms, detected through their impact on pH by either a colorimetric or a fluorescent sensor placed at the bottom of the bottle.[7]
2. **Sepsis screen:**[8,9] Neonates suspected to have sepsis should undergo a sepsis screen to corroborate the diagnosis. However,

the decision to start antibiotics need not be conditional on the sepsis screen result if there is a strong clinical suspicion of sepsis and the neonate is too sick.

The various components of the sepsis screen include total leukocyte count (TLC), absolute neutrophil count (ANC), immature to total (I/T) neutrophil ratio, microerythrocyte sedimentation rate, and C reactive protein (CRP). The ANC varies considerably in the immediate neonatal period, and the standard reference ranges are available from Manroe's charts for term neonates.[10] The lower limit of ANC begins at 1800/cm^3 at birth, rises to 7200/cm^3 at 12 hours of age and then declines and persists at 1800/cm^3 after 72 hours of age. The reference ranges for VLBW infants are available from Mouzinho's charts.[11]

The I/T ratio is ≤0.16 at birth and reaches a nadir of 0.12 after 72 hours of age. While using a kit-based semiquantitative assay of CRP, always check for the cutoff (usually set at 0.6 or 0.8 mg/L), which can give a higher false positivity rate. The sepsis screen used in our unit is described in Table 24.1.

The presence of two abnormal parameters in a screen is associated with a sensitivity of 93–100%, specificity of 83%, and positive and negative predictive values of 27% and 100%, respectively, in detecting sepsis, especially after the first week of life.[9] Presence of two (or more) abnormal parameters is considered a positive screen, and the neonate may be started on antibiot-ics. If the screen is negative but clinical suspicion persists, it may be repeated within 12 hours. If the screen is still negative, sepsis can be excluded with reasonable certainty.

3. **Procalcitonin (PCT):** PCT is an acute phase protein secreted by several tissues in response to various endogenous and exogenous stimuli such as cytokines and lipopolysaccharides.

Table 24.1: Components of sepsis screen

Component	*Abnormal value*
Absolute neutrophil count	Low counts as per Manroe's chart for the term and Mouzinho's chart for VLBW infants
Immature/total neutrophil ratio	>0.2
Micro-ESR	>15 mm in 1st hour
C reactive protein (CRP)	>1 mg/L

ESR: Erythrocyte sedimentation rate

In healthy neonates, plasma PCT values increase gradually after birth, reach peak values after 24 hours of age (mean 1.5–2.5 ng/ml, range 0.1–20 ng/ml) and then decrease to typical values below 0.5 ng/ml by 48–72 hours of age.[12] Age-specific cutoffs have been devised for preterm, late preterm, and term infants within the first 5 days.[13] A recent meta-analysis found only a moderate accuracy with a sensitivity of 85% and specificity of 54% at a cut-off of 2–2.5 ng/ml.[14] We do not use PCT to diagnose sepsis in our unit.

4. **Other biomarkers:** Other biomarkers, besides CRP and PCT, have been evaluated for early diagnosis of sepsis in neonates, including serum amyloid A, hepcidin, CD64, CD11b, IL-1, IL-6, IL-8, TNF-α, soluble TNF receptor, E-selectin, ICAM, etc.[15] Among these, serum amyloid A has shown some promising results; however, none of these biomarkers are currently in routine use.
5. **Molecular assays:** Molecular pathogen detection methods are based on the hybridization or amplification of pathogen DNA. Neonatal studies have been conducted using amplification methods (e.g. polymerase chain reaction; PCR) that can be completed in less than 12 hours and may have better sensitivity than microbial cultures. A recent Cochrane review in 2017 concluded that molecular assays may perform well as 'add-on' tests.[16] However, molecular assays do not provide information on antibiotic susceptibility. These are not recommended for routine practice, given insufficient evidence, high cost, and lack of widespread availability.
6. **Lumbar puncture (LP):** The incidence of meningitis in neonatal sepsis has varied from 0.3 to 3% in various studies.[2] The clinical features of sepsis and meningitis often overlap; it is possible to have meningitis without any specific symptomatology. This justifies the extra-precaution of performing LP in neonates suspected of sepsis.

   In EOS, lumbar puncture is performed in the presence of a positive blood culture in an asymptomatic neonate with a maternal risk factor or if the neonate is symptomatic with a clinical picture consistent with sepsis. It is not indicated if antibiotics have been started solely because of risk factors in asymptomatic neonates. In late-onset sepsis, LP should be done in all neonates before antibiotics because up to 1/3rd of VLBW neonates with meningitis can have negative blood

cultures. Lumbar puncture may be postponed in critically sick neonates. It should be performed as soon as the clinical condition stabilizes. The cerebrospinal fluid characteristics are unique in the newborn period, and normal values are given in Table 24.2.[17,18]

The NNF CPG guidelines[19] summarize the performance of cellular and biochemical parameters in diagnosing neonatal meningitis. The guidelines recommend using CSF WBC count and protein but not CSF glucose for diagnosis.

7. **Radiology:** Chest X-ray should be considered in the presence of respiratory distress or apnea.

   An abdominal X-ray is indicated in the presence of abdominal signs such as abdominal distension. Neuroimaging should be performed in neonates suspected to have complications secondary to meningitis (intracranial abscesses, ventriculitis, hydrocephalus, etc.).

8. **Urine culture:** Urine cultures have a low yield and are not indicated routinely. However, neonates at risk for fungal sepsis, with urogenital malformation or vesicoureteral reflex, or suspected urinary tract infection (crying during micturition) should have a urine examination to exclude UTI. Urine cultures are obtained by suprapubic puncture, bladder catheterization, or clean catch samples from midstream urine.

   UTI is defined as the growth of a single uropathogenic organism with a colony count of ≥50,000 CFU/ml or between 10,000 and 50,000 CFU/ml with associated pyuria (WBC >5/HPF) detected on a midstream clean catch urine sample or any organism in urine which is obtained by suprapubic aspiration. However, the optimal definition for UTI based on a catheterized specimen in neonates has still not been established.

Table 24.2: Normal CSF parameters in term and preterm neonates

CSF Components	*Term neonates*	*Preterm* very low birth weight neonates
Cells/mm^3	8 (0–32)	5 (0–44)
PMN (%)	60%	8% (0–66)
CSF protein (mg/dl)	90 (20–170)	148 (54–370)
CSF glucose (mg/dl)	52 (34–119)	67 (33–217)

Values expressed as median (range)

MANAGEMENT

Supportive

Adequate and proper supportive care is crucial in sick neonates with sepsis. The neonates should be nursed in a thermoneutral environment to avoid hypo/hyperthermia. Oxygen saturation should be maintained at 91–95%; mechanical ventilation may have to be initiated if needed. If the infant is hemodynamically unstable, intravenous fluids should be administered, and the infant should be monitored for hypo/hyperglycemia. Volume expansion with crystalloids and judicious use of inotropes are essential to maintain normal tissue perfusion and blood pressure. Packed red cells and fresh frozen plasma may be required in anemia or bleeding diathesis.

Antibiotic Therapy

i. **Early-onset sepsis:** In high-income countries, various approaches have been described to identify neonates at risk of EOS based on perinatal risk factors to make a timely and rational decision for antibiotic therapy.[20,21] However, due to inherent pathogen related and other differences in developing countries compared to high-income countries, these approaches may not be generalizable to our settings.

   Currently, we consider antibiotics in a neonate with any one of the following:

   a. Presence of ≥3 risk factors for early onset sepsis (*see above*).
   b. Suspected or confirmed Triple I.
   c. Presence of ≥2 risk factor(s) *and* a positive sepsis screen.
   d. A strong clinical suspicion of sepsis.

ii. **Late-onset sepsis:** The indications for starting antibiotics in LOS include:

   a. A positive sepsis screen or
   b. A strong clinical suspicion of sepsis.

iii. **Prophylactic antibiotics:** *We do not use prophylactic antibiotics in any circumstance*, including neonates receiving IV fluids/TPN or with meconium aspiration syndrome or after exchange transfusion.

iv. **Choice of antibiotics:** Empirical antibiotic therapy should be unit-specific and determined by the prevalent spectrum of etiological agents and their antibiotic sensitivity pattern. Antibiotics, once started, should be modified according

to the sensitivity pattern. A simplified stepwise approach to facilitate the choice of an empiric antibiotic regimen is outlined in Table 24.3.

The empirical choice of antibiotics is dependent upon the probable source of infection. A combination of ampicillin or penicillin with gentamicin may be good first-line therapy for infections that are likely to be community-acquired where resistant strains are unlikely.[22] Cloxacillin should be considered if there is evidence of staphylococcal infection.

A combination of beta-lactam antibiotics with an aminoglycoside may be instituted for infections acquired during the hospital stay. However, except in cases of multi-drug resistance, monotherapy with beta-lactam is usually adequate for infections due to common organisms; the addition of an aminoglycoside is proven to be unnecessarily broad with no added survival advantage but an increased risk of toxic effects.[23] Third-generation cephalosporins were considered a good choice for managing nosocomial infections and meningitis. However, recent reports suggest that at least 60–70% of gram-negative organisms are now resistant to them.[24]

A combination of piperacillin-tazobactam with amikacin should be considered if *Pseudomonas* sepsis is suspected. Penicillin-resistant *Staphylococcus aureus* should be treated with cloxacillin, nafcillin, or methicillin. Methicillin-resistant *Staphylococcus aureus* (MRSA) should be treated with vancomycin or oxacillin with an aminoglycoside.

Table 24.3: A stepwise approach for framing empiric antibiotic therapy for a unit

1. Collate the frequency table of isolates and their antibiogram of the last 6–12 months.
2. First-line antibiotics: Combination of common antibiotics that together cover 60–70% of iso-lates.
3. Second-line antibiotics: Other antibiotic combinations cover 80–90% of isolates.

Note:

- The antibiotic regimen needs to be reviewed every 6–12 months.
- Cephalosporins are generally avoided as the first-line antibiotics since they are known to induce ESBL (extended-spectrum beta-lactamases)/cephalosporinases rapidly and are associated with high predilection for fungal colonization.
- Reserve drugs like colistin, meropenem, vancomycin, or linezolid should not be used empirically.

Ciprofloxacin has excellent activity against gram-negative and gram-positive organisms; however, it does not have good CSF penetration. It may be used to treat resistant gram-negative bacteremia after excluding meningitis. For *Enterococcus* sepsis, a combination of ampicillin and gentamicin is a good choice for initial therapy. *Enterococcus* is inherently resistant to cephalosporins. Vancomycin should be used to treat *Enterococcus* resistant to first-line antibiotics.

v. **Rationalization of antibiotic usage:** Once initiated, it is essential to regularly review the need for antibiotics to minimize the development of antibiotic resistance. A few salient principles of antibiotic stewardship are highlighted below:
   1. Downgrade to a narrower spectrum or lower-cost antibiotic to which the organism is sensitive, irrespective of clinical response to antibiotics already being used.
   2. A single sensitive antibiotic should suffice for almost all pathogens except *Pseudomonas*.
   3. In the case of pan-resistant organisms with intermediate sensitivity to one or the other antibiotics, consider a higher dose of that antibiotic, preferably in combination.
   4. Antibiotic usage can further be rationalized using risk scores or prediction modeling techniques to detect sepsis using maternal and neonatal characteristics. The web-based EOS calculator[25] has been shown to reduce antibiotic usage by 50% in high-income countries.[26] The generalisability of the calculator is, however, limited due to striking differences between high-income countries (where it is developed) and low-income countries. Further, it incorporates maternal group B *Streptococcus* colonization as a risk factor which is extremely rare in our population. Also, it only applies to neonates more than 35 weeks of gestation, limiting its usage in our NICUs.

vi. **Reserve antibiotics:** Newer antibiotics like aztreonam, meropenem, and imipenem are classified as 'reserve' antibiotics based on the AWaRe classification by WHO. Aztreonam has excellent activity against gram-negative organisms, while meropenem is effective against most bacterial pathogens except MRSA and *Enterococcus*. Imipenem is generally avoided in neo-nates because of a reported increase in seizures following its use. Empiric use of these

Table 24.4: Duration of antibiotic therapy in neonatal sepsis	
Diagnosis	*Duration*
Meningitis (with or without positive blood/CSF culture)	21 days
Blood culture positive but no meningitis	14 days
Culture-negative sepsis (clinical course consistent with sepsis)	5–7 days

antibiotics should be avoided; they should be reserved only for situations where the sensitivity of the isolated organism warrants its use.

vii. **Duration of antibiotic therapy:** The antibiotic therapy duration depends upon clinical course, culture positivity and presence of absence of meningitis (Table 24.4).

Adjunctive Therapy

i. **Exchange transfusion (ET):** ET removes inflammatory cytokines and bacterial products, offering an immunological advantage. One study demonstrated a 50% reduction in sepsis-related mortality following double-volume exchange transfusion in septic neonates with sclerema.[27] In another study, ET conferred cardiovascular and hematological benefits without reducing mortality.[28] A recent narrative review discussed the pros and cons of ET and cautioned against using it as a last resort in cases of sclerema and multi-organ failure.[29]

ii. **Immunotherapy:** A recent network meta-analysis evaluated therapy with immunoglobulins (IgG, IgM enriched IgG, and colony-stimulating factors [G-CSF or GM-CSF]).[30] None of them were superior to placebo in reducing all-cause mortality. A Cochrane review of the use of immunoglobulin conclusively declared no benefit of the same for suspected or proven sepsis.[31]

iii. **Lactoferrin:** A Cochrane review evaluating the use of lactoferrin in preterm infants reported a significant decrease in the incidence of sepsis and necrotizing enterocolitis by 18%.[32]

Another updated meta-analysis revealed a limited but significant reduction in sepsis in very low birth weight neonates. However, the data were considered insufficient to guide clinical practice.[33] We do not use lactoferrin to prevent sepsis.

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