Neonatal sepsis

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Sepsis in the Newborn

- Sepsis is an important cause of morbidity and mortality among newborn infants.
- About 30-50% of the total neonatal deaths in developing countries.
- Sepsis related mortality is largely preventable with prevention of sepsis itself, timely recognition, rational antimicrobial therapy and aggressive supportive care.

Definition

- **Neonatal sepsis is a clinical syndrome in an infant 28 days of life or younger, manifested by systemic signs of infection and isolation of a bacterial pathogen from the blood stream.**

Classification

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

- **Early onset sepsis (EOS):**

  - Within the first 72 hours of life

  - Transmitted vertically by ascending contaminated amniotic fluid or during vaginal delivery from bacteria in the mother's lower genital tract maternal genital tract.

- **Late onset sepsis (LOS):**

  - After 72 hours of age.

- Vertical transmission, neonatal colonization evolves into later infection

- Horizontal transmission either nosocomial (hospital-acquired) or community-acquired

ETIOLOGIC AGENTS

Table 1. Microbial pathogens and risk factors associated with neonatal sepsis

Neonatal sepsis	Microbial pathogens	Risk factors
Early-onset	• Group B streptococci • *Escherichia coli* • *Streptococcus viridans* • Enterococci • *Staphylococcus aureus* • *Pseudomonas aeruginosa* • Other gram-negative bacilli	• Maternal Group B streptococcal colonization • Chorioamnionitis • Premature rupture of membranes • Prolonged rupture of membranes (> 18 h) • Preterm birth (< 37 weeks) • Multiple gestation
Late-onset	• Coagulase-negative Staphylococci • *Staphylococcus aureus* • *Candida albicans* • *Escherichia coli* • *Klebsiella pneumoniae* • Enterococci • *Pseudomonas aeruginosa* • Group B streptococci	• Prematurity • Low birth weight • Prolonged indwelling catheter use • Invasive procedures • Ventilator associated pneumonia • Prolonged antibiotics

Modified from reference 1.

Clinical features

- **Vary by gestational age and severity of infection**
- Earliest signs often subtle, nonspecific; high index of suspicion needed for early diagnosis.
- Temperature instability: Hypothermia or fever
  - Hypothermia is more common upon presentation especially in preterm LBW infants
  - Rarely infants present with fever unless born to febrile mother and fever immediately after delivery, more in term.
- Lethargy, poor cry and Poor feeding
- Pneumonia is often the presenting infection; respiratory symptoms common: apnea, tachypnea, grunting, nasal flaring, and intercostal retractions
- Cardiac symptoms: cyanosis, desaturation, bradycardia, poor perfusion, reduced capillary refill, and hypotension
- Hypotonia, absent neonatal reflexes
- Hypo/hyperglycemia
- Metabolic acidosis
- **Preterm Infants often present with:**
- Apnea, bradycardia, tachycardia, cyanosis
- Lethargy or hypotonia
- Increased respiratory effort or increase in ventilator support in mechanically ventilated patients
- Temperature instability
- Hypotension and poor perfusion ,shock
- Symptoms more severe with Gram-negative & fungal infections than Gram-positive infection

- “Rule out sepsis” or “Suspected sepsis” is one of the most common reasons for admission to a NICU.
- The challenge to the physician has always been trying to differentiate newborns with sepsis from other non-infectious pathology whose clinical features overlap with sepsis.

EVALUATION AND INITIAL MANAGEMENT

- **Early-onset presentation** — The evaluation includes all of the following:
- Review of the pregnancy, labor, and delivery, including risk factors for sepsis and the use and duration of maternal intrapartum antibiotic prophylaxis (IAP).
- Comprehensive physical examination.
- Laboratory testing – The extent of the evaluation is directed by the neonate's signs and symptoms and maternal risk factors

Early-onset sepsis calculator

- The EOS calculator is a web-based tool to estimate the risk of EOS in individual patients based on risk factors (eg, newborn clinical condition, highest intrapartum maternal temperature, maternal group B *Streptococcus* [GBS] status, administration of maternal IAP, gestational age, duration of rupture of membranes).
- The calculator provides guidance on whether diagnostic evaluation and empiric antibiotic treatment are warranted.

- **Symptomatic neonates** — Neonates with signs and symptoms of EOS should undergo a full diagnostic evaluation and should receive empiric antibiotic treatment.
- **Well-appearing neonates** — with identified risk factors for EOS, particularly GBS, should be observed for 36 to 48 hours.
- may require a limited diagnostic evaluation

Late-onset sepsis

- The evaluation includes all of the following:
- Review of the pregnancy, labor, and delivery, including risk factors for sepsis and the use and duration of maternal intrapartum antibiotic prophylaxis (IAP).
- Comprehensive physical examination.
- Laboratory testing includes **all** of the following:
- Blood culture.LP.Chest radiograph.Urine culture
- Empiric antibiotic treatment.

Investigations

Bacterial cultures:

- Blood culture is the gold standard for diagnosis of septicemia.
- It should be done before starting antibiotics.
- **One-ml** sample of blood should be adequate.
- Sensitivity of a single blood culture to detect neonatal bacteremia is approximately 90%.
- **Time to positivity**

  Automated systems for continuous monitoring of blood cultures shortened the time to identify positive blood cultures (positive within 24-48hr).

Complete Blood Count:

- **WBC counts**. (5000/mm3 to 30000/mm3)

  have a poor positive predictive value and have poor diagnostic accuracy
- **Absolute neutrophil count (ANC).** neutropenia in term and late preterm infants is < 1800/mm3 at birth and <7800/mm3 at 12–14 hours of age with peak values occurring between 6 and 8 h for infants more than 28 weeks gestation and between 12 and 24 h for infants delivered at less than 28 weeks
- **Absolute band count**.
- **The ratio of immature to total neutrophils (I/T).**

  I/T ratio of >0.2 is suspicious for sepsis

- WBC counts and the components of WBC, absolute neutrophil count (ANC), absolute band count and the ratio of immature to total neutrophils (I/T) in the blood are parameters that are commonly used as screening tests for the diagnosis of sepsis.
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- Platelet counts and volume: Platelet counts are characterized by poor sensitivity and specificity for the diagnosis of neonatal sepsis and hence are unreliable for initiating or discontinuing antibiotics

Biomarkers

Newer diagnostic tests can be grouped into:

- Acute phase reactants
- Cell surface markers
- Granulocyte colony-stimulating factor
- Cytokines
- Molecular genetics

C-REACTIVE PROTEIN (CRP)

- An acute phase reactant produced in the liver
- Plays a central role in the humoral response to bacterial invasion
- A late marker of sepsis.
- Non specific
- CRP is useful for monitoring the response to treatment and guiding antibiotic therapy.
- synthesized within six to eight hours of exposure to an infective process or tissue damage, with a half life of 19 hours.
- It is elevated in numerous noninfective conditions like maternal fever, fetal distress stressful delivery, perinatal asphyxia, meconium aspiration and IVH

PROCALCITONIN

- Propeptide of calcitonin
- Produced by monocytes and hepatocytes.
- Early marker
- The advantages of PCT over CRP in sepsis include:
  - rapid rise in response to infection (useful in EOS)
  - levels decline with control of infection (half life is 24h),
  - not typically affected by viral infections (specific for bacterial sepsis)
  - it correlates with severity of infection.

A meta-analysis of 29 studies revealed a sensitivity of 81% (74– 87%) and specificity of 79% (69–87%).

The Pitt fall of PCT is increased in newborns requiring neonatal resuscitation, maternal GBS colonization and prolonged rupture of membranes ≥18 h.

Levels increase rapidly in 2-4h and peaks at 6-8h in response to bacterial endotoxins, and remains raised for at least 24 hours, with a half life of 24–30 hours.

Cell surface markers

- Neutrophil CD64 appear to be promising markers for the diagnosis of early- and late-onset infections.
- A highly sensitive marker for neonatal sepsis, with a sensitivity of 80% , a specificity of 79%, and a cutoff value of 4.02.

Lumbar Puncture

- Perform a lumbar puncture:
- A strong clinical suspicion of infection.
- A clinical symptoms or signs suggesting meningitis.
- An LP must be done whenever the blood culture is positive.
- The CSF culture may be negative but pleocytosis, low glucose and/or elevated protein may be observed with meningitis

Urine Culture

- Urine cultures obtained by suprapubic puncture or bladder catheterization have been recommended in all cases of LOS.
- The rate of positive urine culture in infants with EOS is low and should not be part of the traditional sepsis evaluation.

Radiology

- Chest X-ray is done in cases of respiratory distress or apnea. Abdominal X-ray should be done for diagnosis of necrotizing enterocolitis.

Management

Supportive:

- A thermo-neutral environment to avoid hypo/hyperthermia.
- Oxygen saturation should be maintained in the normal range; mechanical ventilation may have to be initiated if necessary.
- If the infant is hemodynamically unstable, intravenous fluids should be administered and the infant is to be monitored for hypo/hyperglycemia.
- Volume expansion with crystalloids/colloids and judicious use of inotropes are essential to maintain normal tissue perfusion and blood pressure.
- Packed red cells and fresh frozen plasma might have to be used in the event of anemia or bleeding diathesis.

Management

Antimicrobial therapy:

There cannot be a single recommendation for the antibiotic regimen of neonatal sepsis for all settings.

The choice of antibiotics depends on the prevailing flora in the given unit and their antimicrobial sensitivity.

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Empirical antibiotic therapy

- **Initial choice of parenteral antibiotics for suspected sepsis in term and late preterm neonates is based on:**
- The infant's age
- Likely pathogens
- Susceptibility patterns of organisms in a particular nursery
- Presence of an apparent source of infection (eg, skin, joint, or bone involvement)
- Antibiotics once started should be modified according to the sensitivity reports.

Empirical antibiotic therapy

- Early onset sepsis
- Ampicillin and an aminoglycoside provide coverage for GBS, *E coli* and most other common pathogens causing EOS. third-generation cephalosporin e.g. cefotaxime, is added if meningitis is present in these cases.

Third generation Cephalosporins

- Have very good CSF penetration and antimicrobial activity against Gram-negative organisms.
- At least 60-70% of the Gram-negative organisms are resistant to them.
- Cephalosporins are not active against *L. monocytogenes*.
- Routine use might increase the risk of the following:

  - infections with (ESBL) positive organisms.

  - Increase in serious complications as (NEC) and death

  - Increase in prevalence of invasive candidiasis
- In large cohort study, infants received ampicillin plus Cefotaxime had a 1.5-fold increase in mortality compared with those treated with ampicillin plus gentamicin.

Late-onset sepsis

Admitted from the community:

- If no apparent focus of infection empiric regimens:

- Combination of Ampicillin and Gentamicin or Ampicillin and Cefotaxime
- Add third-generation cephalosporin to Ampicillin and gentamicin regimen if suspected meningitis

Hospitalized since birth:

- Vancomycin substituted for ampicillin
- Meropenem In ESBL-producing E. coli infections and other highly resistant MO.

- empiric antibiotic treatment should be started depending upon :
- lower risk for infection caused by multidrug resistant pathogens
- Local antibiotic resistance patterns must be considered
- Higher risk for multidrug-resistant organisms

Duration of antibiotic treatment

- Review clinical progress and microbiology results at 36 hours.
  - If cultures negative consider stopping therapy.
  - Continue therapy if cultures positive or sepsis very likely.

Duration of antibiotic treatment

Infection type	Duration (days) of therapy
Pneumonia	5-7
Septicaemia	7-10
Urinary Tract Infection	7-10
Meningitis	14-21 (depending on organism isolated)
Skin conditions	5
Conjunctivitis	5-7
Oral thrush	7-10

Adjunctive therapy

- ***Intravenous Immune Globulin (IVIG)***
- ***Granulocyte colony-stimulating factor (G-CSF)***

  There is currently insufficient evidence to support the introduction of either one into neonatal practice, either as the treatment of established systemic infection to reduce resulting mortality, or as prophylaxis to prevent systemic infection in high-risk neonates.

Exchange transfusion

- Exchange transfusion in neonatal sepsis has not been extensively studied. It may be used with caution in neonatal sepsis associated with neutropenia, earliest evidence of disseminated intravascular coagulation, and metabolic acidosis (pH <7.2)

Follow up testing

- Repeat blood cultures within 24 h- 48 hr of presumed effective therapy:
- Document clearance, (persistent positive cultures could mean failure of therapy or evidence of intravascular site infection),
- Adjust antibiotic coverage and duration
- Monitor trends in WBC counts, CRP levels, and I:T ratios to assess the response to therapy.

- Repeat CSF samples:
- Neonatal HSV CNS infection, HSV PCR of CSF should be repeated at end of therapy,
- At 24 - 48 h of treatment for GBS meningitis and E.coli meningitis
- Persistent fever, increasing elevations of peripheral WBC counts and CRP levels, abnormal I:T

Thank you for your time and attention