# Neonatal Sepsis Evaluation

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- 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 bloodstream
- A consensus definition for neonatal sepsis is lacking .

# PIDEMIOELOGY

- The overall incidence of neonatal sepsis ranges from one to five cases per 1000 live
- accounting for approximately 15 percent of all neonatal deaths
- Rates of neonatal sepsis increase with decreasing gestational age
- Black race has been identified as an independent risk factor for early- and late-onset GBS sepsis

# Early-onset sepsis

- onset of symptoms before 7 days of age, although some experts limit the definition to infections occurring within the first 72 hours of life

# Late-onset sepsis

- onset of symptoms at ≥7 days of age
- Similar to early-onset sepsis, there is variability in the definition, ranging from an onset at >72 hours of life to ≥7 days of age

# PATHOGENESIS — Early-onset infection

- vertical transmission by ascending contaminated amniotic fluid or during vaginal delivery from bacteria in the mother's lower genital tract
- Maternal chorioamnionitis
- Maternal group B streptococcal (GBS) colonization is another important risk factor

# PATHOGENESIS -Late-onset infections

- Vertical transmission, resulting in initial neonatal colonization that evolves into later infection
- Horizontal transmission from contact with care providers or environmental sources Disruption of the intact skin or mucosa

# Metabolic factors,

- hypoxia
- Acidosis
- hypothermia
- inherited metabolic disorders (eg, galactosemia)
- These factors are thought to disrupt the neonate's host defenses (ie, immunologic response

# high disease inBlack race

- prematurity
- adequacy of prenatal care
- socioeconomic status

# ETIOLOGIC AGENTS

| Bacterial species | Bacterial species | Frequency of isolation | |
|---|---|---|---|
| | | Early-onset | Late-onset |
| Group B Streptococcus | Group B *Streptococcus* | +++ | +++ |
| Escherichia coli | *Escherichia coli* | +++ | ++ |
| Klebsiella spp. | *Klebsiella* spp. | + | + |
| Enterobacter spp. | *Enterobacter* spp. | + | + |
| Listeria monocytogenes | *Listeria monocytogenes* | + | + |
| Other enteric gram-negatives | Other enteric gram-negatives | + | + |
| Non-enteric gram-negatives* | Non-enteric gram-negatives* | + | + |
| Viridans streptococci | Viridans streptococci | + | + |
| Staphylococcus aureus | *Staphylococcus aureus* | + | +++ |
| Citrobacter spp. | *Citrobacter* spp. | 0 | + |
| Salmonella spp. | *Salmonella* spp. | 0 | + |
| Coagulase-negative staphylococci | Coagulase-negative staphylococci | 0 | + |
| Enterococcus spp. | *Enterococcus* spp. | 0 | + |

# Common nonbacterial agents associated with neonatal sepsis

- Herpes simplex virus
- Enterovirus
- parechovirus
- Candida

# MATERNAL RISK FACTORS

- Chorioamnionitis
- Intrapartum maternal temperature ≥38ºC (100.4ºF).
- Delivery at <37 weeks gestation.
- Maternal GBS colonization and other findings that increase the risk of GBS infection in the neonate, including any of the following:
- Positive GBS vaginal-rectal screening culture in late gestation during current pregnancy.
- Previous infant with GBS disease.
- Documented GBS bacteriuria during the current pregnancy.
- Intrapartum nucleic acid amplification test positive for GBS.
- Membrane rupture ≥18 hours – The risk of proven sepsis increases 10-fold to 1 percent when membranes are ruptured beyond 18 hours .

# CLINICAL MANIFESTATIONS

- subtle symptoms include temperature instability (primarily fever), irritability, lethargy, respiratory symptoms (eg, tachypnea, grunting, hypoxia), poor feeding, tachycardia, poor perfusion, and hypotension

# نکات مهم در علائم سپسیس

- Fetal and delivery room distress
- Intrapartum fetal tachycardia
- Meconium-stained amniotic fluid, which is associated with a twofold increased risk of sepsis
- Apgar score ≤6, which is associated with a 36-fold increased risk of sepsis
- Respiratory and cardiocirculatory symptoms . Approximately 85 percent of newborns with early-onset sepsis present with respiratory distress

# نکات مهم در علائم سپسیس

- Temperature instability – The temperature of an infected infant can be elevated, depressed, or normal. Term infants with sepsis are more likely to be febrile than preterm infants who are more likely to be hypothermic
- Tachycardia is a common finding in neonatal sepsis but is nonspecific.
- Bradycardia may also occur.
- Poor perfusion and hypotension are more sensitive indicators of sepsis, but these tend to be late findings

- Neurologic manifestations of sepsis in the neonate include lethargy, poor tone, poor feeding, irritability, and seizures
- Seizures are an uncommon presentation of neonatal sepsis but are associated with a high likelihood of infection].

# full =Symptomatic neonates diagnostic evaluation

- Blood culture.
- Lumbar puncture (LP) (if the infant is clinically stable enough to tolerate the procedure).
- Complete blood count (CBC) with differential and platelet count.
- Chest radiograph (if respiratory symptoms are present).
- Cultures from tracheal aspirates if intubated.
- C-reactive protein (CRP)
- procalcitonin (PCT) levels

# Blood culture

- sensitivity of a single blood culture to detect neonatal bacteremia is approximately 90 percent
- Volume of blood . A minimum blood volume of 1 mL is desirable for optimal detection of bacteremia when a single blood culture bottle is used . At the author's institution, the suggested optimal volume is 2 mL for infants weighing ≤3 kg and 3 mL for those who weigh >3 to 5 kg.
- Anaerobic cultures are generally not necessary

- An approach outlined by a 2012 American Academy of Pediatrics (AAP) clinical report recommends that LP be performed in an infant with any of the following clinical conditions
- A positive blood culture
- Clinical findings that are highly suggestive of sepsis
- Laboratory data strongly suggestive of sepsis
- Worsening clinical status while on antibiotic therapy

- Blood culture may be negative in as many as 38 percent of infants with meningitis
- A urine culture need not be routinely performed in the evaluation of an infant ≤2-3 days of age, because a positive urine culture in this setting is a reflection of high-grade bacteremia rather than an isolated urinary tract infection

# Early-onset sepsis CBC

.1 low white blood cell (WBC) count (<5000/microL),

.2 absolute neutropenia (ANC <1000 neutrophils/microL),

.3 relative neutropenia (ANC <5000 neutrophils/microL)

.4 elevated. I/T ratio

.5 CBCs obtained 6 to 12 hours after delivery are more predictive of sepsis

# I/T ratio

1. An elevated I/T ratio (≥0.2) has the best sensitivity of the neutrophil indices for predicting neonatal sepsis
2. A normal I/T ratio can help rule out sepsis;
3. elevated value is not highly predictive of sepsis and may be observed in 25 to 50 percent of uninfected infants

# Absolute neutrophil count

.1 neutropenia has greater specificity

- pre-eclampsia
- counts decrease with decreasing gestational age
- type of delivery (counts are lower in infants born by cesarean delivery)
- site of sampling (counts are lower in arterial than in venous samples)
- altitude (counts are higher at elevated altitudes)
- timing after delivery (counts increase during the first six hours of life).

# C-reactive protein

1. cause elevated CRP,
- maternal fever,
- fetal distress
- stressful delivery
- perinatal asphyxia
- meconium aspiration
- intraventricular hemorrhage

# C-reactive protein

- A single measurement of CRP soon after birth is not a useful marker in the diagnosis of neonatal sepsis
- sequential assessment of CRP values may help support a diagnosis of sepsis
- If the CRP level remains persistently normal (<1 mg/dL [10 mg/L]), neonatal bacterial sepsis is unlikely

# C-reactive protein

- Infants with elevated CRP levels that decrease to <1 mg/dL (10 mg/L) 24 to 48 hours after initiation of antibiotic therapy typically are not infected and generally do not require further antibiotic treatment if cultures are negative
- routine use of serial CRP measurements can be associated with longer length of hospital stay
- An elevated CRP level alone does not justify continuation of empiric antibiotics for more than 48 hours in well-appearing infants with negative culture results

# Procalcitonin (PCT)

- the peptide precursor of calcitonin. It is released by parenchymal cells in response to bacterial toxins, elevated serum levels in patients with bacterial infections
- the sensitivity of PCT for detection of neonatal sepsis ranged from 72 to 79 percent and the specificity ranged from 72 to 90 percent
- does not  reliable as the sole or main diagnostic indicator for neonatal sepsis.
- PCT seems to have some utility in guiding the duration of antibiotic therapy in neonates with suspected sepsis

# Cytokines, chemokines, and other biomarkers

1. proinflammatory cytokines
   - interleukin-6 (IL-6)
   - tumor necrosis factor-alpha (TNF-alpha)
2. anti-inflammatory cytokines
   - IL-4
   - IL-10) are increased in infected infants
   - Elevations of serum amyloid A
   - the cell surface antigen CD64 also have high sensitivity for identifying infants with sepsis
   - biomarkers are not routinely measured because of the cost of testing and because no single biomarker or panel is sufficiently sensitive to reliably detect neonatal sepsis

# DIAGNOSIS

- The diagnosis of neonatal sepsis can be established only by a positive blood culture. Other than blood culture, no specific finding or test reliably identifies infected infants

# Probable sepsis

.1 a pathogen may not be isolated in culture

.2 the neonate has a clinical course that is concerning for sepsis

- ongoing temperature instability
- ongoing respiratory
- cardiocirculatory
- neurologic symptoms not explained by other conditions
- ongoing laboratory abnormalities suggestive of sepsis [ie, cerebrospinal fluid (CSF) pleocytosis, elevated ratio of immature to total neutrophil counts, or elevated C-reactive protein]).

# Infection unlikely

- Infants with mild and/or transient symptoms (ie, fever alone or other symptoms that quickly resolve)
- who remain well-appearing
- normal laboratory values
- negative cultures at 48 hours

---- unlikely to have sepsis. Empiric antibiotic therapy should be discontinued after 48 hours in these neonates [6,67].

# SUPPORTIVE CARE

- Maintaining adequate oxygenation and perfusion
- Prevention of hypoglycemia
- metabolic acidosis
- Maintenance of normal fluid and electrolyte status
- Severely ill patients may require ventilatory, volume, and/or vasopressor support

# Radiology

- CXR
  - Obtain in infants with respiratory symptoms
  - Difficult to distinguish GBS or *Listeria* pneumonia from uncomplicated RDS
- Renal ultrasound and/or VCUG in infants with accompanying UTI

# Treatment

Prevention – vaccines, GBS prophylaxis, HAND-WASHING

Supportive – respiratory, metabolic, thermal, nutrition, monitoring drug levels/toxicity

Specific – antimicrobials, immune globulins

Non-specific – IVIG, NO inhibitors & inflammatory mediators

# Treatment

- hrs8-6 mg/kg/dose IV every 50-25Ampicillin
- hrs12-8 mg/kg/dose IV every 2.5Gentamicin
- Therapy tailored to specific organsim if positive culture
- Remember Ampicillin and Gentamicin can both be give IM as well
- Avoid prolonged use of antibiotics in culture negative patients

# Chorioamnionitis

- 1-4% of all births in US
- Diagnosis
- Maternal Temp ≥ 38 ° C and at least one of:
  - Uterine Tenderness
  - Maternal or Fetal Tachycardia
  - Foul/Purulent Amniotic Fluid
  - ROM greater than 12-18 hrs
  - Elevated maternal WBC

TABLE 3. Indications and nonindications for intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal (GBS) disease

| Intrapartum GBS prophylaxis indicated | Intrapartum GBS prophylaxis not indicated |
|---|---|
| • Previous infant with invasive GBS disease | • Colonization with GBS during a previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy) |
| • GBS bacteriuria during any trimester of the current pregnancy* | • GBS bacteriuria during previous pregnancy (unless an indication for GBS prophylaxis is present for current pregnancy) |
| • Positive GBS vaginal-rectal screening culture in late gestation† during current pregnancy* | • Negative vaginal and rectal GBS screening culture in late gestation† during the current pregnancy, regardless of intrapartum risk factors |
| • Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following:<br>– Delivery at <37 weeks' gestation§<br>– Amniotic membrane rupture ≥18 hours<br>– Intrapartum temperature ≥100.4°F (≥38.0°C)¶<br>– Intrapartum NAAT** positive for GBS | • Cesarean delivery performed before onset of labor on a woman with intact amniotic membranes, regardless of GBS colonization status or gestational age |

**Abbreviation:** NAAT = Nucleic acid amplification tests

* Intrapartum antibiotic prophylaxis is not indicated in this circumstance if a cesarean delivery is performed before onset of labor on a woman with intact amniotic membranes.

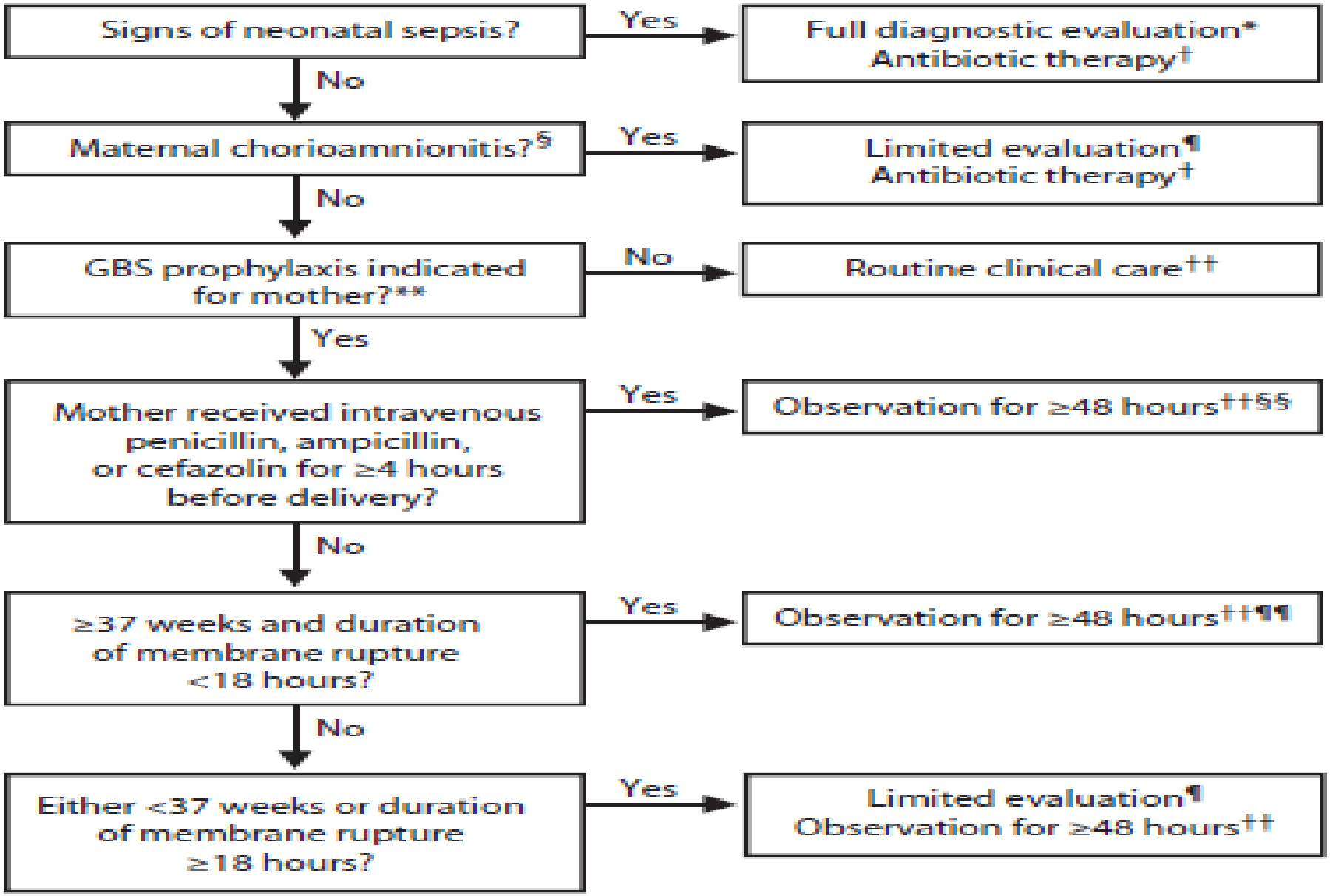
† Optimal timing for prenatal GBS screening is at 35–37 weeks' gestation.

§ Recommendations for the use of intrapartum antibiotics for prevention of early-onset GBS disease in the setting of threatened preterm delivery are presented in Figures 5 and 6.

¶ If amnionitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.

** NAAT testing for GBS is optional and might not be available in all settings. If intrapartum NAAT is negative for GBS but any other intrapartum risk factor (delivery at <37 weeks' gestation, amniotic membrane rupture at ≥18 hours, or temperature ≥100.4°F [≥38.0°C]) is present, then intrapartum antibiotic prophylaxis is indicated.

**FIGURE 9. Algorithm for secondary prevention of early-onset group B streptococcal (GBS) disease among newborns**



# Prognosis

- Fatality rate 2-4 times higher in LBW than in term neonates
- Overall mortality rate 15-40%
- Survival less likely if also granulocytopenic (I:T > 0.80 correlates with death and may justify granulocyte transfusion).


QUESTIONS


THANK YOU!
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