Neonatal infection

Dr.Eremciuc Rodica

1

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.

2

Sepsis is classified according to the infant's age at the onset of symptoms.

- **Early-onset sepsis** is defined as the onset of symptoms before seven days of age, although some experts limit the definition to infections occurring within the first 72 hours of life.
- **Late-onset sepsis** is generally defined as the 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.

3

PATHOGENESIS

The pathogenesis differs based on the timing of onset:
- **Early-onset infection** – Early-onset infection is usually due to vertical transmission by ascending contaminated amniotic fluid or during vaginal delivery from bacteria in the mother's lower genital tract. Maternal chorioamnionitis (or intraamniotic infection) is a well-recognized risk factor for early-onset neonatal sepsis. Maternal group B streptococcal (GBS) colonization is another important risk factor.

Use of forceps during delivery and electrodes placed for intrauterine monitoring have been implicated in the pathogenesis of early-onset sepsis because they penetrate the neonatal defensive epithelial barriers.

4

MATERNAL RISK FACTORS

Maternal factors that are associated with an increased risk of early-onset sepsis in the neonate, particularly group B *Streptococcus* (GBS) infection, include:
- chorioamnionitis (intraamniotic infection),
- intrapartum maternal fever,
- maternal GBS colonization,
- preterm delivery, and
- prolonged rupture of the membranes

5

Risk factors for neonatal sepsis

Maternal	Neonatal
• Chorioamnionitis	• Gestational age
• Intrapartum fever	• Birth weight
• Membrane rupture >18 hours	• Twin gestation
• GBS colonization	• Fetal tachycardia
• Intrapartum antibiotics	• Low apgar score
• Age and race	• Clinical illness
• Obstetrical interventions	• Lab abnormalities

6

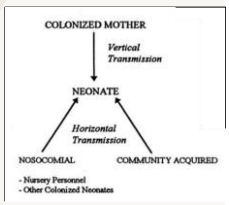
PATHOGENESIS

Late-onset infection – Late-onset infections can be acquired by the following mechanisms:
•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, which can be due to invasive procedures (eg, intravascular catheter), increases the risk of late-onset infection. Late-onset sepsis is uncommonly associated with maternal obstetrical complications.

Metabolic factors, including hypoxia, acidosis, hypothermia, and inherited metabolic disorders (eg, galactosemia), are likely to contribute to risk for and severity of neonatal sepsis (including both early- and late-onset). These factors are thought to disrupt the neonate's host defenses (ie, immunologic response).

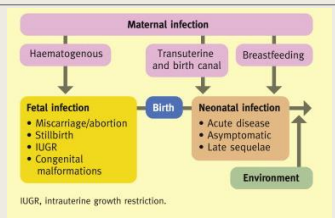
7

Routes of infection transmission

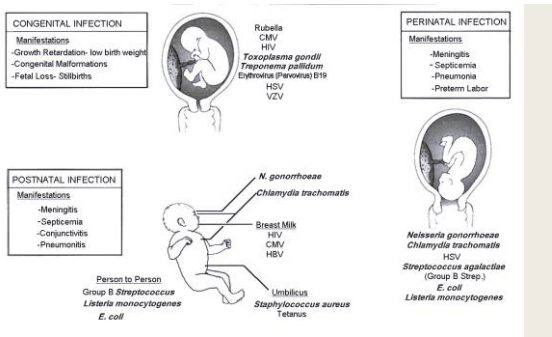


8

Routes of infection transmission



9



10

ETIOLOGIC AGENTS

Group B *Streptococcus* (GBS) and *Escherichia coli* are the most common causes of both early- and late-onset sepsis, accounting for approximately two-thirds of early-onset infections.

Other bacterial agents associated with neonatal sepsis include:
- *Listeria monocytogenes*, although a well-recognized cause of early-onset sepsis, only accounts for rare sporadic cases of neonatal sepsis and is more commonly seen during an outbreak of listeriosis.
- *Staphylococcus aureus*, including community-acquired methicillin-resistant *S. aureus*, is a potential pathogen in neonatal sepsis. Bacteremic staphylococcal infections in term infants usually occur in association with skin, bone, or joint sites of involvement.
- *Enterococcus*, a commonly encountered pathogen among preterm infants, is a rare cause of sepsis in otherwise healthy term newborn infants.
- Other gram-negative bacteria (including *Klebsiella*, *Enterobacter*, and *Citrobacter* spp) and *Pseudomonas aeruginosa* are associated with late-onset infection, especially in infants admitted to neonatal intensive care units.
- Coagulase-negative staphylococci often are a cause of hospital-associated infection in ill infants (primarily in premature infants and/or infants who have indwelling intravascular catheters). Coagulase-negative staphylococci may be considered a contaminant in otherwise healthy term infants who have not undergone invasive procedures.

11

Bacterial pathogens in neonatal sepsis and focal neonatal infections

	Common pathogens*	Some less common pathogens*
Early onset¶		
Term and late preterm infants (GA ≥34 weeks)	▪ GBS ▪ *E. coli*	▪ *Enterobacter*, *Enterococcus*, *Klebsiella*, *Listeria*, nontypeable *H. influenzae*, other enteric gram-negative bacilli, *S. aureus*, viridans streptococci
Preterm infants (GA <34 weeks)	▪ *E. coli* ▪ GBS	▪ CoNS, *Enterobacter*, *Klebsiella*, *Listeria*, other enteric and nonenteric gram-negative bacilli, *S. aureus*, viridans streptococci
Late onset¶		
Term and late preterm infants (GA ≥34 weeks)	▪ *E. coli* ▪ GBS ▪ Additional pathogens seen in the NICU setting – *S. aureus*, CoNS	▪ *Enterobacter*, *Klebsiella*, *Listeria*, *N. meningitidis*, other enteric and nonenteric gram-negative bacilli, *Salmonella*, *S. pneumoniae*, viridans streptococci ▪ Additional pathogens seen in the NICU setting – *Citrobacter*, *Enterococcus*, *Pseudomonas*, *Serratia*
Preterm infants (GA <34 weeks)	▪ CoNS ▪ *S. aureus* ▪ *E. coli* ▪ *Klebsiella* ▪ GBS	▪ *Citrobacter*, *Enterobacter*, *Enterococcus*, *Listeria*, other enteric and nonenteric gram-negative bacilli, *Pseudomonas*, *Salmonella*, *Serratia*, viridans streptococci

12

ETIOLOGIC AGENTS

Common nonbacterial agents associated with neonatal sepsis include:

- Herpes simplex virus
Neonates can acquire HSV infection by intrauterine, perinatal, or postnatal transmission of the virus; most cases are acquired perinatally. Neonatal HSV infection causes serious morbidity and mortality and leaves many survivors with permanent sequelae.

- Enterovirus and parechovirus
Neonates are uniquely susceptible to enterovirus disease, which can be self-limited (eg, viral meningitis, exanthema) or fulminant and life-threatening. The group B coxsackievirus serotypes 2 to 5 and echovirus 11 have most frequently been associated with overwhelming systemic neonatal infections.
Newborns presenting with serious enterovirus disease typically acquire the infection from a symptomatic mother in the perinatal period; up to 60 percent of mothers of infected infants report a febrile illness during the last week of pregnancy. However, infection may also be acquired via nosocomial transmission and spread through nurseries by caregivers engaged in mouth care, gavage feeding, and other activities requiring direct contact.
More serious infections have been observed in neonates with parechovirus serotype 3 infection, including meningoencephalitis and fulminant hepatitis. A distinctive form of neonatal encephalitis with white matter abnormalities that mimic hypoxic-ischemic encephalopathy has been described in association with parechovirus serotype 3 infection

- *Candida*

13

CLINICAL MANIFESTATIONS

Clinical manifestations range from subtle symptoms to profound septic shock. Signs and symptoms of sepsis are nonspecific and include temperature instability (primarily fever), irritability, lethargy, respiratory symptoms (eg, tachypnea, grunting, hypoxia), poor feeding, tachycardia, poor perfusion, and hypotension.

Because the signs and symptoms of sepsis can be subtle and nonspecific, it is important to identify neonates with risk factors for sepsis and to have a high index of suspicion for sepsis when an infant deviates from his or her usual pattern of activity or feeding

14

CLINICAL MANIFESTATIONS

Signs and symptoms of neonatal sepsis include:

- **Fetal and delivery room distress** – The following signs of fetal and neonatal distress during labor and delivery may be early indicators of neonatal sepsis:
•Intrapartum fetal tachycardia, which may be due to intraamniotic infection
•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

- **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. Temperature elevation in full-term infants is concerning and, if persistent, is highly indicative of infection.

15

CLINICAL MANIFESTATIONS

- **Cardiorespiratory symptoms** – Respiratory and cardiocirculatory symptoms are common in infected neonates. Approximately 85 percent of newborns with early-onset sepsis present with respiratory distress (eg, tachypnea, grunting, flaring, use of accessory muscles).

Apnea is less common, occurring in 38 percent of cases, and is more likely in preterm than term infants. Apnea is a classic presenting symptom in late-onset group B streptococcal (GBS) sepsis. Early-onset disease can be associated with persistent pulmonary hypertension of the newborn.

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. In a prospective national surveillance study, 40 percent of neonates with sepsis required volume expansion and 29 percent required vasopressor support

16

CLINICAL MANIFESTATIONS

- **Neurologic symptoms** – 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. In a prospective study in a single neonatal unit, 38 percent of neonates with seizures had sepsis as the etiology. Seizures are a presenting feature in 20 to 50 percent of infants with neonatal meningitis.

- **Other findings** – Other findings associated with neonatal sepsis are:
  - Jaundice
  - Hepatomegaly
  - Poor feeding
  - Vomiting
  - Abdominal distension
  - Diarrhea

17

Clinical features of severe infections [WHO Young Infant study 2003]

1. Feeding ability reduced
2. No spontaneous movement
3. Temperature >38^0 C
4. Prolonged capillary refill time
5. Lower chest wall indrawing
6. Resp. rate > 60/minute
7. Grunting
8. Cyanosis
9. H/o of convulsions

18

EVALUATION AND INITIAL MANAGEMENT

Because the signs and symptoms of sepsis are subtle and nonspecific, laboratory testing is performed in any infant with identifiable risk factors and/or signs and symptoms concerning for sepsis.

Early-onset sepsis — The evaluation of a neonate with suspected early-onset sepsis 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 diagnostic evaluation for sepsis is directed by the infant's symptoms and maternal risk factors.

19

EVALUATION AND INITIAL MANAGEMENT

Symptomatic neonates

Infants with signs and symptoms of sepsis should undergo a **full diagnostic evaluation** and should receive empiric antibiotic treatment.

A **full diagnostic evaluation** includes:

- Blood culture
- Lumbar puncture (if the infant is clinically stable enough to tolerate the procedure and it will not delay initiation of antibiotic therapy)
- 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) and/or procalcitonin (PCT) levels – These tests are not routinely required but may be helpful in determining length of therapy if followed serially

20

EVALUATION AND INITIAL MANAGEMENT

Late-onset sepsis

Infants presenting with signs and symptoms at ≥7 days of age should undergo prompt evaluation and empiric antibiotic treatment.

A **full diagnostic evaluation** should be performed. In addition to the tests described above for early-onset sepsis, the following should also be obtained:

- Urine culture
- Cultures from any other potential foci of infection (eg, tracheal aspirates if intubated, purulent eye drainage, or pustules)

Infants with late-onset sepsis generally present to the outpatient or emergency department setting unless comorbid conditions have prolonged the birth hospitalization.

21

LABORATORY TESTS

The goals of the diagnostic evaluation are to identify and treat all infants with bacterial sepsis and minimize the treatment of patients who are not infected. Laboratory assessment includes cultures of body fluids that confirm the presence or absence of a bacterial pathogen and other studies that are used to evaluate the likelihood of infection.

- Blood culture
- Lumbar puncture
- Urine culture
- Other cultures
- Complete blood count
- Other inflammatory markers

22

Blood culture

A definitive diagnosis of neonatal sepsis is established by a positive blood culture.

Blood cultures can be obtained by venipuncture or arterial puncture or by sampling from a newly inserted umbilical artery or vascular access catheter. Positive culture results of blood drawn from indwelling umbilical or central venous catheters can be difficult to interpret since they can indicate contamination or catheter colonization rather than a true systemic infection.

It is recommended to obtain at least one culture prior to initiating empiric antibiotic therapy in neonates with a high clinical suspicion for sepsis.

23

Lumbar puncture

The clinical presentation of neonatal meningitis is indistinguishable from that of neonatal sepsis without meningitis. Specific clinical signs of meningitis (eg, bulging fontanelle, nuchal rigidity) are often lacking in neonates. For this reason, we suggest performing a lumbar puncture as part of the diagnostic evaluation in symptomatic neonates. Lumbar puncture should ideally be performed before the initiation of antibiotics for infants in whom the clinical suspicion for sepsis is high, particularly those with critical illness.

Lumbar puncture is indicated in neonates with:
- Clinical findings concerning for sepsis
- Positive blood culture
- Worsening clinical status while on antibiotic therapy

24

Urine culture

Urine culture obtained by catheter or bladder tap should be included in the sepsis evaluation for infants one week of age or older.

A urine culture need not be routinely performed in the evaluation of an infant ≤6 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

25

Other cultures

In patients with late-onset infection, cultures should be obtained from any other potential foci of infection (eg, purulent eye drainage or pustules).

Tracheal aspirates can be of value if obtained immediately after intubation. However, they may reflect lower respiratory tract colonization rather than indicating a causative pathogen in an infant who has been intubated for several days.

Gram stain or culture of other sites (eg, gastric aspirate, body surface sites [eg, axilla, groin, and external ear canal]) add little to the evaluation and should not be performed

26

Complete blood count

A complete blood count (CBC) is used to evaluate the likelihood of sepsis in a neonate with risk factors or signs of infection. Abnormal findings on a CBC cannot be used to establish the diagnosis of sepsis.

The CBC does not perform well in predicting risk of infection in neonates and should not be used as the sole determinant of whether to treat empirically with antibiotics. However, when used in conjunction with other assessments, it may be useful in the evaluation of infants with suspected early- or late-onset sepsis. The CBC is more useful in identifying neonates who are unlikely to have sepsis than in identifying infants with sepsis.

CBCs obtained 6 to 12 hours after delivery are more predictive of sepsis than those obtained immediately after birth because the WBC and ANC normally increase during the first six hours of life.

27

I/T ratio

An elevated I/T ratio (≥0.2) has the best sensitivity of the neutrophil indices for predicting neonatal sepsis and can be helpful as an initial screen when used in combination with risk factors, clinical assessment, and/or other tests. A normal I/T ratio can help rule out sepsis; however, an elevated value is not highly predictive of sepsis and may be observed in 25 to 50 percent of uninfected infants

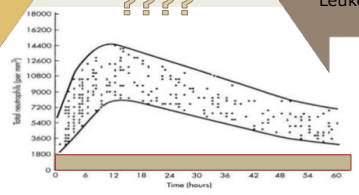
28

Manroe graph

Leucocytosis

????

Leukopenia



The total neutrophil count reference range in the first 60 hours of life for a group of term neonates. Points represent single values; numbers represent the number of values at the same point; *(From **Manroe** BL: The neonatal blood count in health and disease I: Reference values for neutrophilic cells. J Pediatr 95:91, 1979.)*

29

ANC

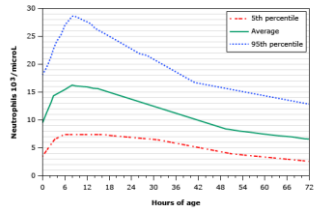
Although both elevated and low neutrophil counts can be associated with neonatal sepsis, neutropenia has greater specificity since few conditions other than sepsis and preeclampsia depress the neutrophil count in neonates.

Neutrophil counts vary with gestational age (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), and timing after delivery (counts increase during the first six hours of life).

The lower limit of a normal neutrophil count for infants >36 weeks of gestation is 3500/microL at birth and 7500/microL six to eight hours after delivery.
For infants born at 28 through 36 weeks of gestation, the lower limits of normal neutrophil counts at birth and at six to eight hours after birth are 1000/microL and 1500/microL, respectively.

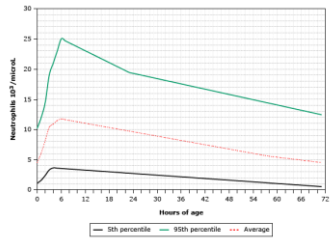
30

Range of neutrophil count for newborn infants born with a gestational age >36 weeks during the first 72 hours of life



31

Normal range of neutrophil count for newborn infants with a gestational age between 28 and 36 weeks during the first 72 hours of life



32

Other inflammatory markers

33

C-reactive protein

CRP is increased in inflammatory conditions, including sepsis.

A variety of noninfectious inflammatory conditions can also cause elevated CRP, including:

- ❑ maternal fever,
- ❑ fetal distress,
- ❑ stressful delivery,
- ❑ perinatal asphyxia,
- ❑ meconium aspiration, and
- ❑ intraventricular hemorrhage

34

C-reactive protein

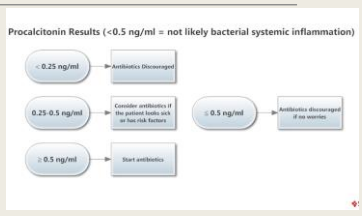
- A single measurement of CRP is **not** a useful aid in the diagnosis of neonatal sepsis.
- However, sequential assessment of CRP values may help support a diagnosis of sepsis.
- If the CRP level remains persistently normal (<1 mg/dL [10 mg/L]), neonatal bacterial sepsis is unlikely.
- CRP levels can be helpful in guiding the duration of antibiotic therapy in suspected neonatal bacterial infection. 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.
- An elevated CRP level alone does not justify continuation of empiric antibiotics for more than 36 to 48 hours in well-appearing infants with negative culture results

35

Procalcitonin

It is released by parenchymal cells in response to bacterial toxins, leading to elevated serum levels in patients with bacterial infections.

PCT may have utility in guiding the duration of antibiotic therapy in neonates with suspected sepsis.



36

Cytokines, chemokines, and other biomarkers

Both proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-alpha, and antiinflammatory cytokines (interleukin-4 and interleukin-10) are increased in infected infants compared with those without infections.

Elevations of serum amyloid A and the cell surface antigen CD64 also have high sensitivity for identifying infants with sepsis.

However, these biomarkers are generally not used in clinical practice.

37

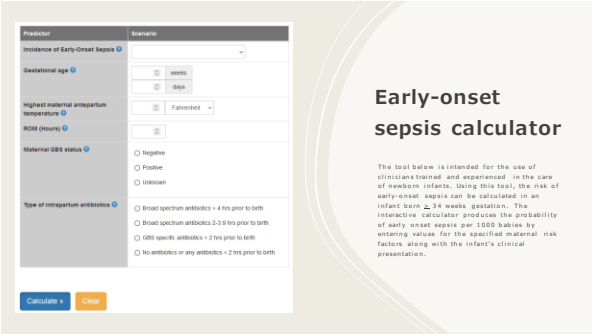
Early-onset sepsis calculator

38

Early-onset sepsis calculator

- Multivariate predictive models for risk of early-onset sepsis have been developed and validated in clinical use, including the early-onset sepsis calculator.
- The early-onset sepsis calculator is a web-based tool that can be used to estimate the risk of early-onset sepsis 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 requires the user to input the local incidence of early-onset sepsis. If the local incidence of early-onset sepsis is unknown, the users should enter "0.5 per 1000."
- The calculator provides guidance on the diagnostic evaluation and empiric antibiotic treatment. The threshold used to trigger evaluation and empiric treatment varies depending on the clinical circumstances.
- The early-onset sepsis calculator is **not** valid for preterm infants (<34 weeks gestation) and does not apply to late-onset sepsis.

39



40

DIAGNOSIS

Culture-proven sepsis	Probable sepsis	Infection unlikely
The isolation of pathogenic bacteria from a blood culture is **the gold standard** to confirm the diagnosis of neonatal sepsis. A positive blood culture is diagnostic of sepsis when a bacterial pathogen is isolated.	In some cases, a pathogen may **not be isolated** in culture, yet the neonate has a clinical course that is concerning for sepsis (eg, ongoing temperature instability; ongoing respiratory, cardiocirculatory, or neurologic symptoms not explained by other conditions; or ongoing laboratory abnormalities suggestive of sepsis	Infants with mild and/or transient symptoms (ie, fever alone or other symptoms that quickly resolve) who remain well-appearing with normal laboratory values and **negative cultures** at 36 to 48 hours are unlikely to have sepsis.

41

Differential diagnosis

42

	Early-Onset Sepsis	Late-Onset Sepsis
Timing	Presents 0 to 6 days of life (some studies narrow to 0–3 days)	Presents 7 to 10 days of life (may occur later in premature infant)
Acquisition	From maternal genital tract	Either maternal genital tract or postnatal environment
Organisms	GBS, *E. coli*, *Listeria*, nontypeable *H. influenzae* (*H flu*), and *Enterococcus*	*Staphylococcus* (*Staph*) coagulase-negative, *Staph aureus*, *Pseudomonas*, GBS, *E Coli*, and *Listeria*
Clinical	Fulminant Multisystem involvement (greater risk of pneumonia)	Usually slowly progressive Focal involvement (greater risk of meningitis)
Mortality	Greater mortality (15%–45%)	Lower mortality (10%–20%)

43

Differential diagnosis of neonatal sepsis

Diagnosis	Distinguishing features	Diagnostic tests
Other systemic neonatal infections		
Viral infections:		
Herpes simplex virus	Mucocutaneous vesicles, CSF pleocytosis, elevated CSF protein, thrombocytopenia, hepatitis	Viral culture; HSV PCR
Enteroviruses	Fulminant systemic disease, myocarditis, hepatitis, encephalitis	Viral culture; EV PCR
Parechovirus	Encephalitis/meningitis, rash on palms and soles	HPeV PCR (available through CDC)
Cytomegalovirus	Thrombocytopenia, periventricular intracranial calcifications, microcephaly, sensorineural hearing loss, chorioretinitis	Viral culture; CMV PCR
Influenza viruses	Respiratory symptoms, rhinorrhea, gastrointestinal symptoms	Viral culture; influenza-specific antigen detection or immunofluorescence assay
Respiratory syncytial virus	Respiratory symptoms, rhinorrhea, cough, apnea, pneumonia	Viral culture; RSV-specific antigen detection or immunofluorescence assay
Spirochetal infections – Syphilis	Skeletal abnormalities (osteochondritis and periostitis), pseudoparalysis, persistent rhinitis, maculopapular rash (particularly on palms and soles or in diaper area)	RPR or VDRL

44

Differential diagnosis of neonatal sepsis

Diagnosis	Distinguishing features	Diagnostic tests
Parasitic infections:		
Congenital malaria	Anemia, splenomegaly, jaundice	Detection of parasitemia on blood smear
Toxoplasmosis	Intracranial calcifications (diffuse), hydrocephalus, chorioretinitis, mononuclear CSF pleocytosis, elevated CSF protein	*Toxoplasma gondii* serology
Fungal infection – Candidiasis	Persistent hyperglycemia, thrombocytopenia, multiorgan failure	Isolation of Candida in blood, urine, or CSF culture
Noninfectious causes of temperature instability in neonates		
Altered environmental temperature	Transient; no other systemic symptoms; resolves with simple nonpharmacologic measures	
Dehydration	Clinical history of poor feeding or fluid losses (eg, vomiting and/or diarrhea)	
Neonatal abstinence syndrome	History of maternal drug use; sweating, sneezing, nasal stuffiness, and yawning	Positive drug screening tests
CNS insult (eg, anoxia or hemorrhage)	History of perinatal asphyxia; focal neurologic findings or seizures	Abnormal neuroimaging studies
Hypothyroidism	Hypotonia, lethargy, hypothermia, large fontanels	Abnormal T4 or TSH level on newborn screen
Congenital adrenal hyperplasia	Ambiguous genitalia (females), adrenal insufficiency and salt-wasting (hyponatremia, hyperkalemia, dehydration)	Abnormal 17α-hydroxyprogesterone level on newborn screen

45

Differential diagnosis of neonatal sepsis

Diagnosis	Distinguishing features	Diagnostic tests
Noninfectious causes of respiratory and cardiocirculatory symptoms in neonates		
Transient tachypnea of the newborn	Onset of symptoms within two hours after delivery; symptoms usually resolve within 24 hours	CXR findings include increased lung volumes, mild cardiomegaly, prominent vascular markings, fluid in the interlobar fissures, and pleural effusions
Respiratory distress syndrome	Most common in preterm infants; rare in term infants; onset of symptoms within first few hours after delivery, progressively worsens over first 48 hours of life	CXR findings include low lung volume and diffuse reticulogranular ground glass appearance with air bronchograms
Meconium aspiration	History of meconium-stained amniotic fluid; respiratory distress occurs immediately after birth	Initial CXR may show streaky, linear densities; as the disease progresses, the lungs may appear hyperinflated with diffuse patchy densities
Pneumothorax	Asymmetric chest rise, decreased breath sounds on affected side; hypotension (in cases of tension pneumothorax)	CXR will usually detect symptomatic pneumothoraces
Congenital anomalies (including tracheal-esophageal fistula, choanal atresia, and diaphragmatic hernia)	Often occur with other congenital anomalies including VACTERL and CHARGE associations; choanal atresia is characterized by noisy labored breathing while feeding	CDH is often diagnosed by routine antenatal ultrasound screening; postnatal CXR shows herniation of abdominal contents into hemithorax; TEF is diagnosed with upper gastrointestinal series and/or bronchoscopy
Neonatal abstinence syndrome	History of maternal drug use; sweating, sneezing, nasal stuffiness, and yawning	Positive drug screening tests
Cardiac arrhythmias (eg, supraventricular tachycardia)	Abrupt onset and termination of rapid heart rate	Abnormal ECG
Congenital heart disease	Infants with ductal-dependent lesions may initially lack symptoms then develop cyanosis and rapid clinical deterioration as the PDA closes in the first few days of life	Abnormal hyperoxia test; abnormal echocardiography

46

Differential diagnosis of neonatal sepsis

Diagnosis	Distinguishing features	Diagnostic tests
Noninfectious causes of neurologic symptoms in neonates		
Hypoglycemia	Common in infants who are large for gestational age and/or infants of diabetic mothers	Abnormal blood glucose level
Hypercalcemia	Increased neuromuscular irritability and seizures; associated with prematurity, maternal diabetes, and perinatal asphyxia	Abnormal serum calcium level
Hypermagnesemia	Generalized hypotonia, respiratory depression and apnea; typically results from maternal treatment with magnesium sulfate	Abnormal serum magnesium level
CNS insult (eg, anoxia or hemorrhage)	History of perinatal asphyxia; focal neurologic findings or seizures	Abnormal neuroimaging studies
Congenital CNS malformations (eg, hydrocephalus)	Abnormal head circumference	Abnormal neuroimaging studies
Neonatal abstinence syndrome	History of maternal drug use; sweating, sneezing, nasal stuffiness, and yawning	Positive drug screening tests
Inborn errors of metabolism	Otherwise unexplained acid-base disorders, hyperammonemia, hypoglycemia, hematologic abnormalities, liver dysfunction, and renal disease	Positive newborn screen for inborn errors of metabolism
Pyridoxine deficiency	Refractory seizures	Abnormal plasma pyridoxal-5-phophate level

47

DIFFERENTIAL DIAGNOSIS

- Appropriate microbiologic testing distinguishes neonatal bacterial sepsis from nonbacterial systemic infections.
- The clinical history, disease course, chest radiograph, electrocardiogram (ECG), hyperoxia testing, drug screening, neuroimaging, blood glucose, serum electrolytes, and newborn screening may assist in distinguishing noninfectious disorders from neonatal sepsis.
- It is often difficult to differentiate neonatal sepsis from other conditions. However, given the morbidity and mortality of neonatal sepsis, empiric antibiotic therapy should be provided (after cultures are obtained) to infants with suspected sepsis pending definitive culture-based diagnosis.

48

Treatment

49

SUPPORTIVE CARE

Symptomatic infants should be treated in a care setting with full cardiopulmonary monitoring and support because the clinical course of these infants can deteriorate rapidly. Although there are no data demonstrating the importance of supportive care measures in neonates with sepsis, it is generally accepted that the following supportive measures are critical components of management:

- Maintaining adequate oxygenation and perfusion
- Prevention of hypoglycemia and metabolic acidosis
- Maintenance of normal fluid and electrolyte status

Severely ill patients may require ventilatory, volume, and/or vasopressor support to maintain adequate oxygenation and perfusion.

50

ANTIBIOTIC THERAPY

The decision to start antibiotic therapy is based on assessment of risk factors, clinical evaluation, and laboratory tests.

51

Empiric antibiotic therapy

Indications for empiric antibiotic therapy (after obtaining cultures) include:

- Ill appearance
- Concerning symptoms, including temperature instability or respiratory, cardiocirculatory, or neurologic symptoms
- Cerebrospinal fluid pleocytosis (white blood cell [WBC] count of >20 to 30 cells/microL)
- Confirmed or suspected maternal chorioamnionitis (intraamniotic infection)
- High estimated sepsis risk based on a validated risk calculator

52

Empiric antibiotic therapy

The empiric antibiotic regimen should include agents active against GBS and other organisms that most commonly cause neonatal sepsis (eg, *E. coli* and other gram-negative pathogens) .

The combination of ampicillin and gentamicin or ampicillin and an expanded-spectrum cephalosporin (eg, cefotaxim, ceftazidime, or cefepime) are appropriate regimens that provide empiric coverage for these organisms until culture results are available.

Ampicillin and gentamicin is generally the preferred regimen; however, local antibiotic resistance patterns must be considered.

53

Suggested antimicrobial regimens in the management of neonatal sepsis in term and late preterm infants

	Antibiotic regimen
Empiric therapy	
Early onset (<7 days)	Ampicillin **and** gentamicin
Late onset (≥7 days) – Admitted from the community	Preferred regimen – Ampicillin **and** gentamicin Alternative – Ampicillin **and** an expanded-spectrum cephalosporin (eg, ceftazidime, cefepime, or ceftaxime [where available])
Late onset (≥7 days) – Hospitalized since birth	Gentamicin **and** vancomycin
Special circumstances:	
Suspected meningitis – Early onset	Ampicillin **and** gentamicin[¶]
Suspected meningitis – Late onset, admitted from the community	Ampicillin, gentamicin, **and** an expanded-spectrum cephalosporin (eg, ceftazidime, cefepime, or ceftaxime [where available])[¶]
Suspected meningitis – Late onset, hospitalized since birth	Gentamicin, vancomycin, **and** an expanded-spectrum cephalosporin (eg, ceftazidime, cefepime, or ceftaxime [where available])[¶]
Suspected pneumonia	Ampicillin **and** gentamicin Alternatives: • Ampicillin **and** expanded-spectrum cephalosporin, **or** • Vancomycin **and** expanded-spectrum cephalosporin, **or** • Vancomycin **and** gentamicin
Suspected infection of soft tissues, skin, joints, or bones (*S. aureus* is a likely pathogen)	Vancomycin **and** gentamicin, **or** Vancomycin, nafcillin, **and** gentamicin, **or** Vancomycin **and** an expanded-spectrum cephalosporin (eg, ceftazidime, cefepime, or ceftaxime [where available])
Suspected intravascular catheter-related infection	Vancomycin **and** gentamicin
Suspected infection due to organisms found in the gastrointestinal tract (eg, anaerobic bacteria)	Ampicillin, gentamicin, **and** clindamycin Alternatives: • Ampicillin, gentamicin, **and** metronidazole **or** • Piperacillin-tazobactam **and** gentamicin

54

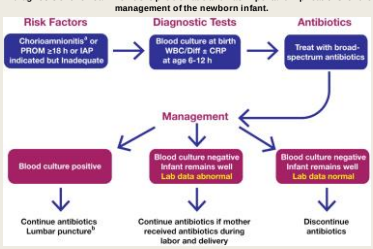
Pathogen-specific therapy

Pathogen-specific therapy	
Group B Streptococcus	Penicillin G
E. coli – Ampicillin-sensitive	Ampicillin
E. coli – Ampicillin-resistant	Expanded-spectrum cephalosporin (eg, ceftazidime, cefepime, or ceftriaxime [where available]) Alternative: • Meropenem
Multidrug-resistant gram-negative bacilli (including ESBL-producing organisms)	Meropenem
L. monocytogenes	Ampicillin **and** gentamicin
MSSA	Nafcillin **or** cefazolin
MRSA	Vancomycin
Coagulase-negative staphylococci	Vancomycin

S. aureus: *Staphylococcus aureus*; *E. coli*: *Escherichia coli*; ESBL: extended-spectrum beta-lactamase; *L. monocytogenes*: *Listeria monocytogenes*; MSSA: methicillin-susceptible *S. aureus*; MRSA: methicillin-resistant *S. aureus*.

55

Evaluation of asymptomatic infants <37 weeks' gestation with risk factors for sepsis. aThe diagnosis of chorioamnionitis is problematic and has important implications for the management of the newborn infant.

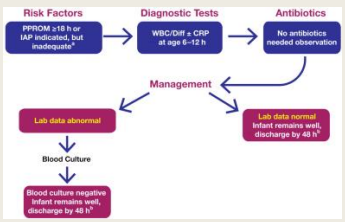


Richard A. Polin, and the COMMITTEE ON FETUS AND NEWBORN Pediatrics 2012;129:1006;1015

PEDIATRICS

56

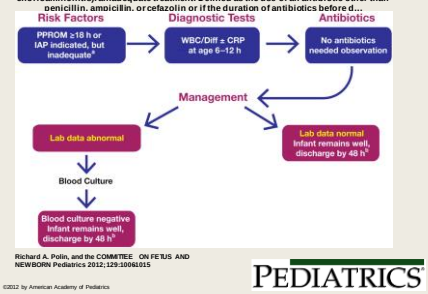
Evaluation of asymptomatic infants ≥37 weeks' gestation with risk factors for sepsis (no chorioamnionitis). aInadequate treatment: Defined as the use of an antibiotic other than penicillin, ampicillin, or cefazolin or if the duration of antibiotics before d...



Richard A. Polin, and the COMMITTEE ON FETUS AND NEWBORN Pediatrics 2012;129:1006;1015

PEDIATRICS

57



58

ADJUNCTIVE THERAPIES

The following adjunctive immunotherapeutic interventions have been studied in neonatal sepsis but should **not** be routinely administered, because they have not been shown to conclusively improve outcomes:

- Intravenous immune globulin (IVIG) infusions
- Granulocyte transfusions
- Granulocyte and granulocyte-macrophage colony-stimulating factor (G-CSF and GM-CSF)
- Pentoxifylline

59

60

Prevention

The primary intervention to prevent neonatal sepsis is the use of intrapartum antibiotic prophylaxis (IAP) in mothers with group B streptococcal (GBS) colonization and other risk factors.

Although IAP has resulted in a decrease in the incidence of early-onset GBS invasive neonatal infection, it has not had a similar impact on the rate of late-onset GBS disease.

Comprehensive prevention of neonatal sepsis will require a multi-interventional program including effective maternal vaccination, reduction in preterm delivery, and limited exposure of term infants to potential pathogens.

Probiotics and lactoferrin have been investigated as potential preventative interventions in preterm neonates; however, neither approach has been conclusively proven to reduce the risk of sepsis and these interventions are not routinely used in clinical practice.

61

OUTCOME

Overall mortality in term and late preterm infants with neonatal sepsis is approximately **2 to 3 %.**

Mortality estimates vary depending on:

- **the gestational age** of the infant (lower gestational age is associated with higher mortality),
- **pathogen** (*E. coli* is associated with higher mortality than group B *Streptococcus* [GBS]), and
- **sepsis definition** (lower mortality rates tend to be reported if infants with culture-negative clinical sepsis are included compared with cases of culture-proven sepsis only).

62

OUTCOME

Mortality rates for GBS sepsis in term infants after the introduction of IAP and routine use of empirical antibiotic therapy range from 2 to 3 percent for early-onset disease and 1 to 2 percent for late-onset disease.

The risk of mortality is higher in infants with birth weight <2500 g, absolute neutrophil count <1500 cells/microL, hypotension, apnea, and pleural effusion.

The risk of mortality is particularly high in neonates with early-onset sepsis caused by *E. coli*. Estimated mortality rates for term neonates with *E. coli* sepsis are 6 to 10 percent

63