

Neonatal Sepsis Syndrome (Early Onset)

Background

1. Definition

- Clinical syndrome of systemic illness suggestive of bacteremia seen in infants within the first 7 days of life

2. General information

- 85% of early onset infections present within 24 hours of birth
- 90+% present within 48 hrs. of birth
- **NOTE: This monograph does not cover:**
 - Infants <34 wks and infants <1,500 g
 - Infants born to HIV positive mothers
 - Late-onset sepsis (>7 days age) and nosocomial sepsis
 - Neonatal Gonorrhea and Chlamydia infections
- This monograph briefly addresses Herpes, excludes other TORCH infections

Pathophysiology

1. Pathology of disease

- Infection by:
 - Group B streptococcus (GBS) - most common
 - Gram-negative rods (E. coli, less commonly H. influenzae)
 - Listeria monocytogenes
- Enterovirus, coxsackievirus, and TORCH organisms (toxoplasmosis, rubella, CMV, HSV, syphilis) are rare cause of early onset sepsis in US
- Neonates have weaker cellular and humoral immunity vs. older children

2. Incidence

- 1-8 cases of culture positive sepsis per 1,000 live term births
- 13-27 per 1,000 for infants <1,500 grams
- 7-13% of infants are evaluated for sepsis; of these only 3-8% are culture positive
- Meningitis:
 - 2-4 cases per 1,000 live births
 - 1 in 3 infants with positive blood cultures
- HSV incidence:
 - 0.1-0.3 cases per 1,000 live births
- Neonatal HSV presents between birth and 5 weeks of age as:
 - 45% SEM
 - Disease limited to skin, eyes, and/or mouth
 - Vesicular lesions most common finding
 - 30% CNS disease
 - Signs include seizures, temp instability, bulging fontanel, lethargy, poor feeding
 - Peak incidence around day 16-19 of life
 - 25% Disseminated
 - Respiratory collapse, liver failure, DIC, hepatitis, pneumonitis
 - 80% will have cutaneous findings
 - Peak onset is day 10-12 of life
 - 9% of neonatal HSV cases become symptomatic on the 1st day of life
 - 30-40% of cases become symptomatic in the 1st week of life

3. Risk factors

- Bacterial risk factors
 - Maternal GBS colonization
 - Odds ratio: 29
 - Incidence of proven sepsis: 1-2%
 - Birth weight =<2,500 g
 - Odds ratio: 7.4
 - Gestational age =<37 weeks
 - Odds ratio: 5.8
 - Prolonged rupture of membranes >18 hrs
 - Odds ratio: 7.3
 - Incidence of proven sepsis: 1%
 - Maternal fever
 - Odds ratio: 4.1
 - Chorioamnionitis
 - Odds ratio: 6.4
 - Incidence of proven sepsis: 3-8%
 - >6 vaginal exams
 - Odds ratio: 2.9
 - GBS bacteriuria
 - Odds ratio: 4
 - Previous infant with GBS sepsis
 - Odds ratio: higher
 - GBS+ & PROM, fever, or preterm
 - Incidence of proven sepsis: 4-7%
 - PROM & preterm
 - Incidence of proven sepsis: 4-6%
 - PROM & low Apgar score
 - Incidence of proven sepsis: 3-4%
- Viral (HSV)
 - Most common with maternal primary herpes infection proximate to delivery (64% of primary maternal infections are asymptomatic)
 - 33%-50% of infants born to women with active primary HSV infection develop HSV
 - 3-5% of infants born to women with active recurrent infection develop HSV
- Increased risk of sepsis also with:
 - Traumatic birth, prolonged resuscitation
 - Meconium
 - Apgar <6 at 5 min
 - Male gender

4. Morbidity / mortality

- Mortality
 - 13-25% for untreated term infants with bacterial sepsis
 - Up to 50% for untreated preterm infants with bacterial sepsis
 - 10% for treated bacterial meningitis
 - 30% for treated HSV disseminated disease
 - 4% for treated HSV CNS disease

- Morbidity
 - Developmental delay
 - Cerebral palsy
 - Seizures
 - Blindness
 - Deafness
 - Severe parenchymal lung disease
 - Primary pulmonary hypertension

Diagnostics

1. History

- See risk factors above
- Fever / hypothermia
- Respiratory distress / apnea / cyanosis
- Feeding difficulties / vomiting / abdominal distention / diarrhea
- Irritability / lethargy / altered level of consciousness
- Early or exaggerated jaundice
- Detailed prenatal and birth history
 - See maternal risk factors
- Medications administered to mother

2. Physical exam

- Signs can be subtle
- Pneumonia most common manifestation of early neonatal sepsis
- Temperature instability
 - $>38.0^{\circ}\text{C}$ or
 - Unable to maintain temp $>36^{\circ}\text{C}$ without radiant heat source
- Change in behavior
 - Lethargy, irritability, poor feeding, hypotonia
- Skin
 - Poor perfusion, early or exaggerated jaundice, cyanosis
- Cardiopulmonary
 - Respiratory distress [grunting, flaring, or retractions]
 - Apnea, tachypnea
 - Tachycardia
 - Delayed capillary refill time
- Hypotension:
 - $\text{MAP} < \text{estimated gestational age (in wks)}$

3. Diagnostic testing

- CBC, manual differential
 - I/T ratio
 - Most sensitive and specific measure of CBC to dx sepsis
 - >0.30 is abnormal and warrants treatment
 - <0.20 reassuring
 - Between 0.20-0.30, may follow serially
 - $\text{I/T} = (\% \text{ immature neutrophils [bands, myelocytes, metamyelocytes]} / \% \text{ immature neutrophils} + \text{mature neutrophils})$
 - In one study, increased I/T ratio >0.3 had a sensitivity of 35% and specificity of 89%, PPV of 89%, and NPV of 98%

- Neutropenia
 - If present, may be consistent with infection
 - For infants >1500g, the following ranges apply:
 - 0-6 hrs: ANC <2,000
 - 6-12 hrs: ANC <4,000
 - 12-24 hrs: ANC <6,000
 - 24-48 hrs: ANC <4,000
 - 48-72 hrs: <2,000
 - >72 hrs: <1,500
 - For infants <1,500g, ANC is much lower
 - ANC varies significantly with age in hours
- Neutrophilia (ANC >25,000)
 - Has lower PPV for infection
 - Upper range of WBC (+2SD) at birth is 30K, at 12 hrs is 38K, and at 24 hrs is 34K
- Thrombocytopenia (Platelets <100,000)
 - Rare in healthy newborns
 - Only 10-60% of septic newborns have thrombocytopenia
 - Sens/spec of thrombocytopenia is poor for dx sepsis
- Single aerobic Blood Cx (> 1 mL of blood)
 - Sensitivity for identifying sepsis is only 50% to 80%
 - In two older studies using autopsies as a gold standard, blood cultures were only 80% sensitive
- Cath U/A and urine Cx if > 24 hrs age
- Consider a blood sugar
 - Hypoglycemia defined as glucose <40-50
 - Glucose <45 may be associated with lethargy, irritability, hypothermia, poor feeding, or seizures
- Consider CRP (controversial)
 - Sensitivity 92% at 8-24 hrs for proven sepsis, so has high NPV (99% in one large RCT)
 - Sensitivity at 30-48 hrs is 98% for proven or probable sepsis, and NPV is 99.7% and 98.7% for proven or probable sepsis in one RCT
 - Thus, CRP may be useful in deciding whether to discontinue antibiotics after 48 hours
 - Sensitivity is only 39% at birth, so if done to R/O sepsis, a second test done 8-24 hrs later is necessary
 - Specificity of CRP is lower (84% at 8-24 hours), as is PPV (35%) so if the CRP >1 mg/dL, the test is not particularly helpful
 - CRP is best to use in conjunction with clinical picture and differential
- Consider ABG
 - If respiratory distress or persistent tachypnea
- Consider Chem-7 if > 24 hrs age
- Consider LP:
 - Meningitis signs present late and very nonspecifically: seizures in 40%, bulging fontanelle in 28%, nuchal rigidity in 15%
 - 15-38% of neonatal meningitis cases have negative blood cultures
 - 5-15% have no CSF pleocytosis (normal neonatal CSF WBC <23/hpf)

- Meta-analysis: up to 1/3 of cases of neonatal meningitis (<7 do) will have the diagnosis missed or delayed if CSF examination is omitted
 - Recent review recommends LP if :
 - Infant has positive blood cultures
 - Infant shows possible signs of meningitis
 - Lethargy, hypo- or hypertonia, seizures, apnea, excessive irritability, bulging fontanelle, or septic shock
 - Infant is symptomatic and has sepsis as the leading diagnosis.
 - Consider HSV PCR on CSF if HSV in differential: sens. 75-100% and spec. 71-100% for CNS HSV disease
 - Herpes viral culture of any skin or mucous membrane lesions, herpes viral culture from the mouth, nasopharynx, conjunctivae, and rectum recommended prior to initiating antiviral therapy and/or if HSV possible
 - Blood HSV PCR not recommended due to poor sensitivity
 - Urine bacterial antigens not recommended
4. Diagnostic imaging
- CXR
 - If any signs of respiratory distress or cardiac disease
 - Echocardiogram
 - If murmur present, may consider to rule out congenital heart disease
 - Head U/S
 - If focal neuro exam, seizures, extreme prematurity

Differential Diagnosis

1. Respiratory distress syndrome (RDS)
2. Transient tachypnea of the newborn (TTN)
3. Meconium aspiration syndrome
4. Hypoglycemia (blood glucose <40-50)
5. Congenital heart disease (murmur usually present)
6. Diaphragmatic hernia
7. Intraventricular hemorrhage
8. Subgaleal hemorrhage
9. Persistent pulmonary hypertension of the newborn
10. Polycythemia
11. Hypovolemia
12. Hypocortisolism / Addisonian crisis
13. Prematurity
14. Electrolyte abnormalities
15. GERD

Therapeutics

1. Acute treatment
 - ABCs
 - IVF (if unable to feed PO) and electrolyte management
 - 1st 24 hrs:
 - D10W @ 60-80 mL/kg/d

- 2nd 24 hrs:
 - D10W + (2-4 mEq Na / 100 mL) + (1-3 mEq K / 100 mL) at 100 mL/kg/d
 - Electrolytes depend upon Chem-7 results checked q 24 hrs while on IVF
 - Beyond 48 hrs age:
 - Same IVF strategy as 2nd 24 hrs., but increase by 20 mL/kg/day until infant reaches 160 mL/kg/d
 - If prolonged (>48 hrs) IVF and NPO status anticipated, consider early initiation of TPN / PPN
 - Oxygen to keep SaO₂ 93-98%
 - IV antibiotics
 - Ampicillin and gentamicin
 - If suspected meningitis, ampicillin & cefotaxime
 - Consider beginning acyclovir prior to viral cultures coming back, if high suspicion of herpes
 - Continuous cardiorespiratory and pulse oximetry monitoring
 - Avoid hypoglycemia, hypotension
 - G-CSF/GM-CSF/IVIG: experimental, insufficient evidence
2. Further mgmt (24 hrs)
- Management Algorithm (CDC)
 - Footnotes
 - Length of treatment
 - If negative cultures at 48-72 hours and low clinical suspicion, antibiotics usually stopped
 - If high clinical suspicion (and/or maternal Abx may have resulted in falsely negative blood culture), some clinicians elect to continue antibiotics for 7-10 days
 - Alternatively, some clinicians treat until the CRP returns to normal (<1)
 - If GBS bacteremia: 10 days
 - If Gram negative bacteremia: 14 days
 - If uncomplicated meningitis due to GBS or Listeria: 14 days
 - If uncomplicated meningitis due to Gram negative rods: 21 days
 - Critical complications to watch for
 - Necrotizing enterocolitis (NEC)
 - Bacterial dissemination / seeding
 - Hyperbilirubinemia
 - Respiratory failure
 - Hypotension
3. Long-term care
- Hearing screen prior to d/c and repeat at 6 mo
 - Close developmental follow-up

Algorithm For Management of Newborns

CDC Guidelines on Prevention of Perinatal GBS (2002)

- <http://www.cdc.gov/MMWR/preview/mmwrhtml/rr5111a1.htm>

Follow-Up

1. Return to office
 - After short hospital stay, follow-up 2-4 days after d/c is common
 - May elect to follow-up sooner if prolonged stay, complications such as meningitis, or ongoing concerns regarding feeding
 - If meningitis, will need closer monitoring of hearing, visual acuity, and developmental status.
2. Refer to specialist
 - Pediatrician vs neonatologist
 - Consult recommended with a neonatologist or pediatrician with significant neonatal experience if positive blood culture or positive LP. Consult or transfer care if ventilation or pressors are needed, or if complicated course, depending on institutional guidelines and expertise
 - Pediatric Infectious Disease Specialist
 - When infant is not responding to treatment, is infected with an unusual organism, or has a complicated clinical course.
3. Admit to hospital
 - Optimal setting for care
 - Asymptomatic term newborns receiving antibiotics stay with mother in some hospitals
 - Symptomatic newborns should be admitted to nursery for close monitoring and antibiotics
 - Infants with hypotension, needing ventilators, or with seizures should be cared for in NICU

Prognosis

1. Generally good
2. Worse if complications of illness, low birth weight (<2,500) neutropenia, DIC, need for ventilatory or pressor support, seizures, delayed diagnosis, meningitis

Prevention

1. Antibiotics given according to the CDC guidelines decrease the risk of GBS sepsis by up to a third

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