The Sick Newborn: Identifying Congenital, Perinatal, and Postnatal Infections

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Learning Objectives
1. Identify congenital, antenatal and neonatal infections transmitted from a mother to her child.
2. Describe routine maternal screening labs and elements of maternal history that should raise your suspicion for congenital, antenatal and neonatal infections.
3. Describe key components of screening, assessment and diagnosis of infants with congenital, antenatal and neonatal infections.
4. Discuss immediate and long-term consequences of congenital, antenatal and neonatal infections.

Clinical Questions
1. Should I evaluate this newborn for sepsis?
2. Should I start antibiotics?
3. Do I need to transfer this newborn to a higher level of care?

Impact of Early Onset Sepsis
Incidence of Early Onset Sepsis in the US
- 0.77-0.98 per 1000 live births overall
- 0.53 per 1000 live births for infants born at 37 weeks or greater
- 7x higher among infants born <37 weeks
- 20x higher among VLBW infants

Mortality Rate
- 11-16% with more than 90% of the deaths occurring in preterm infants
US Overall
- Approximately 3,300 newborns with early onset sepsis per year
- Approximately 340 newborn deaths per year

Uniqueness of Neonates and Infection
- Diverse modes of transmission of infection.
- Immunologic immaturity of the infant.
- Coexisting conditions complicate diagnosis and management.
- Clinical manifestations vary widely.
- Maternal infection during pregnancy is often undiagnosed.
- Wide variety of agents infect the newborn.
Timing and Mode of Transmission

Routes of infection in the fetus and neonate. CMV, cytomegalovirus; HIV, human immunodeficiency virus; HTLV, human T‐cell lymphotrophic virus.

Obstetric and perinatal infections
Goering, Richard V., BA MSc PhD, Mims' Medical Microbiology, 23, 303‐310

Periods of Transmission of Neonatal Pathogens

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Prenatal</th>
<th>Perinatal</th>
<th>Postnatal</th>
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<tbody>
<tr>
<td>Viruses</td>
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<tr>
<td>Cytomegalovirus</td>
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<tr>
<td>Enterovirus</td>
<td>Rare</td>
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<tr>
<td>Hepatitis B virus</td>
<td>Rare</td>
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<tr>
<td>Herpes simplex virus</td>
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<tr>
<td>Human immunodeficiency virus</td>
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<tr>
<td>Parvovirus B19</td>
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<td>Rubella virus</td>
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<td>Varicella zoster virus</td>
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<td>Protozoa</td>
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<tr>
<td>Toxoplasma gondii</td>
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<tr>
<td>Bacteria</td>
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<tr>
<td>Chlamydia trachomatis</td>
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<tr>
<td>Group B streptococcus</td>
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</tr>
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<td>Enterococcus species</td>
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<td>Enterobacteriaceae</td>
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<td>Listeria monocytogenes</td>
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<td>Neisseria gonorrhoeae</td>
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<td>Staphylococcus species</td>
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<td>Treponema pallidum</td>
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<td>Ureaplasma urealyticum</td>
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<td>Fungi</td>
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<td></td>
<td></td>
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<tr>
<td>Candida species</td>
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</tr>
</tbody>
</table>

Etiology of Fetal and Neonatal Infections


All-cause E coli and GBS early-onset invasive disease, 2005 to 2014, Active Bacterial Core surveillance.

Invasive early-onset GBS disease incidence by gestational age categories, 2005 to 2014, Active Bacterial Core surveillance.
### Univariate Factors Associated With Mortality Among Infants With Invasive Early-Onset Sepsis, Active Bacterial Core Surveillance, 2005 to 2014

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Died (n = 165), %</th>
<th>Exposed</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>Pathogen</td>
<td></td>
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<td></td>
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<tr>
<td>GBS</td>
<td>22.4 37.5</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>E. coli</td>
<td>51.5 21.5</td>
<td>4.0 (2.7–6.1)</td>
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<tr>
<td>Other</td>
<td>26.1 41.0</td>
<td>1.1 (0.7–1.7)</td>
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<tr>
<td>Birth weight &lt;1500 g</td>
<td>75.8 16.7</td>
<td>15.6 (10.6–22.9)</td>
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<tr>
<td>Gestational age &lt;34 wk</td>
<td>82.4 26.0</td>
<td>13.3 (8.8–20.3)</td>
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</tr>
<tr>
<td>Boy</td>
<td>61.8 52.2</td>
<td>1.5 (1.1–2.1)</td>
<td></td>
</tr>
<tr>
<td>Black race</td>
<td>45.5 36.6</td>
<td>1.4 (1.0–2.0)</td>
<td></td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>59.4 44.4</td>
<td>1.8 (1.3–2.5)</td>
<td></td>
</tr>
<tr>
<td>Membrane rupture ≥18 h before delivery</td>
<td>50.3 40.9</td>
<td>1.5 (1.1–2.0)</td>
<td></td>
</tr>
<tr>
<td>Exposure to intrapartum antibiotics</td>
<td>71.5 47.3</td>
<td>2.8 (2.0–4.0)</td>
<td></td>
</tr>
</tbody>
</table>

### Epidemiology of Invasive Early-Onset Neonatal Sepsis, 2005-2014

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B Streptococcus</td>
<td>46% (n = 522)</td>
</tr>
<tr>
<td>E. coli</td>
<td>25% (n = 306)</td>
</tr>
<tr>
<td>Viridans streptococci</td>
<td>26% (n = 306)</td>
</tr>
<tr>
<td>H. Influenza</td>
<td>15% (n = 174)</td>
</tr>
<tr>
<td>S. pneumonia</td>
<td>12% (n = 174)</td>
</tr>
</tbody>
</table>

### Standard Prenatal Testing

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Diagnostic Test</th>
<th>First Visit</th>
<th>Third Trimester</th>
<th>N Delivery</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>Tuberculin skin test</td>
<td>+</td>
<td>Chest radiograph, culture, antituberculous therapy</td>
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<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Serology</td>
<td>+</td>
<td></td>
<td></td>
<td>Antituberculous therapy</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>Serology</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rubella</td>
<td>Serology</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B Streptococcus</td>
<td>Culture</td>
<td>+</td>
<td>Intrapartum antibiotic prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>Examination, PCR, culture</td>
<td>+</td>
<td></td>
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</tr>
<tr>
<td>Influenza</td>
<td>None needed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal pertussis</td>
<td>None needed</td>
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</tr>
</tbody>
</table>

### Special Prenatal Testing if Exposed or with Clinical Signs

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Diagnostic Test</th>
<th>First Visit</th>
<th>Third Trimester</th>
<th>N Delivery</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV</td>
<td>Serology</td>
<td>+</td>
<td>Education regarding hygiene to prevent infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>ELISA + Western blot, RNA testing</td>
<td>+</td>
<td></td>
<td></td>
<td>Anti-retroviral therapy</td>
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<tr>
<td>Malaria</td>
<td>Rapid diagnostic testing, blood smear</td>
<td>+</td>
<td></td>
<td></td>
<td>IPTp and bed nets, antimalarial treatment</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>Ultrasonography, serology</td>
<td>Intrauterine transfusion</td>
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<td></td>
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<tr>
<td>Toxoplasmosis</td>
<td>Serology, PCR assay (amniotic fluid)</td>
<td>Anti-Toxoplasma therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VZV</td>
<td>Examination, PCR, ultrasonography</td>
<td>Antiviral therapy</td>
<td></td>
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</tr>
</tbody>
</table>

### Maternal & Newborn Risk Factors for Early-Onset Sepsis

**Maternal OB & Labor History**
- GBS colonization
- Prolonged or premature rupture of membranes
- Chorioamnionitis
- Urinary tract infections

**Newborn Risk Factors**
- Preterm delivery at gestational age less than 37 weeks
- Low birth weight
- Traumatic delivery
- Fetal anoxia
### Indications and nonindications for intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal (GBS) disease

**INTRAPARTUM GBS PROPHYLAXIS INDICATED**

- Previous infant with invasive GBS disease
- GBS bacteriuria during any trimester of the current pregnancy
- Positive GBS screening culture during current pregnancy (unless a cesarean delivery is performed before onset of labor or amniotic membrane rupture)
- Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following:
  - Delivery at <37 weeks’ gestation
  - Amniotic membrane rupture ≥18 hr
  - Intrapartum temperature ≥38.0°C (100.4°F)
  - Intrapartum nucleic acid amplification test positive for GBS

**INTRAPARTUM GBS PROPHYLAXIS NOT INDICATED**

- Colonization with GBS during a previous pregnancy (unless another indication for GBS prophylaxis is present for current pregnancy)
- GBS bacteriuria during previous pregnancy (unless another indication for GBS prophylaxis is present for current pregnancy)
- GBS bacterium found in vaginal or rectal cultures during a previous pregnancy (unless another indication for GBS prophylaxis is present for current pregnancy)
- Positive GBS screening culture during current pregnancy (unless a cesarean delivery is performed before onset of labor or amniotic membrane rupture)
- Cesarean delivery before onset of labor or amniotic membrane rupture, regardless of GBS colonization status or gestational age
- Unknown GBS status at the onset of labor (culture not done, incomplete, or results unknown) and any of the following:
  - Delivery at ≥37 weeks’ gestation
  - Amniotic membrane rupture ≤18 hr
  - Intrapartum temperature <38.0°C
  - Intrapartum nucleic acid amplification test negative for GBS

### Recommended regimens for intrapartum antibiotic prophylaxis for prevention of early-onset group B streptococcal (GBS) disease

Recommended regimens for intrapartum antibiotic prophylaxis to prevent early-onset group B streptococcal (GBS) disease include:

1. **Penicillin G**
   - **Dose:** 1 million units intravenously (IV) or intramuscularly (IM)
   - **Frequency:** Single dose during labor

2. **Clindamycin**
   - **Dose:** 900 mg IV or IM in two divided doses (600 mg initially, followed by 300 mg 1 hour later)
   - **Frequency:** Single dose during labor

3. **Erythromycin**
   - **Dose:** 500 mg IM or 500 mg oral in two divided doses (250 mg initially, followed by 250 mg 1 hour later)
   - **Frequency:** Single dose during labor

4. **Cefazolin**
   - **Dose:** 1 g IV or IM in single dose during labor
   - **Frequency:** Single dose during labor

5. **Cefuroxime**
   - **Dose:** 1.5 g IV or IM in single dose during labor
   - **Frequency:** Single dose during labor

### Chorioamnionitis

- Maternal fever of greater than 38 degrees C (100.4 F)
- Plus at least 2 of the following criteria:
  - Maternal leukocytosis (greater than 15,000 cells/mm3)
  - Maternal tachycardia (greater than 100 beats/minute)
  - Fetal tachycardia (greater than 160 beats/minute)
  - Uterine tenderness
  - Foul odor of the amniotic fluid

### Risk Factors for Neonatal Sepsis

- Maternal fever of greater than 38 degrees C (100.4 F)
- Maternal tachycardia (greater than 100 beats/minute)
- Fetal tachycardia (greater than 160 beats/minute)
- Uterine tenderness
- Foul odor of the amniotic fluid
Rate of sepsis according to gestational age.

Rate of sepsis according to highest maternal intrapartum temperature.

Rate of sepsis according to duration of ROM.

Maternal Peripartum Risk Factors for Early-Onset Bacterial Infection

Risk Factor | Comment
--- | ---
Preterm delivery | Attack rate inversely related to gestation <37 weeks
Premature rupture of membranes | Rupture of membranes >1 hour before onset of labor at any gestation
Chorioamnionitis | Risk of neonatal sepsis is 5–15%
Urinary tract infection | Higher neonatal risk even when mother asymptomatic
Multiple pregnancy | Only noted for group B streptococcal sepsis
Prolonged rupture of membranes | Attack rate directly proportional to duration of rupture of membranes >18 hours
Early postpartum febrile morbidity | Maternal fever (>38°C) during the first 24 hours postpartum
No prenatal care | Higher neonatal risk
Fetal hypoxia | Apgar score <6 associated with higher risk

Signs and Symptoms of Infections in Neonates

- Temperature instability
- Lethargy
- Irritability
- Apnea
- Respiratory distress
- Hypotension
- Bradycardia
- Tachycardia
- Cyanosis
- Abdominal distention
- Hyperglycemia
- Hypoglycemia
- Jaundice
- Feeding intolerance

Signs & Symptoms of Congenital Infections

- Hepatosplenomegaly
- Jaundice
- Rash
- Microcephaly
- Intracranial calcifications
- Meningoencephalitis
- Chorioretinitis
- Cataracts
- Microphthalmia
- Bone lesions
- Adenopathy
- Cardiac abnormalities
- Pneumonitis
- Thrombocytopenia
- Anemia
- Sensorineural hearing loss

(Edwards & Baker, 2012)

(Sabella, 2015)

(Smith & Benjamin, 2012)
Characteristic Manifestations of Congenital Infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rubella</th>
<th>CMV</th>
<th>Parvovirus B19</th>
<th>Herpes</th>
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<td>Anemia</td>
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<td>Rash</td>
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<td>Grenzocytes</td>
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</table>

(Smith & Benjamin, 2012)

Differential Diagnosis

- The clinical manifestation of newborn sepsis and meningitis are often indistinguishable from other newborn illnesses, such as respiratory distress syndrome, congenital heart disease, and metabolic disorders.

Evaluation of a Newborn for Sepsis

Goals for Testing

- **Sensitive**: Sensitivity - refers to the ability of the test to correctly identify those patients with the disease.
- **Specific**: Specificity - refers to the ability of the test to correctly identify those patients without the disease.
- **Rapid**: Timely

Positive Predictive Value: If the test result is positive, how likely is it that the patient has the disease?
Negative Predictive Value: If the test result is negative, how likely is it that the patient does not have the disease?

Blood Testing for Neonatal Sepsis

- **Complete Blood Count and Differential**
  - WBC
    - Total WBC
    - Absolute neutrophil count
    - Absolute band count
    - Immature to total neutrophil (I/T) ratio
  - Platelet Count – nonspecific, insensitive, late indicator of sepsis

- **Blood Culture**
  - Gold standard
  - Low sensitivity and specificity
  - Often negative even in bacteremia because of inadequate blood volume
  - False positives due to breaks in aseptic technique

Acute Phase Reactants

- C-reactive protein
- Procalcitonin
- Interleukin-6
- Interleukin-8
- Erythrocyte sedimentation rate

(Smith & Benjamin, 2012)
Stratification of Risk of Early-Onset Sepsis in Newborns ≥ 34 Weeks’ Gestation, Escobar et al., 2014

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical illness</td>
<td>In the first 12 h of age, the infant had a 5-min Apgar &lt;5; received nasal continuous positive airway pressure or mechanical ventilation; received continuous infusion of vasoactive drugs; had a clinical seizure; or had significant respiratory distress (nasal flaring, grunting, or retractions were present and the infant received supplemental oxygen within the first 6 h)</td>
</tr>
<tr>
<td>Equivocal presentation</td>
<td>In the first 12 h of age, the infant experienced at least 2 instances of 1 of the following, with “instance” meaning that there were ≥2 measurements ≥2 h apart: Heart rate ≥160, Respiratory rate ≥30, Temperature ≤100.4°F or ≥100.4°F, Respiratory distress (grunting, flaring, or retracting)</td>
</tr>
<tr>
<td>Well appearing</td>
<td>The infant did not fall into one of the above 2 groups in the first 12 h of age</td>
</tr>
</tbody>
</table>

Quantitative Risk Stratification for EOS. Quantitative risk stratification schema for newborns >34 weeks’ gestation developed in this study. Gabriel J. Escobar et al. Pediatrics 2014;133:30-36

What about neonates?
Management of Confirmed or Suspected Sepsis

Specific Infections & Cardinal Presentations

<table>
<thead>
<tr>
<th>HSV</th>
<th>Rubella</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis</td>
<td>CMV</td>
</tr>
<tr>
<td>Parvovirus</td>
<td>Emerging infections</td>
</tr>
</tbody>
</table>

Complications and Prognosis

• Impact of early antibiotic use
• Separation from mother
• Family perception

Prevention

Maternal Prevention

• Maternal Immunization
  – Rubella
  – Hepatitis B
  – Varicella Zoster
• Toxoplasmosis
  – Avoiding exposure to cat feces
  – Appropriate diet
• Malaria
  – Chemoprophylaxis
  – Insecticide-treated bed nets
• Congenital Syphilis
  – Early diagnosis and treatment in infected pregnant women

Chorioamnionitis

• Antibiotic therapy during labor
• Rapid delivery of infant
• Group B Strep
• Screening with appropriate intrapartum antibiotics

Chlamydia

• Identification and treatment of infected pregnant women

Prevention – Newborn Care Practices

• Cord care
• Vernix caseosa
• Breast milk

References

References


References