Treatment Duration of Early Onset Neonatal Sepsis—How Long is Long Enough?

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Disclosure

- I do not have a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

Objectives

- Describe early onset neonatal sepsis pathogens, risk factors, and clinical signs and symptoms of infection.
- Review literature regarding optimal treatment duration and risk factors of prolonged antibiotic courses for neonatal sepsis.

Background

- Antibiotics are most commonly used medications in neonatal intensive care units (NICUs).
- Neonatal sepsis associated with significant morbidity and mortality.
- Signs and symptoms are often subtle and nonspecific.
  - Often leads to antibiotic over-use.
  - Exposure to antibiotics may not be benign.

What is Neonatal Early Onset Sepsis (EOS)?

- Infection occurring in the neonate within 72 hours after birth.
- Low overall incidence but potentially fatal.
  - 0.98 per 1000 live births
  - Incidence higher for birth weight <1.5kg (11 per 1000).
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Clinical Presentation

- Hypoglycemia (<40 mg/dL): 22%
- Hypothermia (<36.5°C): 20%
- Hyperglycemia (>140 mg/dL): 19%
- Apnea: 18%
- Decreased appetite or vomiting
- Hypotension
- Irritability*
- Convulsions*
- Bulging fontanel*

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Risk Factors for Neonatal Sepsis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Proven Sepsis</th>
<th>Suspected Sepsis</th>
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</thead>
<tbody>
<tr>
<td>pPROM &gt; 18 hrs</td>
<td>1%</td>
<td>1-2%</td>
</tr>
<tr>
<td>Maternal GBS</td>
<td>0.5-1%</td>
<td>1-2%</td>
</tr>
<tr>
<td>pPROM + GBS</td>
<td>4-6%</td>
<td>7-11%</td>
</tr>
<tr>
<td>GBS + maternal fever</td>
<td>3-5%</td>
<td>6-10%</td>
</tr>
<tr>
<td>pPROM or GBS + preterm</td>
<td>4-6%</td>
<td>7-11%</td>
</tr>
<tr>
<td>PROM, 5 min AGPAR &lt; 5</td>
<td>3-4%</td>
<td>6-10%</td>
</tr>
<tr>
<td>Male Gender</td>
<td>Increased Risk X 4</td>
<td>Increased Risk X 4</td>
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</tbody>
</table>

pPROM: premature prolonged rupture of membranes; PROM: Prolonged rupture of membranes; GBS: group B strep

What is Chorioamnionitis?

- Diagnosis
  - Definitive diagnosis made by examining placenta after delivery
  - Histological, biochemical, and microbiologic findings

Neonatal Treatment-Maternal Chorioamnionitis

- **Risk Factors**
  - Chorioamnionitis
  - Blood culture at birth
  - Management

- **Diagnosis Tests**
  - Blood culture
  - Bacterial burden

- **Antibiotics**
  - Blood culture positive
  - Continue antibiotics
  - Discontinue antibiotics by 48-72 hours

- **Management**
  - Lumboperitoneal

National Institute of Health and Care Excellence

- 2012 guidelines published
- Goals of treatment:
  - Treating suspected infection as quickly as possible
  - Minimize antibiotic exposure in babies without EOS
- Diagnosis
  - CRP at start of antibiotic therapy, 18-24 hr later
- Treatment duration
  - Stop antibiotics at 36 hr if baby clinically well, blood culture negative, CRP values/trends reassuring

NICE Guidelines

- Symptomatic neonates without risk factors may not require treatment, but do require close monitoring
- Chorioamnionitis significantly increases risk of EOS, but likelihood of sepsis in infant who appears well at birth is low
- Risk of sepsis reduced in infants whose mothers have chorioamnionitis and received intrapartum antibiotics (antibiotics may be less effective once chorioamnionitis established)

- Intrapartum use of antibiotics decreases sensitivity of postnatal blood cultures
- Commonly used laboratory tests have limited positive predictive accuracy
- Should never be used as rationale to continue treatment in otherwise well-appearing term infant at 48-72 hr of life
- Physical exam as good or better than most lab tests for ruling sepsis in or out
**NICE Guidelines**
- Antibiotics may be D/C in well-appearing newborns born to chorio + women by 48 hr of life
- 72 hr treatment may be considered for infants with greater prematurity or abnormal screening studies
- Lumbar puncture required
  - Positive blood culture
  - High probability of sepsis (clinical signs, abnormal labs)
  - No improvement with appropriate antimicrobial therapy

**Maternal Chorioamnionitis**
- Appears to be an important risk factor for development of infection in neonates
- There may be an association with poorer outcomes in very low birth weight infants

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**How is EOS diagnosed in neonates?**

**Diagnostic Evaluation-AAP**
- Clinical presentation in newborns often overlaps with other disease states
- CBC with differential has poor PPV—wait 6 to 12 hours after birth to obtain
- Platelet counts remain low days to weeks after sepsis
  - Not reliable for tracking response to therapy
- Sensitivity CRP improves if done 6 to 12 hours after birth
  - Bacterial sepsis is unlikely if CRP remains normal.

CBC: complete blood count, PPV: positive predictive value, CRP: C-reactive protein

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**Diagnostic Evaluation-AAP**
- Lumbar puncture (LP)
  - Indicated in infants with high suspicion of sepsis, bacteremia, or fail to respond to appropriate antimicrobial therapy
- Urinary tract infections in newborns associated with bacteremia
  - Routine urine cultures not indicated
- Microbiologic evaluation of non-blood sites not routinely recommended
  - Gastric or tracheal aspirates, superficial body site culture

**Diagnostic Evaluation-AAP**
- Blood cultures
  - At least 1 mL may be sufficient from a single culture from a peripheral vein
  - Umbilical artery catheter or vein may be reliable alternatives following aseptic technique
  - Screening blood cultures have not been proven of value and are not recommended
**Blood Cultures**
- Although vital for diagnosis of neonatal bacteremia/sepsis, they may not adequately reflect infection in some infants with low colony count sepsis.
- Higher blood volumes for cultures seem to be more accurate but may not be practical in the smaller infants.

**Diagnosis of EOS**
- The American Academy of Pediatrics endorses the use of CBC with differential, CRP, and blood cultures (at least 1 mL) to guide diagnosis of neonatal EOS.
- No one test is able to determine the presence or absence of neonatal sepsis alone.
- Frequent physical examination appears to be as effective at diagnosing some infants with EOS.

**Maternal Antibiotic Exposure**
- Neonatal antibiotic resistance more common in infants whose mother receive antibiotics.
  - Antepartum, intrapartum, or both.
- Antibiotic-resistant organisms:
  - Preterm neonates
  - Mothers hospitalized prior to delivery
- Increased risk of resistance:
  - Duration of therapy
  - Number of antibiotic courses during pregnancy

**Characteristics of E. coli EOS**
- Preterm birth (<30 weeks gestation)
- Low birth weight (<1500 grams)
- Maternal intrapartum fever
- Preterm premature rupture of membranes (pROM) >24 hours
- Maternal antibiotic exposure (antepartum, intrapartum)
- Onset of sepsis within 24 hours of life

**Treatment Complications**
- Disruption of maternal bonding
- Exposing infant to drugs with potential toxicities
- Fostering development of antibiotic resistance
- Increasing probability that infant with experience more significant morbidity later in course of hospitalization
- Impact on bowel colonization of microflora
EOS Treatment Choices
- Penicillin-type antibiotic + Aminoglycoside
- Penicillin-type antibiotic + 3rd generation cephalosporin

Antibiotic Susceptibility
- GBS isolates penicillin/ampicillin sensitive
- E. coli (n = 103)
  - 78% ampicillin resistant
  - 4% gentamicin resistant
  - 3% 3rd generation cephalosporin resistant

Pencillin versus Ampicillin For EOS
- All neonates admitted within 72 hours of life needing empiric therapy for EOS
- Random assignment to receive either penicillin or ampicillin

Penicillin versus Ampicillin for EOS
- No difference in change of antibiotic regimen within 72 hours, 7-day mortality, and overall treatment failure
- Trend towards improved mortality in ampicillin group in neonates born <26 weeks gestation
- Ampicillin associated with gut colonization with S. aureus and amp-resistant Acinetobacter

Clinical Predictors of Empiric Treatment Failure
- Infants treated with ampicillin/penicillin and gentamicin
  - Gestational age <28 week
  - Birth weight <1500 grams (particularly <750 grams)
  - Surfactant administration
  - Chorioamnionitis
  - Lower APGAR scores at 1 and 5 minutes

Broad-Spectrum Antibiotics
- Cefotaxime may promote bacterial resistance
  - Rates of resistant organisms up to 18-fold higher in cefotaxime-containing empiric regimens compared to PCN+tobramycin
  - Altered gut colonization
  - Increased risk of invasive Candida
  - Increased risk of death
### Empiric Cefotaxime versus Gentamicin

- Retrospective cohort of 128,914 neonates
  - Amp/cefotaxime: 24,111
  - Amp/gentamicin: 104,803

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Amp/Cefotaxime</th>
<th>Amp/Gentamicin</th>
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<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>35 (31-38)</td>
<td>35 (32-38)</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>2.35 (1.5-3.2)</td>
<td>2.42 (1.7-3.2)</td>
</tr>
<tr>
<td>Duration of antibiotics</td>
<td>3 (2-7)</td>
<td>3 (2-6)</td>
</tr>
</tbody>
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Numbers expressed as median (IQR)

### Antibiotic Choice

- Ampicillin and gentamicin are probably reasonable choices for empiric early onset sepsis treatment
  - Near term, term infants
  - No maternal risk factors for resistant gram negative organisms
- Ampicillin and cefotaxime may be a reasonable alternative in some neonates
  - Maternal risk factors/history of resistant gram negative organisms
  - High index of suspicion for sepsis

### How long should we treat?

#### Sepsis Rule Out-"Well Baby"

- Discontinuation of antibiotics at 48 hours
  - Sterile culture
  - Normal screen lab values
  - No signs of infection
- Neonates with 2 normal immature to total neutrophil ratios and negative blood culture at 24 hours rarely develop sepsis

#### Sepsis Rule Out-Higher Risk Baby

- Risk for infection perceived higher than normal
- Initial clinical signs more numerous but transient
  - Clinician can use negative predictive values of additional testing to validate decision to discontinue antibiotics if clinical signs of infection resolved by 24 hours
- Can discontinue antibiotics at 48 hours in the absence of continued signs of infection AND a negative blood culture
  - Despite abnormal initial CBC if repeating testing at 24-48 hours is reassuring
Sepsis Treatment Beyond 48hr

- Neonates with positive cultures
  - Duration dependent on susceptibilities and site of infection
- Neonates with clinical signs of infection beyond postnatal day 1
  - Absence of positive cultures in an infected-appearing neonate probably due in part to false negative cultures
  - False negatives: low bacterial inoculum, antimicrobial exposure prior to obtaining cultures

Risk Factors for Longer Antibiotic Courses

- Younger gestational age
- Lower birth weight
- African American
- Low APGAR scores
- Born >24 hours after rupture of membranes
- Mothers more likely to have received intrapartum antibiotic treatment

Summary

- Empiric therapy for EOS can be safely discontinued in well-appearing infants
  - Negative cultures
  - Absence or normalization of abnormal labs within 24 hours
- Therapy should be continued beyond 48 hours in sick appearing infants even in the absence of positive cultures
- Routine antibiotic use in extremely low birth weight infants ≥ 5 days may be associated with harm

Duration of Empiric Antibiotic Therapy

- 4039 extremely low BW infants (401-1000 grams) in 19 centers that survived more than 5 days
- Most infants received ampicillin+gentamicin
  - Median duration of treatment: 5 days (3 to 9.5 days)
  - 53% of infants received initial treatment ≥5 days
  - Treatment ≥5 days in absence of positive culture: 27-85% of infants at the different centers

Extended Antibiotic Courses

- Each empirical treatment day associated with increased odds of death, necrotizing enterocolitis (NEC), and composite outcome (death, NEC)

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- Empiric antibiotic treatment and the risk of necrotizing enterocolitis and death in very low birth weight neonates.
- Antibiotic use and misuse in the neonatal intensive care unit.
- Characteristics of early-onset neonatal sepsis caused by Escherichia coli.
- Outcomes of very-low-birth-weight infants exposed to maternal clinical chorioamnionitis: a multicenter study.
References


