Recent Advances in the Diagnosis and Prevention of Neonatal Sepsis

Richard A. Polin M.D.
Morgan Stanley Children’s Hospital
Columbia University
Top 5 Reasons for "Hating" the Workup for Neonatal Sepsis

✶ There is no “glory” in performing a sepsis workup

✶ Most “rule outs” occur between 2:00 AM & 5:00 AM

✶ Even when the blood culture is negative, everyone usually ignores the results and treats the baby for 7-10 days.

✶ The probability that the lab will lose the blood specimen is inversely proportional to how difficult it was to draw the blood (and how critical the specimen).

✶ There are too many arbitrary rules and not enough evidence/science to guide decisions in infants with suspected sepsis.
Educational Objectives

- To discuss the importance of chorioamnionitis in the pathophysiology of neonatal sepsis and highlight the difficulties in making that diagnosis.
- To present a scientific rationale for the diagnostic workup and treatment of infants at risk for sepsis.
Clinical Spectrum of Early-onset Neonatal Sepsis

★ There are ~3300 invasive early-onset sepsis cases and 390 deaths in the United states each year (2005-2008 data).
★ GBS is the leading pathogen and *E coli* is second
★ 2/3 *E coli* isolates are resistant to ampicilllin.

<table>
<thead>
<tr>
<th></th>
<th>Rate*</th>
<th>Case fatality ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black preterm</td>
<td>5.14</td>
<td>24.4%</td>
</tr>
<tr>
<td>Non black preterm</td>
<td>2.17</td>
<td>21.5%</td>
</tr>
<tr>
<td>Black term</td>
<td>0.89</td>
<td>1.7%</td>
</tr>
<tr>
<td>Non black term</td>
<td>0.40</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

*/1,000 live births

This was the first pregnancy for a 22 year-old woman with an unremarkable pre-pregnancy history. At 37\(\frac{2}{7}\) weeks gestation, her membranes rupture at 2:00 P M. She enters the hospital at 12 noon the following day because of painful uterine contractions. A rapid NAAT for *GBS* is positive.
The Case Begins

Following placement of an epidural she develops a temperature of 38.0 degrees C. There is no uterine tenderness and her white blood count is 18,000/mm$^3$ with 65% PMNS and 4% band forms. The care providers administered broad spectrum antibiotics because of possible chorioamnionitis (1 hour prior to delivery). The infant exhibits mild respiratory distress at birth, but quickly becomes well.

How would you manage this infant?
The Case Continued

- Observation
- Blood Culture and broad spectrum antibiotics
- Screening WBC and blood culture
Pathways of Neonatal Sepsis

Chorioamnionitis is a key step in the pathway of early-onset neonatal sepsis.
Does the Woman in this Case History Have Chorioamnionitis?

Fever and painful uterine contractions
Clinical Chorioamnionitis: Diagnostic criteria

Presence of otherwise unexplained maternal fever (greater than or equal to 100.4°F, or 38.0°C) plus at least 2 of the following additional clinical findings:

- Maternal tachycardia (> 100 bpm)
- Fetal tachycardia (>160 bpm)
- Elevated maternal white blood cell count (> 15,000 cells/m³)
- Uterine tenderness
- Foul smelling amniotic fluid

Problems with the Current Definition of Chorioamnionitis

★ The diagnosis generally represents a “guess” on the part of the obstetrical provider, before laboratory data are available (lacks precision).

★ Fever is often used as the sole criterion for chorioamnionitis, without other objective data.

★ The source of fever may be extrauterine and may not represent an infectious process in the chorion or amnion.
Chorioamnionitis vs. Intrauterine Inflammation or Infection

In January 2015 a workshop was held at the NICHD proposing new terminology to replace the term chorioamnionitis: *Intrauterine Inflammation and/or Infection (III).*

The purpose was to distinguish women with non-infectious causes of fever from those with true chorioamnionitis.
Classifying Intrauterine Inflammation and/or Infection

Fever in labor was defined as: Two oral temperatures $38^\circ\text{C} (100.4^\circ\text{F})$ to $39^\circ\text{C} (102.2^\circ\text{F})$ at least 30 minutes apart or one oral temperature $>39^\circ\text{C} (102.2^\circ\text{F})$

**Suspected III**: Fever without a clear source and any of the following.
1. Baseline fetal heart rate $>160$ BPM for 10 minutes or longer
2. Maternal WBC $>15,000$ (in the absence of corticosteroids)
3. Purulent fluid from the cervical os.

**Definite III**: All of the above plus objective evidence of an intrauterine infection (+ gram stain or culture from amniotic fluid or low glucose)

**Isolated fever**
The diagnosis of chorioamnionitis is important because it determines subsequent management of the infant.
Evaluation of *Asymptomatic Infants* Risk Factor - *Chorioamnionitis*

**Risk Factors**
- Chorioamnionitis

**Diagnostic Tests**
- Blood culture at birth
- WBC/Diff ± CRP
- at age 6-12 hours

**Antibiotics**
- Broad spectrum antibiotics

★ AAP Recommendation 2012
**National Institute for Health and Clinical Excellence (NICE guideline 2012)**

- Begin antibiotics in any neonate born to a mother who received antibiotics for a confirmed or suspected bacterial infection

**Risk Factors**
- Chorioamnionitis

**Diagnostic Tests**
- Blood culture at birth
- CRP before starting antibiotic

**Antibiotics**
- Benzyl penicillin and gentamicin
**Consequences of CDC/AAP/NICE Guidelines**

- Increased workups for neonatal sepsis in well appearing infants.
- Prolonged antibiotic therapy based solely on abnormal laboratory values.
- Increased length of stay and unnecessary invasive procedures (e.g., LP)

The infant is delivered at 37\textsuperscript{2/7} weeks gestation following rupture of membranes for 26 hours. Intrapartum antibiotics (ampicillin and gentamicin) were given to the mother. He was suctioned and dried by the nurse and placed on NPCPAP with 21\% O\textsubscript{2}. Apgar scores were 6 & 8 and the respiratory distress quickly resolved. The CPAP was discontinued.
How should the workup proceed?
Symptomatic or Asymptomatic

Presence or Absence of Risk Factors
“Rule out sepsis ”-The Process

- Identify the antenatal risk factors for sepsis.
- Perform a careful physical examination and make an estimate of the probability of sepsis based on those signs & history.
- Order the appropriate laboratory test and cultures.
- Decides who need antibiotics based on the above data.
Achieving a Treatment Threshold for Early-Onset Sepsis

- **Critically Ill**
  - Symptomatic: Treatment
  - Observing: Diagnostic testing

- **Asymptomatic and Risk Factors**
  - No risk factors (not critically ill): Observation
  - Treatment

- **Diagnostic testing**
  - Normal: No treatment
  - Abnormal: Treatment
## “Early-onset Sepsis and Risk Factors”

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence of Proven Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROM &gt; 18 hours</td>
<td>1%</td>
</tr>
<tr>
<td>Maternal + GBS (pre-prophylaxis era)</td>
<td>0.5-1.0%</td>
</tr>
<tr>
<td>Maternal + GBS (prophylaxis era)</td>
<td>0.1-0.2%</td>
</tr>
<tr>
<td>Maternal + GBS + other risk factors e.g., PROM)</td>
<td>4-7%</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>3-8%</td>
</tr>
<tr>
<td>GBS + and Chorioamnionitis</td>
<td>6-20%</td>
</tr>
<tr>
<td>PROM &amp; Preterm</td>
<td>4-6%</td>
</tr>
<tr>
<td>PROM &amp; low Apgar score</td>
<td>3-4%</td>
</tr>
</tbody>
</table>

Risk Factors are additive!
Estimating the Probability of Neonatal Early-Onset Infection on the Basis of Maternal Risk Factors

- Nested case control study of infants ≥ 34 weeks gestation
- Cases had early-onset sepsis (≤ 72 hours) n = 350 (1,063 controls)
- Rather than using cutoff values, risk factors were treated as continuous variables.
- The two best predictive values were the highest maternal temperature and gestational age, which accounted for 58% and 17% of the predictive model.

Puopolo et al Pediatrics 128: e1155, 2011
Rate of sepsis according to gestational age
Rate of sepsis according to duration of rupture of membranes
Rate of sepsis according to highest maternal intrapartum temperature
Probability of Neonatal Early-Onset Infection Based on Maternal Risk Factors for Infants > 34 weeks gestation

- Gestational age (weeks/days)
- Temperature
- ROM (Hours)
- GBS status (positive, negative, uncertain)
- Maternal intrapartum treatment (GBS specific or broad spectrum)
- Was IAP given ≥ 4 hours prior to delivery

Predicted probability(/1,000 live births) =


Puopolo et al 2011
Probability of Neonatal Early-Onset Infection Based on Maternal Risk Factors for Infants > 34 weeks gestation

- Gestational age (weeks/days) 37 weeks 2 days
- Temperature 38.0°C
- ROM (Hours) 26 hours
- GBS status (positive, negative, uncertain) Positive
- Maternal intrapartum treatment Broad spectrum
- Was IAP given ≥ 4 hours prior to delivery No

Predicted probability(/1,000 live births) = 1.61


Puopolo et al Pediatrics 128: e 1155, 2011
* Stratification of Risk Early-Onset Sepsis in Newborns > 34 weeks gestation

- Retrospective nested case (n = 350) control (n = 1063) study of infants ≥ 34 weeks gestation
- Probability of sepsis based on the risk estimation at birth (historical data – *pretest probability*) and the infant’s clinical presentation (clinical Illness, equivocal presentation or well appearing) during the first 6-12 hours of life (*post-test probability*). *Bayesian analysis*

*Pretest Probability*
Risk of sepsis based on historical data

*Clinical Presentation*

*Posterior Probability*

*Escobar et al Pediatrics 133: 30-36, 2014*
# Probability of Neonatal Early-Onset Infection Based on Maternal Risk Factors for Infants & Clinical Signs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Predicted probability (/1,000 live births)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well</td>
<td>0.66</td>
</tr>
<tr>
<td>Equivocal</td>
<td>7.98</td>
</tr>
<tr>
<td>Clinical Illness</td>
<td>32.97</td>
</tr>
</tbody>
</table>


*Escobar et al Pediatrics 133: 30-36, 2014*
Our patient: Age 2 hours, estimated gestational age = $37^{2/7}$ weeks, resolved respiratory distress; maternal colonization with group B streptococcus and PROM = 26 hrs, suspected chorioamnionitis.

What testing is indicated at this time?

- Blood culture
- White blood count and differential count
- C-reactive protein
**Blood cultures**

✶ *The key issue is the amount of blood drawn for culture!*

✶ Up to 1/4 of infants with sepsis have low colony count bacteremia* (4 CFU/ml or less) and two thirds of infants 0-2 months have colony counts < 10 CFU/ml**.

✶ In clinical practice the volume of blood inoculated is frequently less than 0.5 ml (the most often recommended amount).

✶ *Whenever possible send 1 ml for culture*

Ancillary Laboratory Studies
What is the Rationale for Adjunct Laboratory Tests?

- In a busy environment, observations occur sporadically.
- Early-onset bacterial sepsis occurs in infants that are initially asymptomatic.
- Tests with a high negative predictive accuracy offer reassurance to the busy clinician that infection is unlikely and allow discontinuation of antibiotics.
Neutrophil Indices Suggestive of Sepsis

\[ I/T > 0.2 \]

\[ \text{Band Count} > 2000/mm^3 \]

\[ \text{Neutropenia} < 8,000/mm^3 \text{ in a late preterm or term infant} \& < 2200mm^3 \text{ in a preterm infant} \]
When Should Laboratory Tests be Drawn

- Counts obtained immediately after birth are frequently normal. Therefore if sepsis is suspected, a count obtained 6-12 hrs following birth is more informative.
Management of Neonates with Suspected Sepsis
Management of Symptomatic Infants

- When sepsis is suspected because of abnormal signs, broad spectrum antibiotics should be given.
- However, some infants will become asymptomatic within 6 hours of birth as they undergo the transition to postnatal life; those infants can be observed (especially if there are no risk factors for sepsis).
Current Controversies

- Does suspected chorioamnionitis in the mother mandate treatment of the healthy-appearing newborn infant?
- Does early-onset sepsis occur in infants who appear completely well at birth?
- What is the relative value of a normal physical examination vs. screening laboratory studies or a blood culture?
Does the Diagnosis of Chorioamnionitis Identify Infants at High Risk for Neonatal Sepsis?
Chorioamnionitis as a Risk Factor

- The risk of sepsis in infants born to women with chorioamnionitis is strongly dependent on gestational age.
- In 3 recent studies the incidence of EOS in infants ≥ 35 weeks gestation born to women with clinical chorioamnionitis ranged from 0.47% to 1.24%
- In a preterm population, the rate of confirmed EOS ranged from 4.8%-16.9% (number of symptomatic babies unknown)**

What is the risk of Sepsis in the Asymptomatic Infant?

Low, but not zero!

Hashavya, Oma Flidel-Roman, Ottolini and Buckler
What is the risk of sepsis in the asymptomatic infant born to a woman with chorioamnionitis?

- Retrospective data from NICHD chorioamnionitis defined clinically or by placental histology.
- Sepsis defined as isolation of a pathogen from blood or CSF and treatment for at least 5 days.
- Infants with positive cultures were separated into those who were asymptomatic or symptomatic at birth.
- There were 389 cases of EOS out of 396,386 live births; 229 charts were available for review.

Wortham et al Pediatrics 2016
**What is the risk of sepsis in the asymptomatic Infant born to a woman with chorioamnionitis?**

- 87% of the infants were symptomatic. All infants who died were symptomatic within 6 hours of birth.
- 28% of term infants with sepsis were *asymptomatic*, but 22% of those developed symptoms with the first 72 hours.
- The authors estimated that 60-1400 well appearing newborns born to mothers with chorioamnionitis might receive empirical antibiotics for each initially asymptomatic infant with a confirmed infection.

Wortham et al Pediatrics 2016
Physical examination or laboratory testing in Asymptomatic infants?

- Clinical signs may not be present at birth: Therefore close observation of at-risk infants is mandatory!
Evaluation of **Asymptomatic Infants** ≥ 35 Weeks Gestation with Risk Factors for Sepsis (including chorioamnionitis/III):

- When chorioamnionitis / “III” is proven, some experts recommend empiric therapy with antibiotics
- Physical examination is better than any laboratory study, but not perfect

**Risk Factors**

1. Chorioamnionitis*
   - PROM ≥18 hours or IAP inadequate
2. Frequent Observation
3. Infant remains well; Discharge by 48 hours
Evaluation of Asymptomatic Infants < 35 weeks Gestation: Risk Factor – Chorioamnionitis/III (suspected or confirmed)

**Risk Factors**
- Chorioamnionitis

**Diagnostic Tests**
- Blood culture at birth
- WBC/Diff \(\pm\) CRP at age 6-12 hours

**Antibiotics**
- Broad spectrum antibiotics

**Management**
- Blood culture positive: Continue antibiotics
  - Lumbar puncture
- Blood culture negative
  - Infant remains well; Lab data reassuring: Discontinue antibiotics by 48 hours
Duration of Antimicrobial Therapy

- Whenever possible, antibiotics should be stopped by 48 hours if the cultures are negative and the infant remains asymptomatic.
- Antibiotics should be continued for 7 days in any critically ill infant.
Conclusions and Recommendations

- Neither identification of risk factors nor routine laboratory testing is of much value in the modern era.
- Babies with clinical signs of EOS should receive empiric antibiotic therapy.
- Asymptomatic late preterm infants and term infants, with risk factors for sepsis (including chorioamnionitis) can be closely observed without empiric therapy.
- Because of the high negative predictive accuracy of screening laboratory studies, diagnostic testing may be of value in deciding which infants need antibiotics and when antibiotics can be safely discontinued.
“A Successful Outcome to our case”

The blood culture was negative and because of the unremarkable laboratory values, the infant was only treated for 48 hours. As the infant grew up he became a politician and eventually became President of the United States.

“Nuculer”