Recent Advances in the Diagnosis and Prevention of Neonatal Sepsis

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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

※ Drawing a blood culture from a preterm infant (24 weeks gestation) is like drawing blood from worm (with small veins).

※ 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).
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 ampicillin.

<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. 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 decide to administer broad spectrum antibiotics because of possible chorioamnionitis. The infant appears well at birth.

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.
Pathogenesis of Chorioamnionitis

A. 

B. 

Chorioamnionitis

Subclinical Chorioamnionitis

Acute Chorioamnionitis
Microbes Responsible for Acute Chorioamnionitis & Subclinical Chorioamnionitis

**Acute chorioamnionitis**
Symptomatic mother

- Group B Streptococcus
- *Escherichia coli*
- *Streptococcus viridans*

- Fulminant sepsis at birth
- Respiratory distress
- Cardiovascular instability

**Subclinical chorioamnionitis**
Preterm labor or completely asymptomatic

- *Ureaplasma urealyticum*
- *Mycoplasma hominis*
- *Gardnerella vaginalis*

- Variable symptoms at birth
- Brain injury
- Chronic Lung Disease

*~25% of infants < 1500 g are bacteremic with one of those organisms at birth.*
The Uterus is not Sterile even in Term Pregnancies with no Labor and Intact Membranes

The Microbiology of Intrauterine Infections is Complex

PTL: intact membranes

PPROM

DiGiulio DB. Semin Fetal Neonatal Med 2012
Does the Woman in this Case History Have Chorioamnionitis?

Fever and painful uterine contractions

Epidural
The clinical significance of fever following an epidural is controversial. There is an increased risk of fever following an epidural (RR 3.67 – CI 2.77-4.86); however, most women with intrapartum fever elevation after an epidural have no evidence of infection.
Diagnosis of Chorioamnionitis

- The diagnosis of chorioamnionitis is problematic (and frequently inaccurate).
- At term gestation, histologic (grade 2) chorioamnionitis is common (8%), but almost always non-infectious (4%).
- Fever is often used as the sole criteria for chorioamnionitis by obstetricians.
- Fever is significantly more common in women with chorioamnionitis (69%), but is also common in women without chorioamnionitis (26%).

Roberts et al PLoS one 2013
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

### How Good are the Diagnostic Criteria?

<table>
<thead>
<tr>
<th>Clinical Diagnostic Criteria</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>95-100%</td>
</tr>
<tr>
<td>Maternal tachycardia</td>
<td>50-80%</td>
</tr>
<tr>
<td>Fetal tachycardia</td>
<td>40-70%</td>
</tr>
<tr>
<td>Fundal tenderness</td>
<td>4-25%</td>
</tr>
<tr>
<td>Foul-smelling discharge</td>
<td>5-22%</td>
</tr>
</tbody>
</table>
Does a History of Chorioamnionitis Identify Infants at High Risk for Neonatal Sepsis?
## Chorioamnionitis and the Risk of Neonatal Sepsis

<table>
<thead>
<tr>
<th></th>
<th>22 wk</th>
<th>23 wk</th>
<th>24 wk</th>
<th>25 wk</th>
<th>26 wk</th>
<th>27 wk</th>
<th>28 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic</td>
<td>70%</td>
<td>61%</td>
<td>59%</td>
<td>51%</td>
<td>48%</td>
<td>41%</td>
<td>34%</td>
</tr>
<tr>
<td>chorioamnionitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>28%</td>
<td>26%</td>
<td>20%</td>
<td>19%</td>
<td>19%</td>
<td>15%</td>
<td>14%</td>
</tr>
<tr>
<td>chorioamnionitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early-onset sepsis</td>
<td>6%</td>
<td>4%</td>
<td>4%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

© Stoll et al Pediatrics 126: 443-456, 2010
The infant is delivered at 37\(^{2}/7\) weeks gestation following rupture of membranes for 26 hours. Intrapartum antibiotics (ampicillin and gentamicin) were given to the mother (< 4 hours prior to delivery. He was suctioned and dried by the nurse and placed on NPCPAP with 21\% O\(_2\). 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

Critical Ill Symptomatic

Observe

Diagnostic testing

No risk factors (not critically ill)

Asymptomatic and Risk Factors

Chorioamnionitis

Treatment

Abnormal

Other risk factors (e.g., PROM)

Normal

No treatment

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

![Graph showing the rate of sepsis according to gestational age.](image-url)
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) 34 weeks 2 days
- Temperature 101.0° F
- 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) = $10.11$


Puopolo et al 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*
Stratification of Risk Early-Onset Sepsis in Newborns > 34 weeks gestation

<table>
<thead>
<tr>
<th>SEPSIS RISK AT BIRTH</th>
<th>CASES</th>
<th>CONTROLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.65</td>
<td>55.7%</td>
<td>93.7%</td>
</tr>
<tr>
<td>0.65 - 1.54</td>
<td>23.1%</td>
<td>5.08%</td>
</tr>
<tr>
<td>≥1.54</td>
<td>21.7%</td>
<td>1.22%</td>
</tr>
</tbody>
</table>
Stratification of Risk Early-Onset Sepsis

Prior Probability: Sepsis risk based on maternal risk factors

<table>
<thead>
<tr>
<th></th>
<th>&lt;0.65</th>
<th>0.65-1.54</th>
<th>≥ 1.54</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Well appearing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability sepsis (Posterior)</td>
<td>0.11</td>
<td>1.08</td>
<td>6.74</td>
</tr>
<tr>
<td>NNT</td>
<td>9370</td>
<td>923</td>
<td></td>
</tr>
<tr>
<td></td>
<td>148</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Equivocal presentation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability sepsis (Posterior)</td>
<td>1.31</td>
<td>11.07</td>
<td></td>
</tr>
<tr>
<td>NNT</td>
<td>763</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Illness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability sepsis (Posterior)</td>
<td>4.66</td>
<td></td>
<td>62.9</td>
</tr>
<tr>
<td>NNT</td>
<td>214</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

Escobar et al Pediatrics 133: 30-36, 2014
<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Sepsis Risk at Birth Estimated from Maternal Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.65/1000 live births</td>
</tr>
<tr>
<td>Well Appearing</td>
<td>Continued Observation</td>
</tr>
<tr>
<td></td>
<td>85% of live births</td>
</tr>
<tr>
<td></td>
<td>NNT = 9,370</td>
</tr>
<tr>
<td>Equivocal Presentation</td>
<td>Observe and Evaluate</td>
</tr>
<tr>
<td></td>
<td>11% of live births</td>
</tr>
<tr>
<td></td>
<td>NNT = 823</td>
</tr>
<tr>
<td>Clinical Illness</td>
<td></td>
</tr>
</tbody>
</table>
Our patient: Age 2 hours, estimated gestational age = 37²/₇ 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).

**Blood Culture Volumes**

<table>
<thead>
<tr>
<th>Blood culture vol.</th>
<th>CFU = 4 / ml</th>
<th>CFU = 1 / ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 ml</td>
<td>0.81</td>
<td>0.36</td>
</tr>
<tr>
<td>1.0 ml</td>
<td>0.92</td>
<td>0.60</td>
</tr>
<tr>
<td>2.0 ml</td>
<td>0.99</td>
<td>0.82</td>
</tr>
</tbody>
</table>

*Whenever possible, try to send 1 ml for culture.*

* Schelonka R L et al J Ped 1996*
The reliability of a blood culture depends on the volume of blood drawn.

An Interventional Study

✓ An adequate volume of blood was considered ≥ 0.5 ml up to one month of age (in this study adequate volumes increased from 65% to 82%).
✓ Blood cultures with an adequate volume were twice as likely to yield a positive result.

Ancillary Laboratory Studies
Laboratory Testing

Sensitivity
Specificity
Positive predictive accuracy
Negative predictive accuracy*

*The purpose of testing is to exclude infection in healthy babies
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 (Escobar 2000).
- Tests with a high negative predictive accuracy offer reassurance to the busy clinician that infection is unlikely.
## Predictive Values of Adjunctive Laboratory Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPA</th>
<th>NPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC ≤ 1750</td>
<td>38-96%</td>
<td>61-92%</td>
<td>20-77%</td>
<td>96-99%</td>
</tr>
<tr>
<td>I/T ≥ 0.2</td>
<td>90-100%</td>
<td>30-78%</td>
<td>11-51%</td>
<td>99-100%</td>
</tr>
<tr>
<td>I/T ≥ 0.25</td>
<td>45%</td>
<td>84%</td>
<td>6%</td>
<td>98%</td>
</tr>
<tr>
<td>I/T ≥ 0.3</td>
<td>35%</td>
<td>89%</td>
<td>7%</td>
<td>98%</td>
</tr>
<tr>
<td>CRP ≥ 1.0 mg/dl</td>
<td>70-93%</td>
<td>78-94%</td>
<td>7-43%</td>
<td>97-99.5%</td>
</tr>
<tr>
<td>Sepsis screen</td>
<td>100%</td>
<td>83%</td>
<td>27%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Gerdes JS Pediatric Clinics of North America 51: 939, 2004*
White Blood Count and Neutrophil Indices

- The normal range for the total white blood count is broad and not usefully clinically, unless it is low (< 5,000/mm³).

- Neutrophil indices: absolute PMN count, absolute band count and the immature to total neutrophil (I/T) ratio are more informative.

- The most sensitive index is the I/T and most specific is neutropenia, but none of them have a good positive predictive accuracy.
Neutrophil Indices Suggestive of Sepsis

$I/T > 0.2$

$\textit{Band Count} > 2000/mm^3$

$\textit{Neutropenia} < 8,000/mm^3 \text{ in a late term or term infant}$

& $< 2200/mm^3 \text{ in a preterm infant}$
Absolute Neutrophil Counts

Counts obtained immediately after birth are frequently normal. Therefore if sepsis is suspected, a count obtained 6-12 hrs following birth is more informative.
Interpreting Complete Blood Counts Shortly After Birth

- Retrospective cross-sectional study of term and late-preterm infants (> 34 weeks) who had a blood culture and CBC within 1 hour of each other.
- Confirmed infection n = 245, no infection n = 67,623
- The ability of the ANC and WBC to discriminate infected from non-infected infants improved between < 1 hour, 1-4 hours and ≥ 4 hours

Newman et al Pediatrics 126: 903-90, 2010
Interpreting Complete Blood Counts Shortly After Birth

Newman et al Pediatrics 126: 903-90, 2010
C-reactive Protein & Neonatal Sepsis

[*] CRP is an acute phase reactant synthesized within 6-8 hours of an infective process with a half-life of 24-48 hours.

* Sensitivity improves (> 90%) if the first determination is obtained 6-12 hours following birth.

* When a cutoff value of $\geq 1$ mg/dl is used, CRP has a high negative predictive accuracy (97-99.5%).

* A variety of non-infectious/stress conditions can elevate the CRP.

* CRP levels may be slow to normalize, limiting their value in following the response to antibiotics.
Algorithms for Diagnosis and Management of Neonatal Sepsis

Major Risk Factors for Neonatal Sepsis

- PROM > 18 hours, signs and symptoms of chorioamnionitis, colonization with GBS*
- Prematurity

*GBS is not a risk factor if there has been adequate intrapartum treatment or the infant is delivered by elective cesarean section with intact membranes and no labor
Evaluation of Asymptomatic Infants (any gestational age)
Risk Factor — Chorioamnionitis

Risk Factors
- Chorioamnionitis\(^a\)

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

Antibiotics
- Broad spectrum antibiotics

Management
- Blood culture negative
  - Infant remains well; Lab data reassuring
  - Discontinue antibiotics by 48 hours
- Blood culture positive
  - Continue antibiotics
  - Lumbar puncture\(^b\)
Evaluation of Asymptomatic Infants ≥ 37 Weeks Gestation with Risk Factors for Sepsis: (No chorioamnionitis)

Risk Factors

PROM ≥18 hours & IAP inadequate

Observation

Frequent observations possible
No testing needed

Infant remains well; Discharge by 48 hours
Evaluation of Asymptomatic Infants (< 37 weeks) with Risk Factors for Sepsis: (No chorioamnionitis)

Risk Factors
- PROM ≥18 hours or IAP inadequate

Diagnostic Tests
- WBC/Diff ± CRP at age 6-12 hours

Management

Lab data abnormal
- Blood Culture & Broad Spectrum Antibiotics
  - Blood culture positive: Continue antibiotics, Lumbar puncture

Lab data normal
- Infant remains well: No antibiotics needed
  - Infant remains well: Discontinue antibiotics after 48-72h
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.
In a multivariate analysis (adjusted for confounding variables) prolonged therapy with antibiotics (≥ 5 days) in the first few days of life was associated with increased mortality, NEC or the combined outcome of death and NEC.

**Prolonged initial empirical antibiotic treatment**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC or Death</td>
<td>1.30 (1.10-1.54)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>NEC</td>
<td>1.21 (0.98-1.51)</td>
<td>.08</td>
</tr>
<tr>
<td>Death</td>
<td>1.46 (1.19-1.78)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Retrospective cohort study of 4039 ELBW infants who survived at least 5 d.
Conclusions

★ Infants with signs indicative of sepsis should be treated with broad spectrum antibiotics after appropriate cultures are taken.
★ The physical examination is as valuable as any laboratory test.
★ Well-appearing, “at-risk” infants should not be treated more than 48 hours if the blood culture is negative and the infant remains well.
★ Critically ill babies (with negative cultures) should be treated for 7 days with broad spectrum antibiotics.
“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”