Recent Advances in the Diagnosis and Prevention of Neonatal Sepsis

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Disclosure Statements

✶ I have no relevant financial relationships to disclose or conflicts of interest to resolve.

✶ I will not discuss any unapproved or off-label, experimental or investigational use of a product, drug or device
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 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

Causes of death in the NICU

- EP/ELBW: 14%
- NEC: 10%
- Lung hypoplasia: 10%
- RDS: 8%
- BPD: 3%
- Pulmonary hemorrhage: 2%
- Airleak: 0.6%
- IVH/ICH: 9%
- Sepsis ≤7 days: 5%
- Sepsis >7 days: 7%
- Lethal anomaly: 8%
- Genetic syndrome: 5%
- CDH: 6%
- Major heart defects: 3%
- Shock/anemia: 10%
- Renal failure: 6%
- Other: 1.1%
- HIE: 6%
- Sepsis ≤7 days: 5%
- Sepsis >7 days: 7%
- Lethal anomaly: 8%
- Genetic syndrome: 5%
- CDH: 6%
- Major heart defects: 3%
- Shock/anemia: 10%
- Renal failure: 6%
- Other: 1.1%

Proportionate Mortality for Major Causes of Death, According to Postnatal Age.

The Case Begins

This was the first pregnancy for a 22 year-old woman with an unremarkable pre-pregnancy history. At 37\(2/7\) weeks gestation, her membranes rupture at 2:00 PM. 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.
Varieties of 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

Term Not in Labor (22)
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

The sensitivities of the diagnostic criteria are highly variable

<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>
Problems with the Current Definition of Chorioamnionitis

- Chorioamnionitis refers to a heterogeneous group of conditions in which inflammation or infection may predominate and intrauterine structures other than the chorion or amnion may be involved.
- The term does not convey the severity of maternal or fetal illness.
- The diagnosis generally represents a “guess” on the part of the obstetrical provider, before laboratory data are available (lacks precision).
- The source of fever may be extrauterine and may not represent an infectious process in the chorion or amnion.
Problems with the Current Definition of Chorioamnionitis

- 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%).

Epidural anesthesia

Roberts et al PLoS one 2013
Maternal fever, Chorioamnionitis and Epidural Anesthesia

- 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.
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° C (100.4°F) to 39° C (102.2° F) at least 30 minutes apart or one oral temperature >39°C (102.2 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.
CDC Recommendations 2010

Signs of neonatal sepsis?

- yes → Full diagnostic evaluation*
  → Antibiotic therapy

- no → Maternal chorioamnionitis?

- yes → Limited evaluation ‡
  → Antibiotic therapy

- no →

* Includes CBC with differential, platelets, blood culture, chest radiograph (if respiratory abnormalities are present), and LP (if patient stable enough to tolerate procedure)

‡ Includes blood culture (at birth) CBC with differential & platelets. The optimal timing of the CBC is 6-12 hours of age.
Evaluation of *Asymptomatic Infants* Risk Factor - Chorioamnionitis

**AAP Recommendation 2012**

- **Risk Factors**: Chorioamnionitis
- **Diagnostic Tests**: Blood culture at birth, WBC/Diff ± CRP at age 6-12 hours
- **Antibiotics**: Broad spectrum antibiotics
- **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 Guidelines

- Retrospective analysis of infants born 2009-2012 born at a single perinatal center (Brigham and Women’s Hospital).
- Over the course of the study more than 2200 nursing hours were required to evaluate 1396 (asymptomatic) infants, including 896 infants who received antibiotics at an estimated cost of $400,000.
- The efforts detected only 2 EOS cases.

Mukhopadhyay et al Pediatrics 2014
When managed according to a strategy similar to recent COFN guidelines, a large number of term and late preterm infants exposed to chorioamnionitis (with sterile blood cultures) were treated with prolonged antibiotic therapy (≥ 7 days) solely based on abnormal laboratory values.

Kiser et al Pediatrics 2014
Consequences of NICE Guidelines

✶ Comparison of two time periods before and after implementation of the guidelines at a single center.
✶ Greater consistency with national guidelines
✶ More babies had longer courses of antibiotics and increased length of stay

Mukherjee et al  ADC-FNN 2014
Case continued

* The infant is delivered at 37\(\frac{2}{7}\) 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\% \text{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

- **Critically Ill Symptomatic**
  - No risk factors (not critically ill)
  - Treatment
  - Diagnostic testing
  - Observation

- **Asymptomatic and Risk Factors**
  - Treatment
  - Diagnostic testing

- **Diagnostic testing**
- **Observation**

- **Treatment**
- **Abnormal**
- **Normal**
- **No 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 \( \geq 34 \) weeks gestation
- Cases had early-onset sepsis (\( \leq 72 \) 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.

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

## 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 $\geq 0.5$ 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.*

Results from Cultures (Day of Birth or Day 1 or 2)

- Negative cultures: 608743 (98%)
- Positive cultures: 12006 (2%)
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, but at a low incidence (Escobar 2000).
- Tests with a high negative predictive accuracy offer reassurance to the busy clinician that infection is unlikely and allow discontinuation of antibiotics.
## 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

\[ I/T > 0.2 \]

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

Neutropenia < 8,000/mm\(^3\) in a late preterm or term infant & < 2200/mm\(^3\) in a preterm infant
Counts obtained immediately after birth are frequently normal. Therefore if sepsis is suspected, a count obtained 6-12 hrs following birth is more informative.
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 $\geq 1 \text{ mg/dl}$ is used, CRP has a high negative predictive accuracy (97-99.5%).
- A variety of non-infectious/stress conditions can elevate the CRP.
Management of Neonates with Suspected Sepsis
The Incidence of Sepsis has Decreased

- With the implementation of IAP, there has been an 85% reduction in the incidence of early-onset GBS sepsis (1.8 >> 0.25 / 1,000 live births).
- The attack rate for other pathogens has similarly decreased (< 1/1,000 live births) and for infant ≥ 34 weeks the incidence is only 0.4-0.5.
The Incidence of Sepsis has Decreased

- From a Bayesian perspective the “prior probability” of sepsis based on historical risk factors has decreased substantially from the time the CDC/AAP recommendations were developed.

- Do the Old Rules Still Apply?
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 is a risk factor for EOS in Term Infants

- Among infants > 37 weeks gestation with proven early-onset sepsis, clinical chorioamnionitis was documented in the medical record about 1/3 of the time (histological chorioamnionitis was documented in 90%)*
- Almost all infants with EOS following chorioamnionitis are symptomatic. (20% of the infected term infants in the Stoll study appeared healthy and were admitted to the well newborn nursery)

* Stoll et al Pediatrics 127:817, 2011
## Chorioamnionitis and the Risk of EOS in Preterm Infants

<table>
<thead>
<tr>
<th>Clinical chorioamnionitis</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></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>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
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?

- Hashavya et al: among 1413 asymptomatic infants born to women who were carriers for GBS, 0 cases of EOS
- Oma Flidel-Romin et al: only one positive blood culture in a preterm infant among 1662 at-risk asymptomatic infants (18% were < 34 weeks gestation)
- Ottolini et al reported 0 cases of EOS among at-risk, asymptomatic infants ≥ 35 weeks gestation.
- Buckler et al reported 0 cases of EOS among 242 asymptomatic at-risk infants > 37 weeks gestation.
What is the risk of Sepsis in the Asymptomatic Infant?

Almost 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.
★ What is the risk of sepsis in the asymptomatic Infant born to a woman with chorioamnionitis?

★ Clinical and histologic chorioamnionitis 48%: histologic alone (34%) and clinical alone (18% with negative histology)

★ 87% received antibiotics within 6 hours of birth; 93% of preterm infants and 77% of term infants.

★ Deaths were attributed to infection in 74% of infected infants

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.
★ What are this Study’s Limitations

★ How many of the women in this study actually had chorioamnionitis?

★ How many of the asymptomatic infants were born to women who had maternal fever as their only symptom?

★ Does a positive blood culture always signify sepsis or can it represent “benign” transient bacteremia?

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

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**Risk Factors**

- Chorioamnionitis*
  - PROM ≥18 hours or IAP inadequate

  - Frequent Observation

  - Infant remains well; Discharge by 48 hours
Evaluation of Asymptomatic Infants < 35 weeks Gestation: Risk Factor – Chorioamnionitis/III (suspected or confirmed)

**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 positive
  - Continue antibiotics
  - Lumbar puncture\(^b\)
- Blood culture negative
  - Infant remains well; Lab data reassuring
  - Discontinue antibiotics by 48 hours
Evaluation of Asymptomatic Infants (< 35 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

**Lab data highly suggestive of sepsis**
- Blood Culture & Broad Spectrum Antibiotics

- Blood culture positive
  - Continue antibiotics
  - Lumbar puncture

- Blood culture negative
  - Infant remains well

**Lab data normal**
- Infant remains well
- No antibiotics needed

**Discontinue antibiotics after 48h**
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”