Stratification of Risk of Early-Onset Sepsis in Newborns ≥ 34 Weeks Gestation

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Dr. Puopolo has disclosed the following financial relationships. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

<table>
<thead>
<tr>
<th>Affiliation / Financial Interest</th>
<th>Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant</td>
<td>Novartis Vaccines</td>
</tr>
</tbody>
</table>
Epidemiology of EOS Among Term Infants: What Do We Know?
Definition of Neonatal EOS

- Culture-proven invasive infection (blood or CSF) that occurs from birth to 6 days of age
- Most perinatal practitioners are concerned about infection in first 24-48 hours of life
- We will not be discussing “culture-negative sepsis” today
Impact of GBS Prophylaxis on EOS at Brigham and Women’s Hospital

* p < 0.0001 for comparison of ‘90-’96 and ‘97-’07

Puopolo and Eichenwald (2010) Pediatrics 125:e1031; and unpublished data
### Incidence of EOS Among Infants Born ≥ 37 Weeks

<table>
<thead>
<tr>
<th>Reference</th>
<th>Site</th>
<th>Years</th>
<th>Number of cases</th>
<th>Incidence per 1000 live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weston, et al (2011)</td>
<td>CDC multi-state surveillance</td>
<td>2005-2008</td>
<td>658</td>
<td>0.77 (0.40 non-black) (0.89 black)</td>
</tr>
</tbody>
</table>

Among infants with BW < 1500 g: EOS incidence ~11/1000

Microbiology of Neonatal EOS

- Mortality from EOS primarily among preterm infants
  - Overall 10.8%
  - < 37 weeks: 22.8%
  - ≥ 37 weeks: 1.6%

Identifying Infants at Risk for EOS
(It Shouldn’t Be So Hard…)

Pennsylvania Hospital
Penn Medicine
Pathogenesis

- Concept that bacterial (unlike viral) neonatal sepsis has an *in utero* pathogenesis
- Most EOS due to ascending colonization and subsequent infection of uterine compartment, (amniotic fluid, placenta, umbilical cord and fetus) with normal flora of maternal GU/GI tracts

Risk Factors for EOS

- **Maternal**
  - Age
  - Black race
  - Intrapartum fever
  - “Chorioamnionitis”
  - Duration of ROM
  - GBS colonization
  - Intrapartum antibiotics
  - Meconium-stained amniotic fluid
  - “Foul-smelling” amniotic fluid
  - Obstetrical interventions

- **Neonatal**
  - Gestational age
  - Birth weight
  - Twin gestation
  - Fetal tachycardia
  - Postnatal distress
  - [CBC and CRP abnormalities]

CDC 2010 Guidelines: Management of Newborns

- EOS evaluation and empiric treatment of:
  - all infants who are not well-appearing
  - all infants if born to a mother with chorioamnionitis

- In the event of inadequate indicated GBS prophylaxis
  - EOS evaluation of preterm infants
  - EOS evaluation of term infants if ROM > 18 hours
AAP Committee on the Fetus and Newborn

Risk Factors
- PPROM ≥18 h or IAP indicated, but inadequate

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

Antibiotics
- No antibiotics needed, observation

Management
- Lab data abnormal
  - Blood Culture
    - Blood culture negative
      - Infant remains well, discharge by 48 h
- Lab data normal
  - Infant remains well, discharge by 48 h

Polin and COFN (2012) Pediatrics
EOS Evaluation Practice Survey

• EOS policies at Level II and III newborn centers in Massachusetts
  – Risk factors
  – Diagnostic tests for evaluation
  – Criteria for empiric antibiotics

• Data collection
  – Web-based survey (Partners Redcap)
  – Telephone call to the units

• Responses from 15 centers (80% of Level III)

Mukhopahyay and Puopolo (2014) unpublished data
Risk Factors Considered in EOS Evaluation

- Gestational Age < 37 wks
- ROM > 18 hrs
- Inadequate GBS IAP
- Chorioamnionitis
- Maternal Fever ≥101F
- Maternal Fever ≥101F
- Fetal Tachycardia
- Others

% of EOS Protocols Obtained

Other considerations: (1) Presence of epidural for interpretation of maternal fever; (2) Intrapartum antibiotics for interpretation of blood culture
Diagnostic Tests Included in EOS Evaluation

- Lumbar puncture
- CRP
- CBC with diff
- Blood culture
Indications for Empiric Antibiotics

Others* include (1) Presence of any 2 risk factors or (2) <37 weeks with any other risk factor.
Basis for EOS Protocols

• For infants born to mothers with inadequate indicated GBS intrapartum prophylaxis, protocols obtained were aligned with
  – CDC 2010 (11)
  – AAP/COFN (2)
  – CDC 2002 (1)
  – Missing treatment information (1)
BWH Local Algorithm for EOS Evaluation of Well-Appearing Infants Born ≥ 35 weeks Gestation

Based on CDC 2002 Guidelines

Notes: (1) Mother with previous child with GBS disease: The infant should have a CBC and blood culture drawn and antibiotics given if there is IAP < 4 hours prior to delivery, or if there is maternal fever ≥ 100.4°

(2) Maternal fever that occurs within one hour of delivery should be treated like intrapartum fever, and the infant should be evaluated as outlined above.

THESE ARE GUIDELINES ONLY AND SHOULD NOT SUBSTITUTE FOR CLINICAL JUDGEMENT.
EOS Evaluations Among ≥ 35 week Well-Appearing Infants, BWH 2008-2009

- ~15% all well-appearing infants born ≥ 35 weeks were evaluated for EOS
- ~8% were treated empirically with antibiotics

BWH Local Algorithm for EOS Evaluation of Well-Appearing Infants Born ≥ 35 weeks Gestation

Based on CDC 2010 Guidelines

Guidelines for the Management of Asymptomatic Infants Born at ≥ 35 weeks Gestation at Risk for Early-Onset Sepsis

- No Maternal Fever
  - GBS + or GBS unknown
    - Routine Care
      - Yes: Adequate GBS prophylaxis given?
        - No: Blood culture, CBC per guideline
          - GA < 37 weeks or ROM ≥ 18 hours
        - Yes: Blood culture, CBC per guideline
          - GA ≥ 37 weeks or ROM < 18 hours
    - No: Maternal Fever 100.4°F - 100.9°F
      - GA < 37 weeks or ROM ≥ 18 hours or GBS +/GBS unknown and adequate GBS prophylaxis NOT given
        - No: Maternal Fever ≥ 101°F
          - Blood culture, CBC per guideline
            - Ampicillin 150 mg/kg IV q12 hrs
            - Gentamicin 4 mg/kg IV q24 hrs

Adequate GBS prophylaxis =
- penicillin G, ampicillin or cefazolin given ≥ 4 hours prior to delivery

Inadequate GBS prophylaxis =
- any antibiotic given < 4 hours prior to delivery or any other antibiotic for any duration

CBC Recommendations by Postnatal Age:
- ≤ 1 hour: do not obtain CBC
- 1-4 hours: CBC not recommended. If obtained, repeat at 6-12 hours to guide treatment decisions.
- > 4 hours: obtain CBC with blood culture

Following values should raise concern for infection:
- WBC < 5000
- ANC < 2000
- I/T ratio ≥ 0.3

ADDITIONAL NOTES

1. Chorioamnionitis is an obstetrical clinical diagnosis made on the basis of clinical findings, laboratory data and fever. If obstetrical staff diagnose chorioamnionitis, the infant should be evaluated for sepsis and receive empiric antibiotic treatment.
2. Maternal fever that occurs within one hour of delivery should be treated like intrapartum fever, and the infant should be evaluated as outlined above.
3. Women with a previous infant with GBS disease should receive intrapartum GBS prophylaxis.
4. Blood cultures should consist of aerobic and anaerobic bottles with minimum 1 cc blood in each bottle.
5. To facilitate family bonding and initiation of breastfeeding, the sepsis evaluation can be delayed for up to one hour after birth, at the discretion of the obstetrical and neonatal caregivers.

These are guidelines only and should not substitute for clinical judgment.

Revised 3/22/2011
6.8% all well-appearing infants born ≥ 36 weeks were evaluated for EOS and 5.2% were treated empirically with antibiotics.

Overall 13.3% evaluated and ~12% treated.
Can We Do Better?

• Could we safely evaluate *fewer* infants and still identify the infected ones?

• Can we *discriminate* better between at-risk infants?
  – Potentially treat fewer infants by identifying those at highest risk

• Can we define risk without using the clinical diagnosis of *chorioamnionitis*?
Multivariate Approach to Identifying Infants at Risk for EOS

(Maybe It Can Be Easier...)

The Children’s Hospital of Philadelphia®
Multivariate Models of EOS Risk

- Algorithms based on cutoff values can waste information

  - There is usually information below the cutoff, as well as differential information above the cut-off

- Univariate consideration of risk factors doesn’t account for interactions between predictors
Risk of EOS: The Bayesian Perspective

• Begin with the population risk (i.e., all you know is that it is a term baby born at 34 weeks or above)
  – Prior probability of EOS

• Add the information you get before you even look at the baby (i.e., maternal fever, duration of ROM, GBS status) and modify the population risk
  – Modified prior probability of EOS

• Add the baby’s clinical status (i.e., now you examine the baby)
  – Final posterior probability of EOS

• Make your decision to evaluate +/- empirically treat the baby for EOS
Risk of EOS Among Infants ≥ 34 weeks

• Nested case-control study in era of GBS prophylaxis

• Goal → to develop a quantitative model to estimate the probability of early-onset bacterial infection based on maternal risk factors and infants’ initial clinical status

• Used only objective data to allow for multivariate computation

Study Design

- **Nested case-control study with Case Infants**
  - GA ≥ 34 weeks with culture-confirmed bacterial infection in first 72 hrs of life
  - No major anomalies

- **Control Infants**
  - Same criteria without culture-proven infection, randomly selected from the total birth cohort
  - Matched for birth hospital and year of birth

- **Data collection**
  - Maternal/infant from hospital admission leading to birth
  - Basic demographic dataset collected for all births ≥ 34 weeks gestation
Sepsis Study Population

Total Birth Cohort
≥ 34 weeks
608,014

Kaiser-Permanente
12 California sites
418,755 births
195 cases
684 controls
1995-2007

Brigham and Women’s
Boston, MA
127,239 births
131 Cases
305 Controls
1993-2007

Beth-Israel Deaconess
Boston, MA
62,020 births
24 Cases
74 Controls
1995-2007

Total 350 cases, 1063 controls
Overall EOS incidence 0.58 cases/1000 live births
Gestational Age and Case Organism Distribution

- **Gestational Age**
  - 34-36 wks: 8.4%
  - 37-40 wks: 76.6%
  - 41+ wks: 15.1%

- **Case Organisms**
  - GBS: 53.1%
  - *E. coli*: 20.3%

- ~20% of *control* deliveries treated with intrapartum antibiotics
### Bivariate Analyses

<table>
<thead>
<tr>
<th></th>
<th>Controls (%)</th>
<th>Cases (%)</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37-40 wks</td>
<td>79.7</td>
<td>67.1</td>
<td>Reference</td>
</tr>
<tr>
<td>34-36 wks</td>
<td>6.5</td>
<td>14.0</td>
<td>2.56 (1.73-3.79)</td>
</tr>
<tr>
<td>≥41 wks</td>
<td>13.8</td>
<td>18.9</td>
<td>1.62 (1.17-2.24)</td>
</tr>
<tr>
<td><strong>Duration of ROM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 12 hrs</td>
<td>81.2</td>
<td>53.6</td>
<td>Reference</td>
</tr>
<tr>
<td>12-17.99 hrs</td>
<td>9.7</td>
<td>23.4</td>
<td>3.65 (2.61-5.11)</td>
</tr>
<tr>
<td>18-23.99 hrs</td>
<td>4.5</td>
<td>8.3</td>
<td>2.81 (1.71-4.62)</td>
</tr>
<tr>
<td>≥ 24 hrs</td>
<td>4.7</td>
<td>14.8</td>
<td>4.81 (3.14-7.38)</td>
</tr>
</tbody>
</table>
Rate of EOS by Duration of ROM

![Graph showing the rate of EOS by duration of ROM](image-url)
Bivariate Analyses

<table>
<thead>
<tr>
<th>Highest maternal temperature</th>
<th>Controls (%)</th>
<th>Cases (%)</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100.5</td>
<td>95.3</td>
<td>70.0</td>
<td>Reference</td>
</tr>
<tr>
<td>100.5-101.4</td>
<td>3.9</td>
<td>13.1</td>
<td>4.53 (2.91 – 7.04)</td>
</tr>
<tr>
<td>101.5-102.4</td>
<td>0.7</td>
<td>9.7</td>
<td>20.08 (8.8 – 45.84)</td>
</tr>
<tr>
<td>&gt;102.5</td>
<td>0.1</td>
<td>7.1</td>
<td>103.37 (13.94 – 766.56)</td>
</tr>
</tbody>
</table>

In the era of GBS IAP, maternal GBS status was NOT a significant predictor on bivariate analysis
Rate of EOS by Highest Maternal Temperature
# Bivariate Analyses

<table>
<thead>
<tr>
<th>Intrapartum Abx</th>
<th>Controls (%)</th>
<th>Cases (%)</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>80.2</td>
<td>68.0</td>
<td>Reference</td>
</tr>
<tr>
<td>Any Abx</td>
<td>19.8</td>
<td>32.0</td>
<td>1.91 (1.45-2.49)</td>
</tr>
<tr>
<td>GBS IAP</td>
<td>18.7</td>
<td>29.0</td>
<td>1.77 (1.34-2.35)</td>
</tr>
<tr>
<td>Broad-spectrum Abx</td>
<td>4.4</td>
<td>22.2</td>
<td>6.25 (4.11-9.5)</td>
</tr>
<tr>
<td>Abx &lt; 4 hrs PTD</td>
<td>81.2</td>
<td>53.6</td>
<td>Reference</td>
</tr>
<tr>
<td>Abx ≥ 4 hrs PTD</td>
<td>9.7</td>
<td>23.4</td>
<td>3.65 (2.61-5.11)</td>
</tr>
<tr>
<td>Delivery anesthesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No epidural</td>
<td>43.0</td>
<td>24.3</td>
<td>Reference</td>
</tr>
<tr>
<td>Epidural</td>
<td>57.0</td>
<td>75.7</td>
<td>2.4 (1.79-3.09)</td>
</tr>
</tbody>
</table>
### Components of Multivariate Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable Type</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBS status</td>
<td>Categorical</td>
<td>Negative, positive, unknown</td>
</tr>
<tr>
<td>Gestational age</td>
<td>Continuous</td>
<td>GA in weeks, specified to day; (GA) and (GA)^2</td>
</tr>
<tr>
<td>Duration of ROM</td>
<td>Continuous</td>
<td>Transformed ROM time [ROM in hrs +0.05]^{0.2}</td>
</tr>
<tr>
<td>Highest intrapartum maternal temperature</td>
<td>Continuous</td>
<td>Value to 0.1°F</td>
</tr>
<tr>
<td>Intrapartum antibiotics:</td>
<td></td>
<td>Indicator variables: 3 mutually-exclusive values</td>
</tr>
<tr>
<td>GBS IAP</td>
<td>Categorical</td>
<td>- No intrapartum abx</td>
</tr>
<tr>
<td>Broad Spectrum abx</td>
<td></td>
<td>- GBS IAP or and abx not given on time</td>
</tr>
<tr>
<td>On time: first dose given ≥ 4 hrs PTD</td>
<td></td>
<td>- Broad-spectrum abx given on time</td>
</tr>
</tbody>
</table>
## Multivariate Model

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational Age</strong></td>
<td>0.001 (0.0001 – 0.014)</td>
</tr>
<tr>
<td><strong>GBS Negative</strong></td>
<td>Reference</td>
</tr>
<tr>
<td><strong>GBS Positive</strong></td>
<td>1.78 (1.11 – 2.85)</td>
</tr>
<tr>
<td><strong>GBS Unknown</strong></td>
<td>1.04 (0.76 – 1.44)</td>
</tr>
<tr>
<td><strong>Duration of ROM</strong></td>
<td>3.41 (2.23 – 5.20)</td>
</tr>
<tr>
<td><strong>Maternal Temperature</strong></td>
<td>2.38 (2.05 – 2.77)</td>
</tr>
<tr>
<td><strong>No Antibiotic</strong></td>
<td>Reference</td>
</tr>
<tr>
<td><strong>GBS IAP or any antibiotic</strong></td>
<td>0.35 (0.23 – 0.53)</td>
</tr>
<tr>
<td><strong>&lt; 4 hrs PTD</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Broad-spectrum antibiotic</strong></td>
<td>0.31 (0.13 – 0.71)</td>
</tr>
<tr>
<td><strong>&gt; 4 hrs PTD</strong></td>
<td></td>
</tr>
</tbody>
</table>

C statistic for model applied to entire dataset: 0.800  
Hosmer Lemeshow p-value: 0.142
Multivariate Model Used to Develop Sepsis Risk Calculator

- Five inputs using only objective data
- Risk expressed as posterior rate of sepsis
  - “Sepsis Risk Score”
- Model meant for incorporation into EMR
- Available via website and smartphone app
- [http://www.newbornsepsiscalculator.org](http://www.newbornsepsiscalculator.org)
## Performance of Current Approaches

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Prevalence (%)</th>
<th>Infected Infants Identified (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest intrapartum temperature &gt; 100.4°F</td>
<td>4.73</td>
<td>30.0</td>
</tr>
<tr>
<td>Highest intrapartum temperature &gt; 101.4°F</td>
<td>0.76</td>
<td>16.7</td>
</tr>
<tr>
<td>Rupture of membranes time ≥ 18 hours</td>
<td>8.66</td>
<td>23.1</td>
</tr>
<tr>
<td>Highest intrapartum temperature &gt; 100.4°F and/or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ROM ≥ 18 hours and/or</td>
<td>16.56</td>
<td>46.6</td>
</tr>
<tr>
<td>• Broad-spectrum antibiotics and/or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• GBS prophylaxis &lt; 4 hrs PTD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Performance of Multivariate Model

<table>
<thead>
<tr>
<th>Sepsis Risk Score (Modified Prior Probability) EOS rate per 1000 live births</th>
<th>Prevalence (%)</th>
<th>Infected Infants Identified (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 0.4</td>
<td>9.1</td>
<td>50.6</td>
</tr>
<tr>
<td>≥ 0.5</td>
<td>6.1</td>
<td>44.9</td>
</tr>
<tr>
<td>≥ 0.6</td>
<td>4.2</td>
<td>39.4</td>
</tr>
<tr>
<td>≥ 1.0</td>
<td>1.8</td>
<td>24.3</td>
</tr>
<tr>
<td>≥ 1.5</td>
<td>0.9</td>
<td>18.0</td>
</tr>
</tbody>
</table>

Model would identify *same* proportion of EOS cases as currently recommended approaches but would evaluate 2/3 *fewer* infants.
### SRS Cutoffs Distinguish EOS Cases and Controls

#### Sepsis Risk at Birth

<table>
<thead>
<tr>
<th></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>&gt; 1.54</td>
<td>21.7%</td>
<td>1.22%</td>
</tr>
</tbody>
</table>
Combining SRS with Newborn Clinical Status: Risk Stratification Approach to Caring for Infants at Risk for EOS
Quantifying EOS Risk Due to Newborn Clinical Status

• Data collected for first 24 hours of life
  – delivery room condition and resuscitation
  – hourly vital signs (i.e., HR, temperature)
  – administered intensive care (i.e., mechanical ventilation, supplemental O2)
  – observed abnormalities such as seizure or grunting

Escobar, et al. (2014) *Pediatrics*
Quantifying EOS Risk Due to Newborn Clinical Status

• Analytic approach
  – recursive partitioning
  – logistic regression
  – visual examination of predictor outcome relationship grids
Infant Condition Categorized into Three States

• **Clinical Illness**
  – 5 minute Apgar < 5
  – Seizure
  – Vasopressor therapy
  – Mechanical ventilation or CPAP
  – Respiratory distress and need for supplemental O2 by 6 hours of life
Infant Condition Categorized into Three States

- **Equivocal Presentation**
  - In the first 12 hrs of life, infant had two instances of an individual abnormality, with “instance” defined as ≥ 2 measurements, ≥ 2 hours apart
    - Heart rate ≥ 160
    - Respiratory rate ≥ 60
    - Temperature ≥ 100.4°F or < 97.5°F
    - Respiratory distress (grunting, flaring, or retracting)

- **Well-appearing**
  - Infant did not meet definition of Clinical illness or Equivocal Presentation
Clinical Status Over 1st Day of Life

<table>
<thead>
<tr>
<th>Status at 6 hrs of age (%)</th>
<th>Controls (N = 1063)</th>
<th>Cases (N = 350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical illness</td>
<td>1.8</td>
<td>24.0</td>
</tr>
<tr>
<td>Equivocal presentation</td>
<td>5.6</td>
<td>18.6</td>
</tr>
<tr>
<td>Well-appearing</td>
<td>92.7</td>
<td>57.4</td>
</tr>
<tr>
<td>Status at 12 hrs of age (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical illness</td>
<td>2.0</td>
<td>27.1</td>
</tr>
<tr>
<td>Equivocal presentation</td>
<td>2.5</td>
<td>17.4</td>
</tr>
<tr>
<td>Well-appearing</td>
<td>95.6</td>
<td>55.4</td>
</tr>
<tr>
<td>Status at 24 hrs of age (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical illness</td>
<td>2.2</td>
<td>29.4</td>
</tr>
<tr>
<td>Equivocal presentation</td>
<td>0.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Well-appearing</td>
<td>97.3</td>
<td>68.3</td>
</tr>
</tbody>
</table>
## SRS + Clinical Status = Posterior Probability of Sepsis

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>Sepsis Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 0.65</td>
</tr>
<tr>
<td><strong>Clinical Illness</strong></td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>5.57 (3.73-8.53)</td>
</tr>
<tr>
<td>NNT</td>
<td>180 (117-268)</td>
</tr>
<tr>
<td><strong>Equivocal</strong></td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>1.31 (0.93-1.84)</td>
</tr>
<tr>
<td>NNT</td>
<td>763 (543-1,076)</td>
</tr>
<tr>
<td><strong>Well-Appearing</strong></td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>0.11 (0.08-0.13)</td>
</tr>
<tr>
<td>NNT</td>
<td>9,370 (7,418-12,073)</td>
</tr>
</tbody>
</table>
Quantitative Risk Stratification: Recommended Care Algorithm

<table>
<thead>
<tr>
<th>Clinical Status in 1st 12 hours</th>
<th>Sepsis Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 0.65</td>
</tr>
<tr>
<td><strong>Clinical Illness</strong></td>
<td></td>
</tr>
<tr>
<td><em>Equivocal</em></td>
<td>Observe and Evaluate</td>
</tr>
<tr>
<td><strong>Well-Appearing</strong></td>
<td>Continued Observation 85% of Births NNT 9370</td>
</tr>
</tbody>
</table>
Advantages of Sepsis Risk Score

- More efficient
  - fewer infants evaluated, same proportion of cases identified

- Better discrimination of risk
  - Could allow birth centers to set locally-appropriate thresholds for evaluation and empiric treatment

- Uses only objective data
  - Could be incorporated into EMR as part of obstetric care
  - Option to adjust initial prior probability if local EOS prevalence different from study prevalence (~0.6/1000)
  - Relieves obstetricians of responsibility of deciding if “chorioamnionitis” present
Advantages of Risk Stratification

- Clearly defines sick and well-appearing
  - Quantifies risk associated with “sick”
  - Defines different levels of “sick”
  - Provides a time frame for “sick” and “well” that is consistent with perinatal transition

- Better discrimination of risk
  - Could allow birth centers to set locally-appropriate settings for evaluation and empiric treatment
  - This may be especially important with movement to “Baby Friendly” practices

- Uses mostly objective data
  - Allows for clinical exam with regard to respiratory status
Conclusions

• Using only maternal predictors, an accurate predictive model can be built based on information available at the moment of birth
  – Establish prior probability for newborn sepsis

• Addition of neonatal status can be used to establish a posterior probability for newborn sepsis to guide treatment decisions

• Treatment algorithms using these estimates may result in more objective and efficient means of identifying infants at risk for EOS and safely decrease the number of infants exposed to empiric antibiotics
Acknowledgements

- **Sepsis and Critical Illness Study Group**
  - Gabriel Escobar, MD
    - Funded by the National Institute of General Medical Sciences R01-GM-80180-01-A2, “Sepsis and Critical Illness in Babies ≥ 34 Weeks Gestation, “ Gabriel Escobar, PI
  - David Draper, PhD
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  - Ellice Lieberman, DrPH, MD
  - Soora Wi, MPH, Myesha Smith, BS, Benjamin Turk, BA
  - Michael Kuzniewicz, MD, MPH
  - Eileen Walsh, RN, MPH
- Allen Fischer, MD, Regional Director of Neonatology KPNC
- Sagori Mukhopadhyay, MD, MMSc
Neonatal Sepsis Risk Calculator

Credit for website: Soora Wi, MPH
Division of Research, Kaiser-Permanente, Northern California

Credit for App: Allen Fischer, MD, Regional Director of Neonatology for Kaiser-Permanente, Northern California


Smartphone (iOS and Android) App: http://www.newbornsepsiscalculator.org
Extra Slides
Cases from the Real World

- 36 3/7 weeks
- Mother 101.6°F
- ROM 32 hrs
- GBS negative
- No intrapartum abx

- 38 0/7 weeks
- Mother 100.2°F
- ROM 9 hrs
- GBS negative
- Broad spectrum intrapartum abx <1 hr PTD

- 39 3/7 weeks
- Mother 103°F
- ROM 11 hrs
- GBS negative
- No intrapartum abx

- 38 5/7 weeks
- Mother 101.5°F
- ROM 5 hrs
- GBS positive
- GBS abx given 9 hrs PTD

In all these cases, obstetrician diagnosed “chorioamnionitis”
- All had blood culture/48 hrs abx
- All remained well/culture negative
- All went home with mother
Role of Complete Blood Count in Assessing Risk of EOS
### Complete Blood Count Results

#### White Blood Cell Count

<table>
<thead>
<tr>
<th>Total WBC (x 1000)</th>
<th>Percent of Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>0</td>
</tr>
<tr>
<td>5.9-9.99</td>
<td>5</td>
</tr>
<tr>
<td>10-14.99</td>
<td>15</td>
</tr>
<tr>
<td>15-19.99</td>
<td>30</td>
</tr>
<tr>
<td>20-24.99</td>
<td>35</td>
</tr>
<tr>
<td>25-29.99</td>
<td>20</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>10</td>
</tr>
</tbody>
</table>

#### Absolute Neutrophil Count

<table>
<thead>
<tr>
<th>ANC</th>
<th>Percent of Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1000-1999</td>
<td>5</td>
</tr>
<tr>
<td>2000-4999</td>
<td>10</td>
</tr>
<tr>
<td>5000-9999</td>
<td>40</td>
</tr>
<tr>
<td>&gt; 10000</td>
<td>50</td>
</tr>
</tbody>
</table>

Complete Blood Count Results

By the criteria in the 2002 EOS algorithm:

35/1084 (3.2%)

of evaluated infants had a CBC with an abnormal total WBC or I/T ratio.

None of these infants had a blood-culture proven infection.

Role of CBC in Predicting Blood Culture-proven Infection

• “Limited evaluation includes blood culture (at birth) and CBC with differential and platelets (at birth and/or at 6-12 hours of life).”

• Landmark 1979 study of Manroe and colleagues established “normal ranges” for WBC, ANC and I/T ratio
  – < 300 WBC values from 108 infants
  – Mix of symptomatic and asymptomatic
  – Wide range of non-infection diagnoses

Fig. 1. The total neutrophil count reference range in the first 60 hours of life. Stars represent single values; numbers represent the number of values at the same point. Heavy lines represent the envelope bounding these data.
Role of CBC in Predicting Blood Culture-proven Infection

• One finding common to all published neonatal WBC data is the “roller coaster” shape of the WBC, ANC and I/T curves in the first 72 hours of life
  – suggests optimal interpretation of WBC data to predict EOS should account for the natural rise and fall in WBC during this period
• One study of 856 infants born to mothers with intrapartum fever > 100.4°F evaluated the use of serial WBC components obtained at < 1 hrs, 12 hrs and 24 hrs of life to predict clinical and culture-proven EOS.
  – Included 38 symptomatic infants, and 4 infants with culture-proven infection.
  – Multiple abnormal values in all study infants compared to the Manroe standard curves and led to conclusion that WBC components have no utility in prediction of clinical or culture-proven EOS.

Jackson, et al Pediatrics 2004
Revisiting “Normal” Neonatal CBC

- Intermountain Healthcare 2008 study
- 30,354 CBC that excluded infants with blood-culture proven infection, extreme values and infants born to mother’s with pre-eclampsia
- Stratified by time after birth and gestational age
- Found WBC and components influenced by
  - Gestational age
  - Time after birth
  - Labor vs no labor (higher upper limit of neutrophil count)
  - Female vs male (higher upper limit of neutrophil count)
  - Influenced by high altitude

Interpreting Complete Blood Counts Soon After Birth in Newborns at Risk for Sepsis

- 67,623 infants with CBC and blood culture within 1 hour of each other, < 72 hrs life
- 245 cases of culture-proven EOS
- Determined value in predicting EOS
- Attempted to adjust for clinical variables
  - GA, BW, gender, mode of birth, PET, 5-minute Apgar
  - No improvement (thankfully!)

Newman, et al *Pediatrics* 2010
Scatter Plots of WBC, ANC, I/T, Plt

**Figure 1**

Test results according to age for complete blood counts performed at <24 hours. A, WBC count according to age; B, ANC according to age; C, I/T according to age; D, platelet count according to age. All counts are thousands per microliter. Cases are shown as red diamonds; only a 20% random sample of the newborns with no infection is shown. Lines indicate the results of quantile regressions at the 1%, 10%, 50%, 90%, and 99% points of the distributions.
FIGURE 2
ROC curves for WBC counts (A), ANC (B), I/T ratio (C), and platelet counts (D) performed at <72 hours according to age at the time of the CBC.
### Likelihood Ratios

**TABLE 4** LR s for Components of the CBC According to Age at the Time of Testing Among Newborns With CBC and Blood Cultures Performed at <72 Hours of Age

<table>
<thead>
<tr>
<th>Age at Time of CBC, h</th>
<th>No. With Infection, Total</th>
<th>% of Those With Infection With Result</th>
<th>% of Those Without Infection With Result</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1</td>
<td>1–3.99</td>
<td>≥4</td>
</tr>
<tr>
<td>Total No. with infection</td>
<td>64</td>
<td>91</td>
<td>90</td>
</tr>
<tr>
<td>% of all with infection</td>
<td>26</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>LR</td>
<td>LR</td>
<td>LR</td>
</tr>
</tbody>
</table>

**WBCs, × 10³/μL**

<table>
<thead>
<tr>
<th>Range</th>
<th>LR</th>
<th>LR</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4.99</td>
<td>27.6</td>
<td>80.5</td>
<td>46</td>
</tr>
<tr>
<td>5–9.99</td>
<td>2.4</td>
<td>6.4</td>
<td>53</td>
</tr>
<tr>
<td>10–14.99</td>
<td>0.65</td>
<td>1.0</td>
<td>53</td>
</tr>
<tr>
<td>15–19.99</td>
<td>0.64</td>
<td>0.41</td>
<td>45</td>
</tr>
<tr>
<td>≥20</td>
<td>1.2</td>
<td>0.77</td>
<td>0.16</td>
</tr>
</tbody>
</table>

**ANC, × 10³/μL**

<table>
<thead>
<tr>
<th>Range</th>
<th>LR</th>
<th>LR</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–0.99</td>
<td>7.5</td>
<td>33.5</td>
<td>115</td>
</tr>
<tr>
<td>1–1.99</td>
<td>2.3</td>
<td>9.3</td>
<td>51.7</td>
</tr>
<tr>
<td>2–4.99</td>
<td>1.0</td>
<td>1.1</td>
<td>6.9</td>
</tr>
<tr>
<td>5–9.99</td>
<td>0.89</td>
<td>0.92</td>
<td>0.64</td>
</tr>
<tr>
<td>≥10</td>
<td>0.93</td>
<td>0.55</td>
<td>0.31</td>
</tr>
</tbody>
</table>

**I/T**

<table>
<thead>
<tr>
<th>Range</th>
<th>LR</th>
<th>LR</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–0.1499</td>
<td>0.45</td>
<td>0.46</td>
<td>0.25</td>
</tr>
<tr>
<td>0.15–0.299</td>
<td>1.3</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>0.3–0.4499</td>
<td>1.4</td>
<td>2.9</td>
<td>3.1</td>
</tr>
<tr>
<td>0.45–0.599</td>
<td>4.8</td>
<td>3.3</td>
<td>8.8</td>
</tr>
<tr>
<td>≥0.6</td>
<td>6.1</td>
<td>8.4</td>
<td>10.7</td>
</tr>
</tbody>
</table>

95% confidence intervals for LR s are available from the authors on request.

* The point estimate of this LR was 0, but there were only 56 infants in this cell.
Conclusions

• CBC most informative after the first 4 hours of life
• If the infant is sick => blood culture, antibiotics and don’t rely on CBC
• If intent of CBC is to aid in decision-making in absence of culture-proven sepsis => get it later
• Most informative:
  – WBC < 5000
  – I/T > 0.3
  – ANC < 2000
Impact of GBS Intrapartum Prophylaxis

Cases from the Real World

- Infant born at 37 6/7 weeks
- Mother 102.5°F with ROM 5 hrs PTD
- GBS negative/ampicillin and gentamicin ~2 hrs PTD
- Infant depressed at birth, requiring PPV
  - Admitted to NICU from the delivery room, with respiratory distress, poor perfusion, metabolic acidosis

- No one needs a multivariate model to decide whether or not to evaluate or treat this infant
- Even if you hesitated – the blood culture was growing *H. influenzae* by 20 hours of incubation
More Cases from the Real World

- 36 3/7 weeks
  - Mother 101.6°F
  - ROM 32 hrs
  - GBS negative
  - No intrapartum abx

- 38 0/7 weeks
  - Mother 100.2°F
  - ROM 9 hrs
  - GBS negative
  - Broad spectrum intrapartum abx <1 hr PTD

In all these cases, obstetrician diagnosed chorioamnionitis
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- 38 5/7 weeks
  - Mother 101.5°F
  - ROM 5 hrs
  - GBS positive
  - GBS abx given 9 hrs PTD
CDC Surveillance: GBS EOS 2000-2006

- 28% early-onset disease in preterm infants
- 42% late-onset disease in preterm infants

Sepsis Evaluations Among Infants with BW > 2000 g

- 2785 infants born in Kaiser-Permanente hospitals 1995-1996, evaluated for EOS on the basis of symptoms and/or risk factors
- Well-performing multivariate models could be built to determine who was infected within this at-risk cohort
  - Few predictors needed
  - Maternal fever could be substituted for clinical diagnosis of “chorioamnionitis”
  - Intrapartum antibiotics modified risk
  - Looking well at birth was protective (associated with an odds ratio of ~0.3)

Variable Use of CBC

Number of CBC’s sent varied from 0-3 in course of evaluation

Timing of CBC

- Birth: 70%
- 1 hr: 10%
- 2 hr: 5%
- 4 hr: 2%
- 12 hrs: 3%

WBC Indices

- ANC high: 6 units ≥0.2
- WBC: 4 units ≥0.3
- I/T: 4 units ≥0.3
## Relative Contribution to Model

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age</td>
<td>16.7%</td>
</tr>
<tr>
<td>GBS Status</td>
<td>2.3%</td>
</tr>
<tr>
<td>Duration of ROM</td>
<td>12.6%</td>
</tr>
<tr>
<td>Maternal Temperature</td>
<td>58.4%</td>
</tr>
<tr>
<td>Intrapartum Antibiotic</td>
<td>10.0%</td>
</tr>
</tbody>
</table>