Sepsis Risk Assessment Among Term and Preterm Infants

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DISCLOSURE STATEMENT

Karen M. Puopolo MD, PhD

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Learning Objectives

To understand the impact of a multivariate risk model for assessing early-onset sepsis among term
To categorize risk of EOS among very-low birth weight infants
To identify opportunities to reduce early antibiotic exposures among all newborns
Outline for Today

• Discuss for term and VLBW infants
  – Epidemiology of EOS
  – Current approaches to EOS risk assessment
  – Alternative approaches to EOS risk assessment that can reduce early antibiotic exposures

Definition of Neonatal EOS

• Culture-proven invasive infection (blood or CSF) that occurs from birth to 6 days of age
• Among term infants, perinatal practitioners are concerned about infection in first 24-48 hours of life
• Among VLBW infants, timing is restricted to <72 hours of life
• We will not be discussing “culture-negative sepsis” today

Does it Matter What We Do with Term Infants?

• Among well-appearing term infants, EOS evaluation results in 4-fold increase in late initiation of breastfeeding and 2-fold increase in non-medically indicated formula supplementation
• Multiple observational studies associate early-life antibiotics with impact on gut microbiome, wheezing, IBD, childhood obesity

It Matters for VLBW Infants: Antibiotic Exposure and Risk of NEC

- 1/7% increase in odds of NEC with each additional day of empiric antibiotics
- 2-fold higher incidence of LOS, NEC, or death


Epidemiology of EOS Among Term and Very-Low Birth Weight Infants

Pathogenesis

- Bacterial (unlike viral) neonatal sepsis has an in utero pathogenesis
- EOS due to ascending colonization and subsequent infection of uterine compartment with maternal GI/GU flora
- Listeria is notable exception
- Preterm pathogenesis may be different

Risk Identified Factors for EOS

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Neonatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and race</td>
<td>Birth Weight</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>Gestational age</td>
</tr>
<tr>
<td>Duration of ROM</td>
<td>Twin gestation</td>
</tr>
<tr>
<td>“Foul-smelling” fluid</td>
<td>Fetal tachycardia</td>
</tr>
<tr>
<td>GBS colonization</td>
<td>Clinical illness</td>
</tr>
<tr>
<td>Intrapartum antibiotics</td>
<td>Laboratory abnormalities</td>
</tr>
<tr>
<td>Intrapartum fever</td>
<td></td>
</tr>
<tr>
<td>Meconium-stained fluid</td>
<td></td>
</tr>
<tr>
<td>Obstetrical interventions</td>
<td></td>
</tr>
</tbody>
</table>

Mukhopadhyay and Puopolo (2012, Semin Perinatol)

Impact of GBS Intrapartum Prophylaxis

CDC 2013 Surveillance
EOS 0.26/1000 LB
LOS 0.29/1000 LB


Impact of GBS Intrapartum Prophylaxis

V LBW EOS Incidence 10-20X Higher than Term Incidence

<table>
<thead>
<tr>
<th>Site</th>
<th>Years</th>
<th># of cases</th>
<th>Incidence per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC multi-state</td>
<td>2005-2008</td>
<td>658</td>
<td>0.77</td>
</tr>
<tr>
<td>California and Boston</td>
<td>1993-2007</td>
<td>301</td>
<td>0.53</td>
</tr>
<tr>
<td>Boston</td>
<td>1993-2007</td>
<td>52</td>
<td>22.7</td>
</tr>
<tr>
<td>NICHD NRN</td>
<td>2002-2003</td>
<td>109</td>
<td>17.0</td>
</tr>
<tr>
<td>NICHD NRN</td>
<td>2006-2009</td>
<td>147</td>
<td>11.0</td>
</tr>
</tbody>
</table>

Microbiology of Neonatal EOS

- Mortality from EOS primarily derives from preterm infants
  - Overall 10.8%
  - ≥ 37 weeks: 1.6%

- GBS: 38%
- Other GP: 22%
- Other GN: 16%
- E. coli: 24%


Microbiology of Neonatal EOS

- Mortality from EOS is high among preterm infants:
  - < 37 weeks: 23%
  - 25-28 weeks: 30%
  - 22-24 weeks: 54%

- GBS: 20%
- Fungal: 2%
- Other GN: 10%
- Other GP: 28%
- Bacteroides: 6%
- E. coli: 34%


Term vs. VLBW EOS

- Incidence ~1/2000
- Infection usually develops during labor and delivery
- Risk factors are common
- Need to decide who to evaluate and who to treat

- Incidence ~1/100
- Infection often underlies preterm birth
- Risk factors are universal
- Need to decide who NOT to evaluate and who NOT to treat
Identifying Term Infants at Risk for EOS:
It Shouldn’t Be So Hard…

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

- Endorsed CDC 2010 recommendations
- Additional algorithms for term and preterm infants with goal of reducing empiric treatment of “culture-negative” EOS
Newborns Are Frequently Evaluated and Empirically Treated for Risk of EOS

<table>
<thead>
<tr>
<th>Site</th>
<th>Policy</th>
<th>Years</th>
<th>Births included</th>
<th>Blood culture and/or labs</th>
<th>Empiric Antibiotics</th>
<th>Rate of EOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston</td>
<td>CDC</td>
<td>2010-2012</td>
<td>≥ 36 weeks</td>
<td>N = 6544</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Philadelphia</td>
<td>AAP</td>
<td>2013-2014</td>
<td>≥ 36 weeks</td>
<td>N = 7943</td>
<td>24%</td>
<td>7%</td>
</tr>
<tr>
<td>Northern California</td>
<td>CDC</td>
<td>2010-2012</td>
<td>≥ 35 weeks</td>
<td>N = 95,354</td>
<td>14%</td>
<td>5%</td>
</tr>
</tbody>
</table>


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 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
Multivariate Approach to Identifying Infants at Risk for EOS
(Maybe It Can Be Easier…)

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

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: 408,014
- Kaiser-Permanente: 12 California sites, 416,730 births
- Brigham and Women’s: Boston, MA, 137,239 births
- Beth Israel Deaconess: Boston, MA, 62,020 births

- Total 350 cases, 1063 controls
  - Cases: ~50% GBS, 20% E. coli
  - Controls: ~20% received intrapartum antibiotics
  - Overall EOS incidence: 0.58 cases/1000 live births

Rate of EOS by Gestational Age

- Graph showing the rate of EOS by gestational age.

Rate of EOS by Highest Maternal Temperature

- Graph showing the rate of EOS by highest maternal temperature.
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>[ROM in hrs +0.05]^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>Categorical</td>
<td>Indicator variables: 3 mutually-exclusive values</td>
</tr>
<tr>
<td>GBS IAP</td>
<td></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</td>
<td></td>
<td>- Broad spectrum abx given on time</td>
</tr>
<tr>
<td>≥ 4 hrs PTD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Current Practice vs. Multivariate Model

<table>
<thead>
<tr>
<th>Sepsis Risk Score (SRS)</th>
<th>EOS rate per 1000 live births</th>
<th>Prevalence (%)</th>
<th>Infected Infants Identified (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest intrapartum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>temperature &gt; 100.4°F</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and/or</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ROM ≥ 18 hours</td>
<td></td>
<td>16.56</td>
<td>46.6</td>
</tr>
<tr>
<td>• Broad-spectrum antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• GBS prophylaxis &lt; 4 hrs PTD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SRS ≥ 0.5</td>
<td></td>
<td>6.1</td>
<td>44.9</td>
</tr>
</tbody>
</table>

Model would identify same proportion of EOS cases as currently recommended approaches but would evaluate 2/3 fewer infants

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

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

**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

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**Likelihood Ratios for Clinical Presentation**

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>LR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-appearing</td>
<td>0.36</td>
<td>0.31 - 0.41</td>
</tr>
<tr>
<td>Equivocal</td>
<td>3.75</td>
<td>2.83 – 5.00</td>
</tr>
<tr>
<td>Clinical Illness</td>
<td>14.5</td>
<td>10.2 – 21.2</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>9.57 (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>1,080 (923-1,480)</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>Observe and Evaluate</td>
<td></td>
</tr>
<tr>
<td>Treat Empirically 4% of Births</td>
<td></td>
</tr>
<tr>
<td>NNT</td>
<td>118</td>
</tr>
<tr>
<td><strong>Equivocal</strong></td>
<td></td>
</tr>
<tr>
<td>Observe and Evaluate</td>
<td></td>
</tr>
<tr>
<td>NNT</td>
<td>883</td>
</tr>
<tr>
<td><strong>Well-Appearing</strong></td>
<td></td>
</tr>
<tr>
<td>Observe and Evaluate</td>
<td></td>
</tr>
<tr>
<td>Evaluate</td>
<td>11% of Births</td>
</tr>
<tr>
<td>NNT</td>
<td>9,370</td>
</tr>
</tbody>
</table>

Neonatal Sepsis Risk Calculator

- Clinical care algorithms updated to include implementation work done at KPNC since 2014 publication
- Risk estimates can be incorporated into local algorithms by individual centers

New website: http://neonatalsepsiscalculator.kaiserpermanente.org
Also reached at: http://kp.org/eoscalc
Credits for websites: Soora Wi, MPH; Allen Fischer, MD, Regional Director of Neonatology; Michael Kuzniewicz, MD, Director, Perinatal Research Unit Kaiser Permanente Northern California
SRS Implementation
(What Happens if You Really Use it…)

Blood Cultures in the 1st 24 hours
January 2010-January 2015

Antibiotics in the 1st 24 hours
January 2010-January 2015
Significant Decrease in EOS Evaluation at KPNC Birth Centers

<table>
<thead>
<tr>
<th>Time Period</th>
<th>N</th>
<th>Blood Culture 1st 24 hrs</th>
<th>P value</th>
<th>Ax1 1st 24 hrs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC Guidelines 1/2010-11/2012</td>
<td>95,354</td>
<td>14.4%</td>
<td>Ref.</td>
<td>5.0%</td>
<td>Ref.</td>
</tr>
<tr>
<td>EOS Calculator #1 12/2012-6/2014</td>
<td>52,929</td>
<td>12.6%</td>
<td>&lt;0.001</td>
<td>4.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EOS Calculator #2 7/2014-10/2014</td>
<td>12,684</td>
<td>5.6%</td>
<td>&lt;0.001</td>
<td>2.8%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Readmissions within the 1st 7 days of life with a positive blood or CSF culture were rare:

- CDC guidelines (5)
- EOS Calc 1.0 (1)
- EOS Calc 2.0 (0)

Sepsis Risk Calculator at Pennsylvania Hospital

- Pennsylvania Hospital is the nation's oldest hospital
  - Founded by Benjamin Franklin in 1751
  - One of the oldest maternity services (1803)
- Currently delivers ~5300 infants annually
- Local algorithm combined recommendations of CDC 2010 and AAP 2013
- Established as standard of care for EOS risk assessment in July 2015

PAH SRS Implementation

- Nurses call Neonatology if SRS ≥ 0.7
  - If 0.7-1.49 and well-appearing => enhanced vital signs for 36 hours
  - If SRS ≥ 1.5, currently blood culture done and antibiotics regardless of clinical status
- Today I will present results of 5033 infants born ≥ 36 0/7 weeks gestation
  - Born 7/14/2015 - 7/31/2016
**Post-SRS Delivery Characteristics (N = 5,033*)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational Age (weeks)</strong></td>
<td></td>
</tr>
<tr>
<td>36 0/7 – 37 6/7</td>
<td>770 (15.3)</td>
</tr>
<tr>
<td>38 0/7 – 40 6/7</td>
<td>3,755 (74.6)</td>
</tr>
<tr>
<td>≥ 41 0/7</td>
<td>508 (10.1)</td>
</tr>
<tr>
<td><strong>GBS positive</strong></td>
<td>1,490 (29.6)</td>
</tr>
<tr>
<td><strong>GBS unknown</strong></td>
<td>262 (5.2)</td>
</tr>
<tr>
<td><strong>C-section any</strong></td>
<td>1,881 (37.4)</td>
</tr>
</tbody>
</table>

*4 infants in post SRS period that were outborn and SRS was not applied to them

**Sepsis Risk Score Distribution**

<table>
<thead>
<tr>
<th>SRS Category</th>
<th>N (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.50</td>
<td>4,669 (92.8)</td>
</tr>
<tr>
<td>&lt; 0.70</td>
<td>4,795 (95.3)</td>
</tr>
<tr>
<td>0.70-1.49</td>
<td>147 (2.9)</td>
</tr>
<tr>
<td>≥ 1.50</td>
<td>75 (1.5)</td>
</tr>
</tbody>
</table>

*SRS missing for 16 records

**Sepsis Risk Score Distribution**

49.4% of SRS < 0.10
Decrease in EOS-Associated Antibiotics

Antibiotic Use for Risk of EOS

<table>
<thead>
<tr>
<th></th>
<th>Pre SRS (n = 6,394)</th>
<th>Post SRS (n = 5,037)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics &lt;72 hrs, N (%)</td>
<td>406 (6.4)</td>
<td>180 (3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antibiotics &lt;7 days, N (%)</td>
<td>411 (6.4)</td>
<td>182 (3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lab Tests* &lt;72 hrs, N (%)</td>
<td>704 (11.0)</td>
<td>320 (6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lab Tests* &lt;7 days, N (%)</td>
<td>738 (11.5)</td>
<td>351 (7.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

“Lab tests included CBC, CRP and/or blood culture” and includes only infants that were admitted to the NICU for any indication

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
Identifying VLBW Infants at Risk for EOS: Why Is It So Hard?

Antibiotic Initiation

- 7% received Amp/gent
- 3% received Amp/Cef
- 2% received Amp/other
- 3% received Amp alone
- 2% received Gent/other
- 3% received Other
- 83% received antibiotics in the first 3 days of life


Prolonged Early Antibiotic Exposures are Common in NICU

53% of uninfected infants with BW < 1000 g received early antibiotics ≥5 days

Rock and a Hard Place

- Incidence 20-40X higher and mortality 30-50X higher compared to term infants
- National recommendations are to begin empiric antibiotics among all clinically ill premature infants
- Risk factors for EOS intersect with reason for being premature, and therefore add little to individual risk assessment
- The challenge is not to identify WHO is at risk, but who is at LOWEST RISK

VLBW EOS Study Design

- Retrospective cohort study
- All liveborn infants with BW < 1500 gram
  - Brigham and Women’s Hospital, Boston
  - January 1990-May 2015
- Blood-culture proven bacterial or fungal infection occurring < 72 hours of age
- Detailed review of maternal and infant medical records and microbiology database

Case Identification

- Identified 109 cases of culture-confirmed infection
  - Standard practice: two blood culture bottles sent, one aerobic/one anaerobic, 1 mL blood each
  - Case definitions
    - Pathogenic species treated with appropriate course of antibiotics or until death
    - Commensal organisms (CONS) included if grew from both blood culture bottles and treated with appropriate type and duration of antibiotics (1)
    - Contaminant species (micrococcus, diphtheroids) excluded
Data Collection

- Variables collected included GA, BW, duration of maternal hospitalization leading to delivery, mode of delivery, reason for delivery (PROM, PTL, PET, fetal distress), maternal fever, obstetrical diagnosis of chorioamnionitis, duration of ROM, antenatal and intrapartum antibiotic exposures, infant survival
- Microbiology records reviewed to determine antibiotic susceptibility data and time to culture positivity

Focus on Reasons for Preterm Birth

- Review of obstetrical records
- PROM defined as preterm spontaneous ROM
  - Duration not considered in this analysis
- “Chorioamnionitis” by obstetrical diagnosis
  - Included one more of maternal fever, maternal leukocytosis, fetal tachycardia, uterine tenderness

Reasons for Preterm Birth

- “Fetal distress” by obstetrical diagnosis
  - Included decreased fetal movement, poor biophysical profile, and/or poor umbilical arterial doppler studies
  - Often diagnosed in context of PTL, chorioamnionitis or maternal pre-eclampsia - but only recorded here if it was the primary reason for proceeding with delivery
Delivery Characteristics of EOS Case Mothers

<table>
<thead>
<tr>
<th>Reason for Preterm Birth</th>
<th>N (% total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm labor</td>
<td>80 (73.4)</td>
</tr>
<tr>
<td>PROM alone</td>
<td>63 (57.8)</td>
</tr>
<tr>
<td>- PROM &gt; 12 hours</td>
<td>55 (50.5)</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>54 (49.5)</td>
</tr>
<tr>
<td>- maternal fever &gt; 38.0°C</td>
<td>25 (22.9)</td>
</tr>
<tr>
<td>Maternal antibiotics</td>
<td>74 (67.9)</td>
</tr>
<tr>
<td>- ≥4 hours prior to delivery</td>
<td>55 (50.5)</td>
</tr>
</tbody>
</table>

One EOS Case Infants Born Due to Maternal Pre-Eclampsia Only

- Infant born at 26 weeks, BWH 510 grams
- CSxn without ROM or labor for evolving maternal condition
- Blood culture grew *Streptococcus mitis* from 1/2 culture bottles
  - Bacteremia cleared despite treatment with antibiotics to which organism was resistant (ampicillin and gentamicin)
  - ? contaminant species

Reasons for Preterm Birth and EOS: Lessons Learned

- 97% occurred in context of some combination of PROM, PTL or concern for chorioamnionitis
- Two cases occurred with delivery due to concern for unexplained fetal distress – both *Listeria monocytogenes*
  - mothers presented with otherwise uncomplicated pregnancy, with concern for decreased fetal movement, with delivery for poor fetal testing
Time to Blood Culture Positivity

- 24 hours: 10%
- 25-36 hours: 15%
- 37-48 hours: 2%
- >48 hours: 73%

Median TTP < 24 Hours

Anaerobic Culture Improves 'Blood Culture Yield'

- 16% of EOS cases due to strict anaerobes
  - Primarily *Bacteroides fragilis*
- 30% of EOS cases grew in anaerobic bottle only
- 54% of EOS cases grew in both aerobic and anaerobic culture
Do We Recognize Differential Risk?

- Antibiotic use among VLBW infants
- ICD-9 codes, 1999-2012
- 2851 VLBW admissions
  - 55 infants died < 24 hours
  - 48 infants without maternal ICD-9 codes
- 605/2748 (22%) born to mothers with discharge diagnosis of pre-eclampsia, without PROM or chorioamnionitis

Antibiotic Use Among Different EOS Risk Categories

<table>
<thead>
<tr>
<th></th>
<th>PET/no RF N = 605</th>
<th>Others N= 2143</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood culture, N (%)</td>
<td>591 (99.8)</td>
<td>2019 (99.7)</td>
<td>0.52</td>
</tr>
<tr>
<td>Antibiotics, N (%)</td>
<td>506 (85.3)</td>
<td>1990 (94.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EOS, N (cases/1000 VLBW infants)</td>
<td>1 (1.7)</td>
<td>45 (21.0)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Can We Do Better for VLBW Infants?

- Can we discriminate better between at-risk infants?
  - 25 years of data reveals that EOS does not occur among VLBW infants in the absence of premature rupture of membranes, preterm labor or unexplained fetal distress
- Could we safely evaluate fewer infants and still identify the infected ones?
  - 20-25% of VLBW infants are at such low risk of EOS we could refrain from evaluation and initiation of antibiotics or extension of antibiotics despite negative cultures
Use Microbiology to Minimize 'Duration of Antibiotics'

- 97% of pathogens identified grow in modern blood culture bottles by 48 hours of incubation
  - Median TTP <24 hours with or without maternal intrapartum antibiotics
  - Subsequent risk is associated with duration of non-culture mandated antibiotic exposures
- If you base decisions on blood culture – optimize your blood culture technique
  - 2 blood culture bottles/ minimum 1 ml blood/bottle
  - Consider aerobic and anaerobic incubation

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“Every critically ill infant should be evaluated and receive empirical broad-spectrum antimicrobial therapy after cultures, even when there are no obvious risk factors for sepsis.”