Early Onset Neonatal Sepsis: Update 2011

Mead Johnson Virtual Neonatal Journal Club

Karen M. Puopolo, MD, PhD
Division of Newborn Medicine, Brigham and Women’s Hospital
Assistant Professor of Pediatrics, Harvard Medical School
Disclosures

- I have no conflicts of interest to disclose
- I will not discuss off-label uses of medications
- I had complete and independent control over the planning and content of this presentation
- I am not receiving any compensation for the presentation
Outline

• Epidemiology of EOS
• Microbiology of EOS
• CDC 2010 GBS Guideline
  – Changes relative to CDC 2002 recommendations
• Current Issues
  – Frequency of EOS Evaluations among Asymptomatic Term Infants
Learning Objectives

• To describe the risk factors for early-onset sepsis in term and preterm infants

• To describe the microbiology of early-onset sepsis in term and preterm infants in the era of GBS prophylaxis, and how this influences empiric antibiotic choice

• To understand the evolution of the CDC guidelines for intrapartum GBS prophylaxis
Epidemiology of EOS
Definition of Neonatal EOS

- Culture-proven invasive infection (blood or CSF) that occurs from birth to 6 days of age
- Among continuously hospitalized primarily low-birth weight NICU population, EOS is defined as occurring at < 72 hours of age
  - Risk factors reflect specifics of NICU care rather than perinatal risk factors
  - Microbiology reflects nosocomial NICU flora rather than perinatally-acquired maternal flora
## Incidence of EOS – All Live Births

<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>Puopolo &amp; Eichenwald (2010)</td>
<td>Brigham and Women’s Hospital</td>
<td>1997-2007</td>
<td>161</td>
<td>1.6</td>
</tr>
</tbody>
</table>
## Incidence of EOS – Preterm Births

<table>
<thead>
<tr>
<th>Reference</th>
<th>Category of Infant</th>
<th>Sites</th>
<th>Years</th>
<th>Number of cases</th>
<th>Incidence per 1000 live births</th>
</tr>
</thead>
</table>
## Incidence of EOS – VLBW Births

<table>
<thead>
<tr>
<th>Reference</th>
<th>Category of Infant</th>
<th>Sites</th>
<th>Years</th>
<th># of cases</th>
<th>Incidence per 1000 live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puopolo &amp; Eichenwald (2010)</td>
<td>&lt; 1500 g</td>
<td>Brigham and Women’s Hospital</td>
<td>1997-2007</td>
<td>52</td>
<td>22.7</td>
</tr>
<tr>
<td>Stoll, et al (2005)</td>
<td>&lt; 1500 g</td>
<td>NICHD 16 NICU’s</td>
<td>2002-2003</td>
<td>102</td>
<td>17.0</td>
</tr>
<tr>
<td>Stoll, et al (2011)</td>
<td>&lt; 1500 g</td>
<td>NICHD 16 NICU’s</td>
<td>2006-2009</td>
<td>142</td>
<td>11.0</td>
</tr>
</tbody>
</table>
Mortality from Early-Onset Sepsis

Pathogenesis of EOS

- “Amniotic Infection Syndrome”
- Attributed to Blanc (1959) and Benirschke (1960), the concept that most EOS has an *in utero* pathogenesis
  - Onset at birth or < 12 hrs age in most cases
  - Frequency of (presumed) aspiration pneumonia
  - Heavy neonatal surface colonization with bacteremic agent
  - Association with proven amniotic fluid infection and maternal postpartum fever/bacteremia

Blanc WA (1959) *Clin Obstet and Gynecol* 2:705
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 abnormalities
Risk of EOS in Era of Intrapartum Antibiotics

• Most risk factors identified prior to widespread use of intrapartum antibiotics for
  – GBS prophylaxis
  – Maternal fever/chorioamnionitis
  – Preterm labor
• At BWH, intrapartum antibiotics in ~40% of labors
• Concerns for modification of risk factors given extensive use of intrapartum antibiotics
EOS Risk Among Preterm Infants

- Comparison of risk factors among 601 infants with GA < 34 weeks in Northern India NICU
- Admitted to single center over 1 year
  - 12% received full course betamethasone
  - 23% received intrapartum antibiotics
- 85/601 (14%) with culture-proven EOS
  - 19% *Staphylococcus aureus*; no GBS; remainder gram-negative organisms

Multivariate Model of EOS Risk

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW &lt; 1500 g</td>
<td>2.796</td>
<td>1.537 - 5.086</td>
<td>3</td>
</tr>
<tr>
<td>GA &lt; 30 weeks</td>
<td>1.989</td>
<td>1.119 - 3.533</td>
<td>2</td>
</tr>
<tr>
<td>Vaginal exams ≥ 3</td>
<td>9.519</td>
<td>2.968 - 30.530</td>
<td>6</td>
</tr>
<tr>
<td>No intrapartum Abx</td>
<td>2.074</td>
<td>1.047 - 4.109</td>
<td>2</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.704</td>
<td>1.555 - 4.701</td>
<td>3</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>8.842</td>
<td>1.811 - 43.169</td>
<td>6</td>
</tr>
</tbody>
</table>

Add weighted factors to develop “risk score” for likelihood of 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

Funded by the National Institute of General Medical Sciences grant # R01-GM-80180-01-A2, “Sepsis and Critical Illness in Babies ≥ 34 Weeks Gestation, “ Gabriel Escobar, PI
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

Rate of Sepsis by Gestational Age

Rate of Sepsis by Maternal Temperature

Rate of Sepsis by Duration of ROM

# Multivariate Model of EOS Risk

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

### 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>

*Not significant in multivariate model:* maternal age, maternal race, meconium-stained amniotic fluid, maternal treatment with non-antibiotic medications and epidural use
Microbiology of EOS
Changing Microbiology of EOS

Most common EOS pathogen

- 1930’s: Group A Streptococcus
- 1940’s: Gram-negative infections
- 1950’s: Staphylococcal infections
- 1960’s: Gram-negative infections
- 1970’s: Group B Streptococcus

Speculated increased incidence may be due to:

- Changes in newborn bathing practices
- Use of contraception changing the vaginal microflora
- Venereal transmission

Basic Microbiology of GBS

- **Gram-positive diplococcus**
  - Gram stain as pairs and chains
  - Beta-hemolytic on blood agar
  - Produce orange pigment on Granada indicator medium

- **Facultative anaerobe**
  - produce lactic acid
  - sensitive to PMN-burst killing

- **Nutritional requirements make for colonizers and pathogens, not free-living in environment**
Microbiology of Neonatal EOS

All EOS

VLBW EOS

VLBW EOS – Trading One Infection for Another?

- NICHD 16 NICU data

- Yale-New Haven NICU reports tripling of *E. coli* EOS incidence among VLBW admissions comparing pre-GBS IAP and post-GBS IAP eras

No Change in Ampicillin-Resistant EOS

- Decreases in overall EOS driven by decreases in ampicillin-sensitive EOS
- No increase in ampicillin-resistant EOS

Puopolo and Eichenwald, *Pediatrics* 2010;125:e1031
CDC Study of *E. coli* EOS

- 132 cases/1212 controls identified via ABC surveillance from 1997-2001
  - 60% of *E. coli* isolates ampicillin-resistant
- Low gestational age strongly associated with *E. coli* EOS
- Only factors associated with ampicillin-resistant *E. coli* on multivariate analysis were maternal fever and PROM > 18 hrs
- Excluded intrapartum antibiotic exposure as “cause” of resistant infections

Schrag, et al. (2006) *Pediatrics* 118(2);570
Antibiotic Resistance Is Common

Empiric Antibiotic Therapy for EOS

• Although incidence of ampicillin-resistant EOS overall stable, decrease in GBS EOS means proportion of EOS caused by ampicillin-resistant organisms has increased

• Epidemiology in term infants still supports use of ampicillin and gentamicin, especially among asymptomatic infants at risk for infection

• Among term and especially VLBW infants with a high suspicion for infection => addition of cephalosporin may be warranted
Intrapartum Antibiotic Prophylaxis (IAP) to Prevent Neonatal GBS Disease: New CDC 2010 Guideline
Strategies to Prevent GBS EOS

- Antepartum maternal culture/antibiotics
  - complicated by high incidence of recolonization
- Postpartum infant IM penicillin
  - no effect on overall mortality
  - higher mortality from pen-resistant infection
- Intrapartum treatment effective
- Correlation of antepartum culture with labor status best when performed late in 3rd trimester

Impact of GBS Intrapartum Prophylaxis

FIGURE 1. Incidence of early- and late-onset invasive group B streptococcal (GBS) disease — Active Bacterial Core surveillance areas, 1990–2008, and activities for prevention of GBS disease

CDC. Prevention of Perinatal Group B Streptococcal Disease
Revised Guidelines from CDC, 2010. MMWR 2010;59(
CDC Surveillance: GA and Racial Disparities

FIGURE 4. Incidence of early-onset invasive group B streptococcal disease, stratified by race and term — Active Bacterial Core surveillance areas, 2000–2007

Goals of CDC 2010 Revision

• Updated recommended Laboratory Methods
  – Inclusion of chromogenic media and nucleic-acid based tests (NAAT) for laboratory use if proper validation/controls are used
  – Change in definition of GBS bacteriuria
  – Mandate inclusion of inducible clindamycin resistance testing in setting of erythromycin resistance

• Updated algorithms for preterm labor and premature rupture of membranes (PROM)
  – Distinguish between labor/non-labor and use of antibiotics for latency in cases of PROM

CDC. Prevention of Perinatal Group B Streptococcal Disease
Revised Guidelines from CDC, 2010. *MMWR* 201
Goals of CDC 2010 Revision

- Clarification of definition of “serious” penicillin allergy in pregnant women
- Inclusion of NAAT for intrapartum screening
- Change in recommended antibiotics for GBS intrapartum prophylaxis (IAP)
- Revised algorithm for newborn evaluations
FIGURE 2. Indications for intrapartum antibiotic prophylaxis to prevent perinatal GBS disease under a universal prenatal screening strategy based on combined vaginal and rectal cultures collected at 35–37 weeks’ gestation from all pregnant women

Vaginal and rectal GBS screening cultures at 35–37 weeks’ gestation for **ALL** pregnant women (unless patient had GBS bacteriuria during the current pregnancy or a previous infant with invasive GBS disease)

**Intrapartum prophylaxis indicated**
- Previous infant with invasive GBS disease
- GBS bacteriuria during current pregnancy
- Positive GBS screening culture during current pregnancy (unless a planned cesarean delivery, in the absence of labor or amniotic membrane rupture, is performed)
- Unknown GBS status (culture not done, incomplete, or results unknown) and any of the following:
  - Delivery at <37 weeks’ gestation*
  - Amniotic membrane rupture ≥18 hours
  - Intrapartum temperature ≥100.4°F (≥38.0°C)†

**Intrapartum prophylaxis not indicated**
- Previous pregnancy with a positive GBS screening culture (unless a culture was also positive during the current pregnancy)
- Planned cesarean delivery performed in the absence of labor or membrane rupture (regardless of maternal GBS culture status)
- Negative vaginal and rectal GBS screening culture in late gestation during the current pregnancy, regardless of intrapartum risk factors

* If onset of labor or rupture of amniotic membranes occurs at <37 weeks’ gestation and there is a significant risk for preterm delivery (as assessed by the clinician), a suggested algorithm for GBS prophylaxis management is provided (Figure 3).
† If amnioticitis is suspected, broad-spectrum antibiotic therapy that includes an agent known to be active against GBS should replace GBS prophylaxis.

CDC. Prevention of Perinatal Group B Streptococcal Disease
Revised Guidelines from CDC. *MMWR* 2002;51(No.
**Key Change is** partial endorsement of intrapartum use of nucleic acid amplification tests (NAAT)
Nucleic Acid Amplification Tests (NAAT)

- Different commercial sources of GBS NAAT are approved for use by FDA
- All rely on real-time PCR technology to speed detection compared to traditional culture (~48-72 hrs)
  - “bedside” diagnostics amplify DNA directly from vaginal/rectal swabs for detection time ~ 1 hour
  - “laboratory” diagnostics amplify from enriched culture broth to decrease detection time ~ 24 hrs
- Multiple studies demonstrate comparable sensitivity and specificity compared to late antenatal culture
Nucleic Acid Amplification Tests

- Potential advantages include:
  - Determination of GBS status at presentation for delivery
  - Opportunity to treat GBS-unknown women by colonizing GBS status rather than by risk-factor based approach

- CDC concerns regarding:
  - Inability to perform antibiotic sensitivity testing on colonizing isolates in penicillin-allergic women
  - Practicalities of implementation: “...concerns remain regarding real-world turnaround time, test complexity, availability of testing at all times, staffing requirements, and costs.”

CDC. Prevention of Perinatal Group B Streptococcal Disease. Revised Guidelines from CDC, 2010. MMWR 2010;59(No. F
CDC 2002: Antibiotics for IAP

Recommendation to obtain colonizing isolate antibiotic sensitivities if penicillin allergic woman

Change made due 15-40% GBS resistance to erythromycin and clindamycin

Recommended agents:
- Pencillin G or Ampicillin
- Pencillin-allergic women not high risk for anaphylaxis: cefazolin
- High risk for anaphylaxis
  - Clinda/erm if sensitive
  - Vancomycin if not sensitive or unknown
CDC 2010: Antibiotics for IAP

- Defined “high risk” penicillin allergy
- Goal to reduce indiscriminate use of vancomycin
- Recommended agents are *unchanged* except that erythromycin is no longer recommended under any circumstances
Diagnostic evaluation including CBC and blood culture (+/- empiric antibiotics) for:

- Symptomatic infants
- Infants GA <35 wks
- Inadequate GBS IAP
  - Defined as IAP <4 hrs prior to delivery
- Maternal intrapartum antibiotics given for suspected chorioamnionitis
Diagnostic evaluation including (+/- empiric antibiotics) for:
- Symptomatic infants
- Maternal chorioamnionitis
- Inadequate IAP combined with other risk factors
CDC 2010: Newborn Changes

- Redefine “adequate GBS IAP” as ONLY penicillin, ampicillin or cefazolin given for ≥4 hrs prior to delivery
  - Recommend diagnostic evaluation only if inadequate GBS IAP and GA < 37 wks or PROM > 18 hrs
- Suggest delay in CBC until 6-12 hrs of life
- Suggest obstetric consultation to determine level of concern for presence of maternal chorioamnionitis
  - “The diagnosis of chorioamnionitis usually is made clinically on the basis of signs and symptoms such as fever (which might be low-grade), uterine tenderness, fetal tachycardia, maternal tachycardia, and foul-smelling or purulent amniotic fluid. In an effort to avert neonatal infections, maternal fever alone in labor may be used as a sign of chorioamnionitis and hence indication for antibiotic treatment, particularly among women with a significant risk factor for chorioamnionitis (e.g., prolonged labor or prolonged rupture of membranes.)”

CDC. Prevention of Perinatal Group B Streptococcal Disease Revised Guidelines from CDC, 2010. MMWR 2010;5
Risk of Inadequate GBS Prophylaxis?

- Revisit original prophylaxis data
- Randomized non-febrile, high-risk GBS+ mothers in labor to ampicillin or no antibiotic
  - Risk factors ROM > 12 hrs or GA < 37 weeks
  - Febrile women were excluded on ethical grounds
- Published results:
  - Febrile exclusions
  - Nonrandomized women
  - Randomized 77 women to no Rx; 83 women to ampicillin

Intrapartum Ampicillin Prevents GBS Infection

In all categories, there were no infections if mothers received intrapartum ampicillin.

CBC in Predicting EOS

• “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

Change in WBC Values Over First Days of Life

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.

CBC in Predicting Blood Culture-proven EOS

• The “roller coaster” shape of WBC, ANC and I/T curves < 72 hrs is common to all published neonatal WBC data
  
  – 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 - led to conclusion that WBC components have no utility in prediction of clinical or culture-proven EOS.

CBC in Newborns at Risk for EOS

• 67,623 infants with CBC and blood culture within 1 hour of each other, drawn at < 72 hrs life
• 245 cases of culture-proven EOS
• Linear regression models generated to determined value in predicting EOS
• Attempted to adjust for clinical variables
  – GA, BW, gender, mode of birth, PET, 5-minute Apgar did not improve predictive value
  – Accounting for time after birth (in hours) led to best model of predictive value

ROC Curves by Hour of Life

FIGURE 2
ROC curves for WBC counts (A), ANC counts (B), L/T ratio (C), and platelet counts (D) performed at <72 hours according to age at the time of the CBC.

## Likelihood Ratios for EOS

<table>
<thead>
<tr>
<th>WBC</th>
<th>&lt; 1 hr</th>
<th>1-3.99 hrs</th>
<th>≥ 4 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 -4.99</td>
<td>-</td>
<td>27.6</td>
<td>80.5</td>
</tr>
<tr>
<td>5-9.99</td>
<td>1.4</td>
<td>2.4</td>
<td>6.4</td>
</tr>
<tr>
<td>10-14.99</td>
<td>1.1</td>
<td>0.65</td>
<td>1.0</td>
</tr>
<tr>
<td>15-19.99</td>
<td>0.73</td>
<td>0.64</td>
<td>0.41</td>
</tr>
<tr>
<td>≥ 20</td>
<td>1.2</td>
<td>0.77</td>
<td>0.16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ANC</th>
<th>&lt; 1 hr</th>
<th>1-3.99 hrs</th>
<th>≥ 4 hrs</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>

Likelihood Ratios for EOS

<table>
<thead>
<tr>
<th>I/T</th>
<th>&lt; 1 hr</th>
<th>1-3.99 hrs</th>
<th>≥ 4 hrs</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>

- CBC most informative after the first 4 hours of life
- Infant sick => blood culture, antibiotics; 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

Summary of CDC 2010 for Newborns

• Newborn evaluations restricted to infants
  – Symptomatic
  – Maternal Chorioamnionitis is present
  – Inadequate GBS prophylaxis only if additional risk factors are present
    • GA < 37 wks
    • ROM > 18 hrs
• Adequate GBS IAP restricted to pencillin, ampicillin or cefazolin
• Consideration should be given to delay in CBC if needed for clinical decision-making
Current Areas of Controversy:
Impact of Algorithms to Evaluate for EOS
Among Term Infants
### Burden of the Neonatal Sepsis Evaluation

Criteria for evaluation of asymptomatic infants > 34 weeks gestation:
- maternal GBS status and IAP administration
- maternal fever > 100.5 /PROM/chorioamnionitis

<table>
<thead>
<tr>
<th>Year</th>
<th>Well Infants &gt;34 weeks</th>
<th>Total Cultures</th>
<th>True +</th>
<th>False +</th>
<th>True + (%)</th>
<th>Evaluated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>7613</td>
<td>1379</td>
<td>3</td>
<td>4</td>
<td>0.22</td>
<td>18.1</td>
</tr>
<tr>
<td>2007</td>
<td>7425</td>
<td>1270</td>
<td>5</td>
<td>1</td>
<td>0.39</td>
<td>15.3</td>
</tr>
<tr>
<td>2008</td>
<td>7231</td>
<td>1335</td>
<td>4</td>
<td>2</td>
<td>0.30</td>
<td>16.4</td>
</tr>
<tr>
<td>Total</td>
<td>22269</td>
<td>3984</td>
<td>12</td>
<td>9</td>
<td>0.30</td>
<td>17.9</td>
</tr>
</tbody>
</table>

Puopolo, unpublished data
Reasons for EOS Sepsis Evaluations at BWH

• All infants born $\geq 35$ weeks gestation evaluated for EOS during 12 month period
  – 3/1/08 – 8/31/08 and 3/1/09 – 8/31/09

• Restricted to well-appearing infants cared for in Newborn Nursery
  – EOS evaluations prompted by respiratory distress or other symptoms were excluded

• Detailed chart review to determine reasons for evaluation; CBC results; and microbiologic and clinical outcomes

Study Population

- Total Live Births: 8414
  - Births $\geq$ 35 wks: 7943
    - Not well-appearing: Admitted to NICU 700
    - Well-appearing: Admitted to Nursery 7243
      - Evaluated for Sepsis 1064
        - Empiric Antibiotics 590
        - EOS Cases 3 (0.04% of cohort)

- (8.1% of cohort)

## Reasons for EOS Evaluation

<table>
<thead>
<tr>
<th>Reason for EOS Evaluation (1064 total evaluations)</th>
<th>N (% total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal fever 100.4-100.9 °F <em>plus</em></td>
<td>389 (36.6)</td>
</tr>
<tr>
<td>- <em>plus</em> additional risk factors</td>
<td>261 (24.5)</td>
</tr>
<tr>
<td>Maternal fever ≥101 °F</td>
<td>359 (33.7)</td>
</tr>
<tr>
<td>Inadequate GBS IAP</td>
<td>274 (25.8)</td>
</tr>
<tr>
<td>- No IAP given</td>
<td>154 (14.5)</td>
</tr>
<tr>
<td>- IAP given &lt; 4 hours</td>
<td>120 (11.2)</td>
</tr>
<tr>
<td>Other</td>
<td>42 (3.9)</td>
</tr>
</tbody>
</table>
Excluded under CDC 2010 Revision?

- GBS positive/Inadequate IAP: N = 274
- ROM $\geq$ 18 hrs: N = 10 (2 with ROM>18 hrs, 8 unknown)
- GA < 37 wks: N = 18
- Potentially ~250 fewer sepsis evaluations for inadequate GBS prophylaxis (~20% of evaluations eliminated)
### Performance of Cut-off Based Algorithms

<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 antibiotics &lt; 4 hrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-GBS intrapartum antibiotics or GBS prophylaxis antibiotics &lt; 4 hrs</td>
<td>8.4</td>
<td>24.9</td>
</tr>
</tbody>
</table>

# Performance of Multivariate Model

0.5 per 1000 live births is baseline incidence of EOS among infants born 38-40 weeks. Model set at this rate or above identifies same proportion of cases and evaluates 6% vs. 17% of base population.

<table>
<thead>
<tr>
<th>Posterior Rate per 1000 Live Births</th>
<th>Prevalence (%)</th>
<th>Infected Infants Identified (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior rate $\geq 0.4$</td>
<td>9.1</td>
<td>50.6</td>
</tr>
<tr>
<td>Posterior rate $\geq 0.5$</td>
<td>6.1</td>
<td>44.9</td>
</tr>
<tr>
<td>Posterior rate $\geq 0.6$</td>
<td>4.2</td>
<td>39.4</td>
</tr>
<tr>
<td>Posterior rate $\geq 1.0$</td>
<td>1.8</td>
<td>24.3</td>
</tr>
<tr>
<td>Posterior rate $\geq 1.5$</td>
<td>0.9</td>
<td>18.0</td>
</tr>
</tbody>
</table>

Summary

• EOS remains life-threatening but increasingly rare disease of newborns

• Microbiology among term infants still dominated by GBS and other gram-positive pathogens
  – Gram-negative and ampicillin-resistant organisms primarily among VLBW infants

• Risk factors for EOS risk have been modified by widespread use of intrapartum antibiotics
  – Gestational age, maternal fever, duration of ROM and use of intrapartum antibiotics remain strong predictors among both term and preterm infants
Summary

- CDC 2010 GBS revision contains multiple changes that affect obstetric and perinatal practice
  - Potential for fewer EOS evaluations among asymptomatic term infants
- Multivariate, computer-aided approaches to EOS risk may also result in better identification of infants at risk and safely allow for fewer evaluations of asymptomatic term infants