Risk of Early Onset Sepsis

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Disclosure

- None
Overview

Epidemiology of Early Onset Sepsis (EOS) in newborns

National Guidelines

Approaches to management of EOS

Concept behind sepsis calculator
One of the most controversial topics in Neonatology today is one of the most common clinical scenarios:
Management of a newborn with risk factors for EOS!
38 weeker, mom was dx with Chorio. Her temp. was 100.4, ROM was 2hrs, GBS: Neg. APGAR 7 and 9. She received antibiotics. Baby looks good.

Get CBC, Blood cx and I will order IV Ampicillin and Gentamicin.

Why do you even ask, it’s Chorio – same as what we have been doing???
True, but this case is different. I told the parents about the antibiotics and 48hrs stay. They don’t like this idea. They want to take their infant home as soon as possible.

Then I will try to persuade, if not able to then we will call CPS.
Vigintiphobia?

Fear of bilirubin levels greater than 20

Published in 1983
Impact of IAP for GBS sepsis, 1990-2008

CDC

JAMA (2019)

Adapted from www.cdc.gov
Guidelines

**CDC 2010**

1. **Signs of neonatal sepsis?**
   - Yes: Full diagnostic evaluation* Antibiotic therapy†
   - No
     - **Maternal chorioamnionitis?**
       - Yes: Limited evaluation‡ Antibiotic therapy†
       - No: Routine clinical care+++ 
         - **GBS prophylaxis indicated for mother?***
           - Yes: Observation for ≥48 hours†††
           - No
             - **≥37 weeks and duration of membrane rupture <18 hours?**
               - Yes: Observation for ≥48 hours†††
               - No
                 - Either <37 weeks or duration of membrane rupture ≥18 hours?
                   - Yes: Limited evaluation§ Observation for ≥48 hours++
                   - No

**AAP & COFN 2012**

- **Risk Factors**
  - Chorioamnionitis§
- **Diagnostic Tests**
  - Blood culture at birth WBC/Diff ± CRP at age 6–12 h
- **Antibiotics**
  - Broad-spectrum antibiotics

- **Management**
  - Blood culture positive
    - Infant remains well Lab data abnormal
    - Continue antibiotics
    - Lumbar puncture
  - Blood culture negative Infant remains well Lab data normal
    - Continue antibiotics if mother received antibiotics during labor and delivery
    - Discontinue antibiotics and discharge by 48 hours
How many Newborns are being Evaluated and Treated?

- Based on 2010 CDC guidelines:
  - Antibiotics: ~200-fold higher than the incidence of EOS.

- Brigham and Women’s Hospital (Boston)
  - Antibiotics: 8% infants (800 treated to prevent 4 EOS)
  - Incidence of EOS: 0.4/1000 live births.

- Kaiser Permanente Northern California
  - Antibiotics: 5% infants
  - Blood culture: 15% infants
  - Incidence of EOS: 0.4/1000 live births.

Mukhopadhyay, 2013; Kuzniewicz, 2016
Is There a Risk of Treatments?

- Well, it’s just a brief course of antibiotics!
- Increase in prevalence of Asthma and Food allergies.
- Antibiotic exposure in the first 6 months of life: Asthma, food allergy, anaphylaxis, allergic rhinitis, and allergic conjunctivitis. (Mitre et.al. Murk et.al. Hirsch et.al.).
- Diverse microbiome plays a central role.
- Perturbations in the microbiome can increase the risk for allergic diseases.
Is There a Risk of Doing Evaluation and Treatments?

- 4-fold increase in late initiation of breastfeeding
- 2-fold increase in non-medically indicated formula
- IV infiltrations: 20%-44%
- Childhood obesity
- Medical error

Chorioamnionitis

- First report on chorioamnionitis management patterns among US obstetricians.
- Wide variation in practice pattern.
- 26% of obstetricians make the diagnosis from maternal fever alone, leading to overdiagnosis.
Phobia#2

- Choriophobia

Published in 2012

Abstract
The management of a newborn born to a mother with chorioamnionitis is controversial. By using data collected on neonates born in the era of routine maternal screening for Group B Streptococcus, we calculate that the risk of early-onset sepsis in a hypothetical infant born at term to a...
Summary So Far

- Official guidelines from CDC, AAP and the National Institute for Health and Care Excellence (NICE) —all published 2010- mid 2019:
  - Outdated leading to unnecessary overtreatment of babies with almost infinitesimal sepsis risk.
  - Question at the heart of the matter is one of balancing risk and benefit
Pitfalls of Guidelines

- Should a ROM of 6 hour be weighed the same as 16 hours?
- Is a maternal temperature of 100.4°F the same as 102°F?
- No accounting for interactions between predictors.
- How does two variables like GBS colonization and prolonged ROM together affect the risk for EOS?
Challenges

- Overall risk is low but how to assess the individual infants risk?
- What is a good Number Needed to Treat to prevent one case of EOS?
- How to identify the highest risk patients?
- Instead of attributing highest risk for patients with dx of Chorioamnionitis, can we assign risk based on individual variables?
Quantum Leap

Bayesian Model

Kaiser Permanante Study

Binary Decision Model
AAP
CDC
NICE
Do We Have Evidence-based Approach?

- **Bayesian Analysis**

<table>
<thead>
<tr>
<th>Prior Probability of EOS</th>
<th>Modify the probability by adding Maternal Info</th>
<th>Modify again by adding baby Info</th>
<th>Posterior Probability</th>
<th>Decide</th>
</tr>
</thead>
</table>
| Population risk          | Maternal Temperature, ROM Duration, GBS status| Well appearing, sick looking    | Individual Patient Model | 1) Observe  
2) Evaluate and Observe  
3) Evaluate and Treat |

- **Population risk**

- **Bayesian Analysis**

- **Prior Probability of EOS**

- **Modify the probability by adding Maternal Info**

- **Modify again by adding baby Info**

- **Posterior Probability**

- **Decide**

1) Observe  
2) Evaluate and Observe  
3) Evaluate and Treat
 Nested case-control study in the era of GBS prophylaxis

Objective:
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
Criteria:
GA ≥ 34 weeks at 14 different hospitals in CA and MA
Culture confirmed bacterial infection at less than 72 hours of life

Cases: 350 cases identified (from a cohort of 608,014 live births)

Controls: 1063
AIM:

Combine maternal risk factors with the newborn clinical status to further refine the infant’s risk of EOS

Data collected for first 24 hours of life

Three risk groups

Treat empirically

Observe and evaluate

Continued observation
## Clinical Presentation

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical illness</strong></td>
</tr>
<tr>
<td>In the first 12 h of age, the infant had a 5-min Apgar &lt;5; received nasal continuous positive airway pressure or mechanical ventilation; received continuous infusion of vasoactive drugs; had a clinical seizure; or had significant respiratory distress (nasal flaring, grunting, or retractions were present and the infant received supplemental oxygen within the first 6 h)</td>
</tr>
<tr>
<td><strong>Equivocal presentation</strong></td>
</tr>
<tr>
<td>In the first 12 h of age, the infant experienced at least 2 instances of 1 of the following, with “instance” meaning that there were ≥2 measurements ≥2 h apart:</td>
</tr>
<tr>
<td>Heart rate ≥160</td>
</tr>
<tr>
<td>Respiratory rate ≥60</td>
</tr>
<tr>
<td>Temperature ≥100.4°F or &lt;97.5°F</td>
</tr>
<tr>
<td>Respiratory distress (grunting, flaring, or retracting)</td>
</tr>
<tr>
<td><strong>Well appearing</strong></td>
</tr>
<tr>
<td>The infant did not fall into one of the above 2 groups in the first 12 h of age</td>
</tr>
</tbody>
</table>
### Clinical Presentation

<table>
<thead>
<tr>
<th>Sepsis risk at birth estimated from maternal risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.65/1000 live births</td>
</tr>
<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Well appearing</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Equivocal presentation</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Clinical illness</td>
</tr>
</tbody>
</table>
## Contribution of Model

### Relative Contribution to Model Predictor Contribution

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

https://neonatalsepsiscalculator.
Performance of Multivariate Model (Sepsis Calculator)

<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 ≥ 0.4</td>
<td>9.1</td>
<td>50.6</td>
</tr>
<tr>
<td>Posterior rate ≥ 0.5</td>
<td>6.1</td>
<td>44.9</td>
</tr>
<tr>
<td>Posterior rate ≥ 0.6</td>
<td>4.2</td>
<td>39.4</td>
</tr>
<tr>
<td>Posterior rate ≥ 1.0</td>
<td>1.8</td>
<td>24.3</td>
</tr>
</tbody>
</table>

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 the same proportion of cases and evaluate 6% vs 17% of base population.

Puopolo et al. (2011) Pediatrics 128(5)
Advantages of Sepsis Risk Score

- More efficient—fewer infants evaluated, same proportion of cases identified
- Uses only objective data
- Could be incorporated into EMR
- 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
Retrospective review of 698 well appearing newborns ≥ 34 weeks (Mothers with Chorioamnionitis)

Applied the EOS risk calculator retrospectively.
Reduction of Labs and Antibiotics in Newborns (>=35wks) with Chorioamnionitis

Arunachalam et. al. (unpublished)
Reduction of RN Time in Houston Community NICU

Arunachalam et. al. (unpublished)
What is the risk of early-onset GBS disease in term infants born to GBS-negative mothers with chorioamnionitis?

Formula=

Early-onset GBS disease in term infants born to GBS-negative mothers with chorioamnionitis

Number of term live-birth infants born to GBS negative mothers with Chorioamnionitis
Determining Risk in Your Unit

For Determining Numerator:

- Number of term infants with early-onset GBS disease born to mothers with Chorioamnionitis = 39 infants
- Rate of maternal screening for GBS in mothers of term infants who develop early-onset GBS disease = 68.5%
- Rate of term infants with early-onset GBS disease whose mothers were screened negative for GBS = 81%
- Number of term infants who develop early-onset GBS disease born to GBS-negative mothers with chorioamnionitis: $39 \times 0.81 \times 0.685 = 22$ infants
Determining Risk in Your Unit

For Determining Denominator:

- Total number of live births = 396,586
- Term live births = \( \sim 340,000 \) (85% of births)
- Rate of Chorioamnionitis complicating deliveries = 3%
- Number of term live-birth deliveries complicated by Chorioamnionitis: \( 340,000 \times 0.03 = 10,200 \) infants
- Rate of GBS screening of mothers = 85%
- Rate of mothers screened negative for GBS = 75.8%
- Number of term live-birth infants born to GBS negative mothers with Chorioamnionitis: \( 10,200 \times 0.75 \times 0.85 = 6,572 \) infants
Determining Risk in Your Unit

Early-onset GBS disease in term infants born to GBS-negative mothers with chorioamnionitis- 22

Number of term live-birth infants born to GBS negative mothers with Chorioamnionitis- 6572

= 0.334%

- If normal physical exam: risk reduced by 75%. (Escobar et. al-2000)
- If Mom treated with Antibiotics, the risk further decreases.
Conclusions

- Combining maternal predictors with the evolving newborn clinical status can safely reduce antibiotic exposure.
- Possible to still miss cases of EOS by multivariate models.
- Local incidence of sepsis and hospital systems must be considered when implementing EOS management guidelines.

*Neonatal clinicians must transition from worrying about what we will “miss” and to being realistic about what we will “find”.*
Thank You
CONCLUSIONS

- EOS has become one the most vexing types of problems in modern medicine - a low incidence, high-consequence illness, and one that occurs in vulnerable patients who cannot speak to us.
CBC role study

Talk about roller coaster cbc

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
CBC role

- BC 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
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
CONCLUSIONS

- Questions still remained…
- • Does antibiotic administration immediately after birth prevent low-level bacteremia from progressing to clinical illness?
- • Will the sepsis calculator fail to appropriately identify asymptomatic infants who are destined to develop EOS?
- • Is there a risk of delayed antibiotic treatment in infants with EOS who now present with more severe clinical features?
- • Will there be an increase in hospital readmissions for EOS after hospital discharge?