Early-onset sepsis (EOS) calculator & reduction in antibiotic therapy and safety

15th Hot Topics in Neonatal Medicine
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Tromsø, Norway
Outline

• Case
  – What would you do?

• How many infants receive antibiotics?
  – Focus on term newborns

• How do antibiotics affect
  – Antibiotic resistance?
  – Morbidity later in life?

• Tools to reduce antibiotic overuse
  – EOS calculator
  – Structured physical examination
Case

• Baby born after vaginal delivery at 37+2 weeks gestation
  – Apgar 8-9-10

• Rupture of membranes for 19 hours

• Unknown GBS status

• Mother got fever with T 38.3 °C around 1 h before delivery
  – Received no antibiotics at delivery

• Baby is breathing a bit fast the first 60 minutes, thereafter appears perfectly well for the next 2-3 hours, is breathing normally and starts breastfeeding

What would you do?

– Observe only?

– Blood culture and CBC, and when?

– Start antibiotics?
Antibiotics in the first week of life

- International guidelines
  - Local/national guidelines

- Start of antibiotics often based on
  - Risk factors
    - Different interpretations
  - Clinical symptoms
    - Unspecific/different interpretations

In many middle- and high-income countries will 5-10% of all newborn infants receive antibiotics in the first week of life

Cohen-Wolkowiez, PIDJ 2009
Mukhopadhyay, J Perinatol 2013
2009 to 2011 – all Norwegian term infants

- 2.3% received antibiotics in 1st week of life
- 0.05% had a culture proven sepsis, that is only 1 out of 44 who received antibiotics
- 1 of 169 000 infants died (GBS sepsis)
Epidemiology

- Incidence of EOS in term infants is declining
  - Improved perinatal care
    - Mortality varies

- If 5-10% of all newborns are treated?

Up to 100-200 infants receive unnecessary antibiotics for one-1 case of EOS

Benitz W, EClinicalMedicine 2020

0.5-0.8/1000 live births
Infants across the world are massively exposed to antibiotics in the newborn period

Does it matter?
Yes, we think so!

- Antibiotic therapy induces a gut microbiota dysbiosis and increased antibiotic resistance
  - Affects the immature gut microbiota ++
    - Stefka, PNAS 2014

- A healthy gut microbiota stimulates the developing normal immune system
  - E.g. increasing regulatory T cells that can inhibit inflammation
    - Belkaid, Cell 2014
    - Olin, Cell 2018
Antibiotic use and development of antibiotic resistance

- Different definitions for multi-drug resistance among studies included in this systematic review
  - 30/31 studies included Gram-negative bacteria

  All types of antibiotic exposure were associated with an increase in the prevalence of multi-drug resistance in Gram-negative bacteria
# Antibiotic resistance
Prevalence after exposure to broad versus narrow spectrum therapy

## Broad vs. narrow spectrum antibiotics

<table>
<thead>
<tr>
<th>Study</th>
<th>Infection and/or colonization rates</th>
<th>Risk estimates</th>
<th>Colonization or infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdel-Hady, 2008</td>
<td>lower</td>
<td>OR 4.9, 95% CI 1.1-21.5†</td>
<td>Infection</td>
</tr>
<tr>
<td>Acolet, 1994</td>
<td>unchanged</td>
<td>NDA</td>
<td>Colonization</td>
</tr>
<tr>
<td>Caill, 2001</td>
<td>higher</td>
<td>NDA</td>
<td>Colonization</td>
</tr>
<tr>
<td>De Araujo, 2007</td>
<td></td>
<td>NDA</td>
<td>Colonization</td>
</tr>
<tr>
<td>De Champs, 1994</td>
<td></td>
<td>NDA</td>
<td>Colonization</td>
</tr>
<tr>
<td>De Man, 2000</td>
<td></td>
<td>RR 3.14, 95% CI 1.76-5.56</td>
<td>Colonization</td>
</tr>
<tr>
<td>Le, 2008</td>
<td></td>
<td>OR 33.73, 95% CI 1.02-1136.20</td>
<td>Infection</td>
</tr>
<tr>
<td>Linkin, 2004</td>
<td></td>
<td>NDA</td>
<td>Infection</td>
</tr>
<tr>
<td>Mammina, 2007</td>
<td></td>
<td>NDA</td>
<td>Colonization</td>
</tr>
<tr>
<td>Millar, 2008</td>
<td></td>
<td>NDA</td>
<td>Colonization</td>
</tr>
<tr>
<td>Pessoa-Silva, 2003</td>
<td></td>
<td>OR 4.60, 95% CI 1.48-14.31</td>
<td>Colonization</td>
</tr>
<tr>
<td>Thattrimontrchai, 2013</td>
<td></td>
<td>NDA</td>
<td>Infection</td>
</tr>
<tr>
<td>Thattrimontrchai, 2016</td>
<td></td>
<td>OR 4.4; 95% CI 1.2-15.6</td>
<td>Infection</td>
</tr>
</tbody>
</table>
Neonatal early onset sepsis in Middle Eastern countries: a systematic review  
Arch Dis Child 2020;0:1–10.
Nadim Khalil,¹,² Heather B Blunt,³ Zhongze Li,⁴ Tyler Hartman²

• In the Middle East region
  – EOS in middle-income countries was i) more likely to be due to Gram-negative bacteria and ii) less likely to be susceptible to ampicilllin and gentamcin, than EOS in high-income countries

• Antibiotic resistant Gram-negative bacteria a great concern!
  – Need proper treatment, but also proper antibiotic stewardship to avoid further increase
How does antibiotic therapy affect morbidity later in life?

«Early life antibiotics may influence future individual health through collateral damage on bacteria that normally live on and in healthy humans»

- Blaser, Science 2016

- Early life antibiotics associated with increased later risk of
  - Asthma and allergy
  - Obesity
  - Other autoimmune disease (IBD, etc )
Antibiotics are potent medication for newborn infants

1. Can be useful for the individual
2. Can be useful for a society
3. Lead to antibiotic resistance!
4. Can induce immune alterations leading to increased risk of diseases later in life

We have to reduce antibiotic use in the NICU whenever and as much as possible!
What tools do we have?

AAP EOS-guidelines present three approaches to identify and manage neonates at risk of EOS


- Categorical perinatal risk factor assessment

- Multivariate EOS risk assessment using the neonatal EOS calculator

- Performing serial physical examination over the first 24-48 hours of life
Neonatal EOS calculator
http://kp.org/eoscalc

• EOS risk based on
  – Maternal risk factors
  – Neonatal clinical presentation
    • First 4-12 hours

• Stratifies newborns into three levels of risk with recommendations
  – Only observation
  – Blood culture and check vitals
  – Empiric antibiotics

Risk stratification also based on local EOS incidence
GBS status has little impact..
Advantages of the EOS-calculator versus “conventional” risk factor assessment

Neonatal sepsis calculator

- Bayesian approach

- First predictive model - Establishes baseline-risk for EOS based on maternal risk factors
  - Objective variables
  - Incorporate continuous variables

- Second predictive model - Quantifies how the EOS baseline risk is modified by the infant’s clinical examination
  - Classification-scheme for evolving clinical status first 12-24

Old algorithms (CDC, NICE)

- Information is lost as continuous variables are dichotomized
  - ROM ≥ 18 hours
  - Gestational age < 37 weeks

- Chorioamnionitis a “tricky” and subjective clinical diagnosis

- “Coarse classification” leads to overuse of antibiotics
# Neonatal EOS calculator

## Maternal risk factors

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of Early-Onset Sepsis</td>
<td>0.3/1000 live births (KPNC incidence)</td>
</tr>
<tr>
<td>Gestational age</td>
<td>38 weeks 5 days</td>
</tr>
<tr>
<td>Highest maternal antepartum temp.</td>
<td>38.0 °C</td>
</tr>
<tr>
<td>ROM (hours)</td>
<td>12</td>
</tr>
<tr>
<td>Maternal GBS status</td>
<td>Negative, Positive, Unknown</td>
</tr>
<tr>
<td>Type of intrapartum antibiotics</td>
<td>Broad spectrum antibiotics &gt; 4 hrs prior to birth, GBS specific antibiotics &gt; 2 hrs prior to birth, No antibiotics or any antibiotics &lt; 2 hrs prior to birth</td>
</tr>
</tbody>
</table>
## Neonatal EOS calculator

**Clinical neonatal presentation**

<table>
<thead>
<tr>
<th>Clinical illness</th>
<th>Most/all recommended to receive AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Persistent need for NCPAP/ HFNC/mechanical ventilation (outside of the delivery room)</td>
<td></td>
</tr>
<tr>
<td>2. Hemodynamic instability requiring vasoactive drugs</td>
<td></td>
</tr>
<tr>
<td>3. Neonatal encephalopathy/Perinatal depression</td>
<td></td>
</tr>
<tr>
<td>• Seizure</td>
<td></td>
</tr>
<tr>
<td>• Apgar Score @ 5 minutes &lt; 5</td>
<td></td>
</tr>
<tr>
<td>4. Need for supplemental O₂ &gt; 2 hours to maintain oxygen saturations &gt; 90% (outside of the delivery room)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Equivocal presentation</th>
<th>Few recommended to receive AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Persistent physiologic abnormality &gt; 4 hours</td>
<td></td>
</tr>
<tr>
<td>• Tachycardia (HR &gt; 160)</td>
<td></td>
</tr>
<tr>
<td>• Tachypnea (RR &gt; 60)</td>
<td></td>
</tr>
<tr>
<td>• Temperature instability (&gt; 100.4°F or &lt; 97.5°F)</td>
<td></td>
</tr>
<tr>
<td>• Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O₂</td>
<td></td>
</tr>
<tr>
<td>2. Two or more physiologic abnormalities lasting for &gt; 2 hours</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Well appearing</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No persistent physiologcal abnormalities</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. Classification of Clinical Presentation**

NCPAP, nasal continuous positive airway pressure; HFNC, high-flow nasal cannula; HR, heart rate; RR, respiratory rate.
Neonatal EOS calculator
Evidence

• Substantial reduction (44%; 95% CI 41-47%) in antibiotic use
• No «safety problems» compared to conventional strategies
Neonatal EOS calculator

Challenges

• Need to know predictor data and local incidence

• Never forget that sepsis may develop despite a first recommendation to withhold antibiotics
  – «Missed cases»

• Despite a significant reduction compared to «old strategies»; still 2.6% of all near-term and term newborn receive antibiotics
Can we do even better?

• Is a further reduction in antibiotic exposure possible?

• Serial physical examination
  – A strategy proposed initially by Swiss and Italian researchers
    • Duvoisin 2011
    • Berardi 2015

  – Infants at risk undergo a structured clinical examination by a nurse/doctor, regularly during first 24-48 hours
Vatne A, et al. 2020. Reduced antibiotic exposure by serial physical examination in term neonates at risk of EOS
Accepted for publication

Period 1
N= 8825

Period 2
N= 8417

• QI-project, population based data

• 57% reduction in term infants exposed to antibiotics in first week of life
  – 2.9% to 1.3%
Case

- Baby born after vaginal delivery at 37+2 weeks gestation
  - Apgar 8-9-10

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- Unknown GBS status

- Mother got fever with T 38.3°C 1 h before delivery
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- Baby is breathing a bit fast the first 60 minutes, thereafter appears perfectly well for the next 2-3 hours, is breathing normally and starts breastfeeding

Or maybe just observation and SPE..😊

Sepsis calculator....
Aurora borealis over the city of Tromsø

...thank you!