Neonatal Sepsis

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No disclosures
Case presentation

• 30 2/7 week delivery
• Emergent CS due to maternal fever, severe abdominal pain and non-reassuring BPP
• Baby limp with apnea and given PPV and HR <100 with poor response and HR <40 and required chest compressions
• Apgar scores 2/3/5/6/7
• Acidosis and hypoglycemia and given volume and dextrose

Case presentation

• Blood gas: 6.97/78/38/17.5/-16 capillary
• Glucose 35
• Wbc 1.1, hgb 14.1, hct 41.7, platelet 114 CRP 46

Case presentation

• Orotracheal intubation by transport team with 3.0, 8cm at lips. Placement verified via: direct visualization, auscultation, capnography (Waveform), chest rise, moisture in tube, X-Ray, ETCO2 Detector
Case presentation

• Hypotension and treated with volume and dopamine
• Curosurf given for RDS
• Ventilator 20/6 35 and 50%
• Transported uneventfully

Case presentation

• Blood culture positive for Listeria monocytogenes
• Treated for 21 days with ampicillin and gentamicin

Listeria monocytogenes

A Listeria bacterium infecting tissue.
Credit: CDC/ Dr. Balasubramanyam Prabhu Arora
Listeria monocytogenes

- Gram-positive, motile, rod-shaped bacterium that is ubiquitous in the environment. Isolated in soil, wood and decaying matter.
- Principal route of acquisition through ingestion of contaminated food products. Listeria has been isolated from prepared meat (e.g., hot dogs, deli meat), unpasteurized dairy products, unwashed raw vegetables, and seafood.
Women around the world have a craving for dirt during their pregnancies. 
Credit: Sera Young, Columbia University Press

Neonatal Sepsis (Sepsis Neonatorum)

Neonatal sepsis is any infection involving an infant during the first 28 days of life. Neonatal sepsis is also known as “sepsis neonatorum”. The infection may involve the infant globally or may be limited to a single organ. It may be acquired prior to birth (early-onset EOS) or after birth (late-onset LOS).

Early-onset sepsis (EOS)

- Neonatal early-onset sepsis (EOS) is defined by the Center for Disease Control and Prevention (CDC) as blood and/or cerebrospinal fluid culture-proven infection occurring in the newborn at less than 7 days of age.
- For the continuously hospitalized VLBW (<1500 g) infant, EOS is defined as culture-proven infection occurring at less than 72 hours of age.
- VLBW EOS justified by 2 findings: the risks of infection in VLBW infants after age 72 hours primarily derive from the specifics of on-going neonatal intensive care rather than perinatal risk factors and the organisms that cause infection reflect nosocomial flora of the NICU more than perinatal acquired maternal flora.
- 85% presentation prior to 24 hours
Early-onset sepsis (EOS)

- Neonatal early-onset sepsis (EOS) is a significant source of morbidity and mortality among newborns, especially among very low-birth-weight infants.
- Risk factors for EOS have been defined to identify and evaluate infants at risk for EOS.
- Intrapartum antibiotic prophylaxis (IAP) has reduced EOS and influenced microbiology.
- Recommendations for perinatal risk factor-based evaluation and empiric antibiotics resulted in large antibiotic use.
- Risk factor assessment tools have reduced medical intervention and promote antibiotic stewardship.

Epidemiology of Neonatal EOS

- Incidence 0.77-0.98 per 1,000 live births
- Infants >37 weeks 0.53 per 1,000
- Infants <37 weeks 3.71 per 1,000 (7 x higher)
- VLBW 10.96 per 1,000 (20 x higher)
- Fatality 11-16% with more than 90% of the deaths in the preterm population
- 3,300 newborns affected and more than 340 deaths annually in the United States

Epidemiology of Neonatal EOS

- 60 people die per year in the USA from lightning strikes
- 40 people die per year in the USA from skiing/snowboarding accidents
- 5000 people die per year in the USA from choking on food
- 37,000 people die from automobile accidents
Epidemiology of Neonatal EOS

- Group B streptococcus (GBS) was the leading cause of EOS in the 1970s and continues to remain so among the term population, accounting for 40% of EOS cases. National incidence has decreased 87% (1.8/1000 in 1990 to 0.24/1000 in 2013) with widespread intrapartum antibiotic prophylaxis (IAP).
- Gram-negative enteric bacteria (primarily *Escherichia coli*) have become the leading cause of EOS in preterm infants. *E. coli* accounts for more than 38% of EOS in the preterm infant.
- Most pathogenic organisms colonize the maternal GI/GU tract and result in ascending colonization of the fetal compartment through ruptured or less frequently intact membranes.
- *Listeria monocytogenes* is an exception that occurs via hematogenous spread of the organism across the placenta.

Organisms EOS NICHD (06-09)

<table>
<thead>
<tr>
<th>Organism</th>
<th>%</th>
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<tbody>
<tr>
<td>GBS</td>
<td>43%</td>
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<tr>
<td><em>E. coli</em></td>
<td>28%</td>
</tr>
<tr>
<td>Other streptococci</td>
<td>10.5%</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>7.7%</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>3.4%</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>0.8%</td>
</tr>
<tr>
<td>Coagulase-negative <em>Staphylococcus</em></td>
<td>0.5%</td>
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</table>
EOS Caused by GBS

- GBS colonizes the human genital and gastrointestinal tracts and upper respiratory tract in young infants.
- GBS: 10 distinct polysaccharide serotypes (Ia, Ib, and II-IX) most common type Ia, Ib, II, III and V with type III more common in late onset sepsis and meningitis.
- 20-30% of US women are colonized at any given time but 60% are colonized at some point during a 12 month period.
- In the absence of IAP 50% of infants born to GBS positive mother are colonized at birth and 1-2% of colonized infants develop invasive disease.
- Lack of maternally derived, protective capsular, polysaccharide specific antibody associated with invasive disease.
- Other factors that predispose the newborn to GBS disease: complement deficiency, diminished neutrophil function, and decreased innate immunity as well as others that are less well understood.

Clinical Factors of GBS EOS

- Maternal colonization with GBS is the greatest risk factor for neonatal GBS disease.
- GBS bacteriuria during pregnancy is associated with heavy colonization and is considered a significant risk factor.
- Preterm, low birth weight, PROM, ROM >12 hours, chorioamnionitis and no IAP.
- Twice the incidence of neonatal GBS EOS among black infants compared with white infants that is not explained by colonization rates among black women.
Guidelines for GBS IAP

- CDC has published consensus guidelines that endorse universal screening for GBS and the use of IAP for prevention of neonatal GBS disease first in 1996 and revised in 2002 and 2010

- Risk factors
  - GBS colonization determined at 35-37 weeks
  - GBS bacteriuria during pregnancy
  - Prior delivery of infant with GBS disease
  - Preterm labor
  - Unknown GBS combined with temperature >100.4 or ROM >18 hours
  - Inadequate IAP (endorse antibiotic 4 or more hours before delivery)
Guidelines for GBS IAP

- With implementation of CDC recommendations GBS specific EOS incidence decreased to 0.24 per 1,000 US live births with a persistent gap in incidence among white population (0.21 per 1,000 US live births) compared with the black population (0.44 per 1,000 US live births)
- Most GBS EOS among term infants now occurs in mothers who have screened negative for GBS colonization. Rescreen with NAAT

Epidemiology of E coli EOS

- E coli is the second most common organism that causes EOS in all neonates and the single most common EOS organism in VLBW infants
- E coli are anaerobic, gram-negative rods found in the human intestinal tract and commonly in the human vagina and urinary tract
- Hundreds of antigenic types with primary EOS due to strains with K1-type polysaccharide capsule
- Concern regarding GBS IAP resulting in increasing incidence of E coli EOS and particular ampicillin-resistant E coli EOS
  - Conflicting results in VLBW
  - Not found in term infants
Other Organisms (EOS)

- *L. monocytogenes* are gram-positive rod bacterium that most commonly infect humans via the ingestion of contaminated food.
- Principal route of acquisition through ingestion of contaminated food products. Listeria has been isolated from prepared meat (e.g., hot dogs, deli meat), dairy products, unwashed raw vegetables, and seafood. Soft cheeses and unpasteurized milk most frequent.
- Listeria doesn’t generally cause significant disease in immunocompetent adults but can cause severe illness in pregnant women and their fetuses and newborns.
- Many cases undiagnosed in spontaneous abortion of the previable fetus.

Other Organisms (EOS)

- Obligate anaerobic bacteria: *Bacteroides fragilis* justifies sending both aerobic and anaerobic cultures
- Methicillin-sensitive *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus*
  - Hospital-acquired infections in VLBW
  - Community-acquired pediatric infections
  - Rare cause of neonatal EOS
  - Study of 5,732 pregnant women documented 3.5% incidence of MRSA in GBS screening culture but no cases of MRSA neonatal EOS

Empiric Antibiotic Regimen for EOS

- Ampicillin: aminopenicillin that is a bactericidal beta-lactam that works by binding the penicillin-binding proteins (PBPs) and disrupting bacterial wall synthesis. Ampicillin has enhanced penetration through the outer membrane of gram-negative bacteria.
  - Safe antibiotic with rare adverse effects (rash, urticaria, diarrhea, liver dysfunction)
  - Resistance: Beta-lactamase or altered PBPs (78% of *E. coli* resistant)
- Gentamicin: aminoglycosides work by binding the ribosomal RNA and inhibiting protein synthesis as well as disrupting bacterial cell membrane. Highly polar cationic molecules attracted to the negatively charged lipopolysaccharide molecule of gram-negative bacteria. The polar nature prevents efficient passage across the blood brain barrier.
  - Ototoxic and nephrotoxic
  - Low resistance (4% *E. coli*, 60% *Klebsiella* outside US)
**Alternative Antibiotics for EOS**

- **Cephalosporins**
  - Excellent CNS penetration
  - Common adverse effects: phlebitis, fever, emesis, diarrhea, increased LFTs, and cholelithiasis; serious effects: seizures, hemolytic anemia, thrombocytopenia and leukopenia
  - Ceftriaxone is not recommended and displaces bilirubin from albumin as well as precipitates with calcium in newborn lungs and kidneys
  - Increased mortality with use of ampicillin and cefotaxime
  - Increasing rates of cephalosporin resistance

- **Carbapenem ideal for polymicrobial infections**
  - Destroys colonizing flora resulting in an increased risk of fungemia.
  - Risks are phlebitis and seizures (less risk for seizures with meropenem than imipenem in newborns)

**Risk of EOS**

- How do we identify high-risk newborns and prevent the onset and/or progression of the disease?
  - Perinatal risk factors: GBS colonization, prolonged duration of ruptured membranes, maternal fever, gestational age
  - Clinical status: 90% become symptomatic in the first 24-48 hours and asymptomatic is associated with decreased risk
  - Laboratory:
    - Blood culture
    - Complete blood count with differential
    - Biomarkers: CRP, Interleuken 6, Interleuken 8, Tumor Necrosis Factor alpha, Procalcitonin
      - High negative predictive value but not sufficient to restrict the use of empiric antibiotic treatment

**CDC and AAP practice recommendations**

- Advocate evaluation of infants who are born with signs of illness
- Well-appearing infants born in the setting of maternal chorioamnionitis
- Inadequate GBS IAP
- Significant variation in practice using CDC or AAP or variations of both
Consequences of Current Approach

- Low incidence of EOS in term and late preterm infants leads to a relatively high incidence of evaluation and empiric antibiotic treatment of uninfected newborns
- Implementing the 2010 CDC recommendations
  - 7% lowest risk group (asymptomatic term and near-term newborns) evaluated for EOS and 75% of those evaluated received broad spectrum empiric antibiotics
  - Economic cost using hundreds of hours of specialized care
  - Separation for evaluation and delayed breast feeding with increased formula supplementation
  - Association with antibiotic exposure and NEC in VLBW infants and wheezing in the general population

Risk Stratification Using Bayesian Modeling

- Low absolute risk of EOS and effect of current evaluation algorithms suggest a need to improve EOS risk assessment
- EOS risk assessment use individualized risk factors in isolation and in dichotomized form
- Algorithms do not account for interactions between risk factors and impose cut-off points
  - Sudden change of risk at 18 hours

Risk Stratification Using Bayesian Modeling

- Puopolo et al developed a multivariate model that uses established EOS risk factors in a multivariate manner to quantitatively determine risk among infants born at 34 weeks' gestation or greater
- Bayesian approach starting with the prior probability of EOS in the population uses Bayes' theorem
  - P(H|E)=P(E|H)P(H)/P(E)
- Probability modified using objective data from intrapartum risk factors for EOS and then subsequently modified by the newborn's clinical condition
- Developed using 350 EOS cases and 1,063 controls obtained from a birth cohort of more than 600,000 live births in 14 different centers
Risk Stratification Using Bayesian Modeling

- Intrapartum risk
  - Gestational age
  - Duration of rupture of membranes
  - Highest maternal intrapartum temperature
  - Type and timing of intrapartum antibiotics
- Newborn examination
  - Well appearing
  - Equivocal
  - Clinical illness

Well appearing: no persistent physiologic abnormalities
- Equivocal
  - Persistent physiologic abnormality n>4 hours
  - Temperature instability (>=100.4F or <97.5F)
  - Abnormalities during grunting, paroxysm, or retractions not requiring supplemental O2
  - Two or more physiologic abnormalities lasting for >2 hours
  - Tachycardia (HR>=160)
  - Tachypnea (RR>=60)
  - Temperature instability (>=100.4F or <97.5F)

Clinical illness
- Persistent need for NCPAP/HFNC/mechanical ventilation outside DR
- Hemodynamic instability requiring vasoactive drugs
- Neurological abnormalities/Perinatal depression
- Apnea: one @ 3 minutes +
- Need for supplemental O2 in 2 hours to maintain oxygen saturations >90% outside the DR

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Suspected Risk at</th>
<th>Birth Based on</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well appearing</td>
<td>&lt; 0.65/1,000 live births</td>
<td>Birth: 0.65-1.14/1,000 live births</td>
<td>Risk: &gt;1.14/1,000 live births</td>
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<tr>
<td></td>
<td>Continued Observation</td>
<td>Observe and Evaluate</td>
<td>Treat Empirically</td>
</tr>
<tr>
<td></td>
<td>88% of live births</td>
<td>11% of live births</td>
<td>4% of live births</td>
</tr>
<tr>
<td></td>
<td>NMT 970</td>
<td>NMT 823</td>
<td>NMT 118</td>
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Equivocal presentation
Observe and Evaluate 11% of live births NMT 823

Clinical illness
Treat Empirically 4% of live births NMT 118
Online risk calculators

- www.newbornsepsiscalculator.org
- https://neonatalsepsiscalculator.kaiserpermanente.org
- The use of this type of objective, multivariate approach is estimated to safely reduce the number of infants evaluated and empirically treated for EOS by 80,000 to 240,000 infants per year

Vermont Oxford Network (VON)

- Vermont Oxford Network (VON) is a worldwide collaboration of healthcare professionals dedicated to changing the landscape of neonatal care through a coordinated program of data-driven quality improvement, education and research.
- INICQ: Choosing Antibiotics Wisely
  - Decreasing overuse and misuse of antibiotics in the NICU and newborn period
  - Assisting centers, health systems and states to aim for a 25% reduction in the use of antibiotics in the newborn population
iNICQ 2018
Choosing Antibiotics Even More Wisely!
Systematically Addressing Key Conditions
That Commonly Trigger Antibiotic Use
CDC / VON Core Curriculum
January –December 2018
Target Audience for 2018 Core Sessions
Every care team member responsible for caring for infants who may receive antibiotics in your setting (newborn nursery, step-down unit, or NICU)
• Physicians (Obstetricians, Midwives, Pediatric Hospitalists, Neonatologists);
• Nurse Practitioners, PAs, and Trainees
• Pharmacists
• Nurses (OB, Neonatal)
• Respiratory Therapists
• Educators, CNIs, QI Leaders, Senior Leaders
• Data and/or EMR Analyst

A Call to Action!
Reducing Overuse and Misuse of Antibiotics
Learning Objectives
1. Identify key evidence demonstrating the rapid emergence of multi-drug resistance pathogens in perinatal medicine and the need for obstetrician and neonatal care providers to collaborate on antibiotic stewardship efforts.
2. Analyze the evidence identifying key “drivers” of antibiotic use in newborns as well as opportunities to identify opportunities to identify and improve misuse and overuse.
3. Define standardization and review how this quality improvement strategy is a principal tactic of antibiotic stewardship efforts and the quality improvement projects for NICQ2018 improvement teams.
4. Review the importance of tracking antibiotic utilization rates (AUR) and develop a plan to share your “plot the dot” results in real-time with your team.

Smart Aim
• Decrease antibiotic utilization for preterm and term newborns in our NICU by 10%
• Implement antibiotic stewardship program
• Educate parents and make antibiotic information available
Decrease AUR by 10%

Demonstrated Organizational Commitment to reduced AUR

Develop guidelines to decrease AUR

Develop pharmacy driven interventions to decrease AUR

Report regularly on antibiotic use and resistance

DRIVERS OF CHANGE

Driver Diagram!

- Decrease AUR by 10%
- Demonstrated Organizational Commitment to reduced AUR
- Develop guidelines to decrease AUR
- Develop pharmacy driven interventions to decrease AUR
- Report regularly on antibiotic use and resistance

Interventions/Test(s) of Change

- Hard stop antibiotics 36 hours
- Assess Vancomycin usage for central line manipulation
- Documentation of antibiotics during daily rounds
- Perioperative antibiotic guidelines
- ?

Measures

- Measure monthly Antibiotic Utilization Rates as antibiotic days per 1000 patient days per month (antibiotic log for NICU and well newborn nursery at each site)
- Each antibiotic will count as a patient day (Amp/Gent for 48 hours is 4 antibiotic days)
- Antibiotic Utilization Rates (AUR)
- Total number of patient days that infants were exposed to 1 or more antibacterial or antifungal agents administered intravenously or intramuscularly per 1000 patient-days per month.


Puopolo KM, Eichenwald EC. No change in the incidence of ampicillin-resistant, neonatal, early-onset sepsis over 18 years. Pediatrics. 2010;125(5):e1031–e1038


Stoll BJ, Hansen NI, Higgins RD, et al; National Institute of Child Health and Human Development. Very low birth weight ... of gram-negative infections continues in the National Institute of Child Health and Human Development Neonatal...