Antibiotic Stewardship in Neonatal Intensive Care Units

Ashraf Baeshu, MD
Disclaimer

- I have nothing to disclose
Objectives

• Describe antibiotic use in NICU
• Learning benefits of antibiotics stewardship
• Understanding Kaiser sepsis calculator
Background

• Antibiotics are the most commonly prescribed medications given to hospitalized children
• 71% of PICU patients and 43% of NICU patients receive antibiotics in a multicenter study
• Point prevalence of 29 NICUs found that 47% of infants were receiving at least 1 antibiotic

History of antibiotic use in neonates

- **1950s**: Group B Streptococcus was identified as the cause of sepsis in neonates
- **1960s-70s**: Antibiotic prophylaxis against GBS and other infections is routinely given to all preterm infants
- **1980s-90s**: Strategies to treat mother to prevent GBS transmission were implemented
- **2000s-present**: Negative effects of prophylactic antibiotics are increasingly realized

Limiting the use of antibiotics in NICUs

• Broad spectrum antibiotic exposure has been associated with
  – Emergence of multi-drug resistant bacteria
  – Development of invasive candidiasis

• Prolonged duration of empiric antibiotic therapy for EOS in ELBW is associated with
  – Increase risk of death
  – Increase risk of NEC
  – LOS
  – Prolonged hospital stay
Antibiotic use variation among NICUs

- California Children’s Services (CCS) has required NICUs to submit antibiotic use data since 2013
- 132/136 NICUs in California participate in the California Perinatal Quality Care Collaborative (CPQCC) which prepares the data
- 127 NICUs were included in this study (52,061 infants and 746,051 patient-days)

Antibiotic use variation among NICUs
Antibiotic use variation among NICUs

- Overall, AUR varied 40-fold, from 2.4% of patient-days to 97.1% of patient-days
- No statistically significant correlations between AUR and proven infection, NEC, surgical case volume, or NICU mortality
- Highest variation was amongst intermediate NICUs with 31-fold variation
Indication for antibiotic use

- Confirmed vs Suspected
- Confirmed vs Culture negative sepsis (CNS)
- A study of 1607 infants who received 9165 days of antibiotics showed
  - 94% of antibiotics were for suspected sepsis
  - 26% continued >5 days for CNS
- A Study of 754 infants in 2 NICUs showed 8.8-fold increase in antibiotic use to treat CNS vs proven sepsis
Outcomes of prolonged antibiotic use

- Multicenter study in 19 NICUs with 5693 infants was conducted between 1998-2001
- 2147 infants (53%) received prolonged empirical therapy (center range: 27%-85%)
- Prolonged initial empirical antibiotic therapy was associated with increased risk of necrotizing enterocolitis or death
## Outcomes of prolonged antibiotic use

<table>
<thead>
<tr>
<th></th>
<th>Outcome</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
<td>P</td>
</tr>
<tr>
<td><strong>NEC or death, N</strong></td>
<td>3099</td>
<td>918</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prolonged initial treatment, n (%)</td>
<td>1577 (51%)</td>
<td>563 (61%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>NEC, N</strong></td>
<td>3594</td>
<td>440</td>
<td></td>
</tr>
<tr>
<td>Prolonged initial treatment, n (%)</td>
<td>1892 (53%)</td>
<td>255 (58%)</td>
<td>.04</td>
</tr>
<tr>
<td><strong>Death, N</strong></td>
<td>3359</td>
<td>657</td>
<td></td>
</tr>
<tr>
<td>Prolonged initial treatment, n (%)</td>
<td>1716 (51%)</td>
<td>412 (64%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
CDC statement on antibiotic resistance

“Antibiotic resistance is one of the biggest public health challenges of our time. Each year in the U.S., at least 2 million people get an antibiotic-resistant infection, and at least 23,000 people die. Fighting this threat is a public health priority that requires a collaborative global approach across sectors”

- CDC website
12-step campaign

Preventing infection
- Vaccinate
- Get the catheter out

Diagnose and treat effectively
- Target the pathogen
- Access the expert

Choose antimicrobials wisely
- Practice antimicrobial control
- Use local data
- Treat infection not contamination
- Treat infection not colonization
- Know when to say no
- Stop when cured

Prevent transmission
- Isolate the pathogen
- Break the chain of contagion
Compliance with 12-step campaign

• A study reviewed compliance of 4 tertiary NICUs
• 28% of courses and 24% of days were judged to be non-adherent to a CDC 12-Step
• Inappropriate use was more common with continuation of antibiotics (39%) than with initiation of therapy (4%)
• Common reason for non-adherent included
  – Failure to narrow antibiotic coverage
  – Prolonged course post-op or chest tube
Improve Antibiotic Use to Combat Antibiotic Resistance

CDC is working to reduce unnecessary antibiotic use

White House National Action Plan to Combat Antibiotic-Resistant Bacteria (CARB)

Goal: By 2020, reduce inappropriate outpatient antibiotic use by 50%

Find out when antibiotics are necessary. Visit: http://www.cdc.gov/getsmart

70% Necessary Prescriptions
30% Unnecessary Prescriptions

At least

At U.S. Doctors’ Offices and Emergency Departments

FACT SHEET: Obama Administration Releases National Action Plan to Combat Antibiotic-Resistant Bacteria

Judicious use of antibiotics in healthcare and agricultural settings is essential to slow the emergence of resistance and extend the useful lifetime of effective antibiotics. The CDC estimates that up to half of all human antibiotic use is unnecessary or inappropriate. The Action Plan includes activities to foster improvements in the appropriate use of antibiotics (i.e., antibiotic stewardship) by improving prescribing practices across all healthcare settings, preventing the spread of drug-resistant threats in healthcare facilities and communities, and continuing to eliminate the use of medically-important antibiotics for growth promotion in animals.

By 2020, significant outcomes in this area will include:

- Establishment of antimicrobial stewardship programs in all acute care hospitals and improved antimicrobial stewardship across all healthcare settings.
- Reduction of inappropriate antibiotic use by 50% in outpatient settings and by 20% in inpatient settings.
- Establishment of State Antibiotic Resistance (AR) Prevention (Protect) Programs in all 50 states to monitor regionally important multi-drug resistant organisms and provide feedback and technical assistance to health care facilities.
- Elimination of the use of medically-important antibiotics for growth promotion in food-producing animals.
Get Smart About Antibiotics Week
November 14–20, 2016

www.cdc.gov/getspring
Why is antimicrobial stewardship in the NICU challenging?

- Significant consequences of missing an infection
- Nonspecific signs of infection in neonates
- Difficulty in establishing diagnosis of infection
  - Can’t culture PICC lines, only small amounts of blood submitted for culture, invasive procedures often avoided
  - Coagulase negative staph can be a contaminant or pathogen
CDC 12-step in NICU setting

• Patel et al 2012 summarized approach in the NICU by modifying CDC 12-step

1. Before Starting Antibiotics—Diagnostic Strategies
   – Diagnostic markers (CRP vs CRP+IL8)
   – Optimizing blood cultures
   – Obtaining 2 blood cultures
CDC 12-step in NICU setting

2. Starting Antibiotics—Selecting Empiric Therapy
   - Amp and Gent most commonly used for EOS
   - Amp and 3rd generation cephalosporin has shown increasing resistance
   - No double coverage for same bacteria
   - Utilize hospital antibiogram

3. Reevaluating the Antibiotic Regimen
   - Evaluating the site of culture for colonization
   - Following susceptibility
   - Date and time of report, growth after 48hrs is likely to be contamination
CDC 12-step in NICU setting

4. Monitoring for toxicity
   - Dosing schedule should be based on GA, weight

5. Implementing Shorter Duration of Perioperative Prophylaxis
   - 67% of post-op patient receive antibiotics > 1 day
   - 24% receive a combination of drugs
   - Approach in adults is use 1 agent and discontinue in 24hrs

6. Implementing Antibiotic Stewardship Program (ASP)
Core Elements of ASP

• Leadership Commitment: Dedicating necessary human, financial and information technology resources

• Accountability: Appointing a single leader responsible for program outcomes.
Core Elements of ASP

• Drug Expertise: Appointing a single pharmacist leader responsible for working to improve antibiotic use.

• Action: Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e. “antibiotic time out” after 48 hours)

• Tracking: Monitoring antibiotic prescribing and resistance patterns
Core Elements of ASP

• Reporting: Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff

• Education: Educating clinicians about resistance and optimal prescribing
Early Onset Sepsis

- Sepsis developing within 72hrs of birth
- Early Onset Sepsis rate has decreased over the years with introduction of antepartum Abx
- CDC guidelines published in 2002 and revised in 2010
- Rate dropped from 4% to 0.5-2%
- ~ 8-10% of infants of well-appearing infants born >34 wks are treated with Abx
- CDC guidelines uses simple cutoffs for continuous variables
Kaiser sepsis calculator

• Case-control study
• From 1995-2007 in 12 locations
• Reviewed all sepsis cases <72hrs and compared with control cases from same population
• Investigated different prenatal variables
Results

• Out of ~600K births they had 350 cases of EOS
• EOS rates was 0.58 per 1000 births
• GBS 53%, E Coli 20%, others (Staph, Listeria, GNR)
• On initial analysis Preterm and post-term delivery, maternal fever, use of epidural analgesia, and prolonged ROM were strong individual predictors of infection
Results

- NNT using CDC was 1737
- When using KSC NNT was 118 for high risk infants
- Most predictive power comes from maternal fever ~ 60%, followed by GA ~ 17% and then ROM ~ 12%
- Dropped their % of infant needing Abx from 6-10% down to 4%
- Implementing this to all US birth means 80,000-240,000 less infants will receive ABx
ASP in our NICU

- We joined VON choosing antibiotic wisely collaborative in Jan 2016
- Aim was to decrease Antibiotic Utilization Rate (AUR) by 10% over 2 years
- AUR as defined number of antibiotic days per 1000 patient days
- We were able to decrease AUR by 19% in NICU alone and by 34% when combining NICU and Newborn Nursery
Antibiotic Stewardship
NICU: 34+ weeks gestation
Early Onset Sepsis
Antibiotic Usage Rate (AUR) per 1,000 patient days

Sepsis Algorithm was built into
Hard Stop at 4 doses built into Order Set (9/17)
Sepsis Calculator Go Live! (3/17)
It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.
### Predictor vs Scenario

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of Early-Onset Sepsis</td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td>weeks, days</td>
</tr>
<tr>
<td>Highest maternal antepartum temperature</td>
<td>Fahrenheit</td>
</tr>
<tr>
<td>ROM (Hours)</td>
<td></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, Broad spectrum antibiotics 2-3.9 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>

### Risk per 1000/births

<table>
<thead>
<tr>
<th>EOS Risk @ Birth</th>
<th>Risk per 1000/births</th>
<th>Clinical Recommendation</th>
<th>Vitals</th>
</tr>
</thead>
</table>

### EOS Risk after Clinical Exam

<table>
<thead>
<tr>
<th>Clinical Illness</th>
<th>Risk per 1000/births</th>
<th>Clinical Recommendation</th>
<th>Vitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well Appearing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equivocal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Illness</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Classification of Infant's Clinical Presentation

- Clinical Illness
- Equivocal
- Well Appearing
### Classification of Infant's Clinical Presentation

<table>
<thead>
<tr>
<th>Clinical Exam</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Clinical Illness** | 1. Persistent need for NCPAP / HFNC / mechanical ventilation (outside of the delivery room)  
2. Hemodynamic instability requiring vasoactive drugs  
3. Neonatal encephalopathy / Perinatal depression  
   - Seizure  
   - Apgar Score @ 5 minutes < 5  
4. Need for supplemental O₂ ≥ 2 hours to maintain oxygen saturations > 90% (outside of the delivery room) |
| **Equivocal**      | 1. Persistent physiologic abnormality ≥ 4 hrs  
   - Tachycardia (HR ≥ 160)  
   - Tachypnea (RR ≥ 60)  
   - Temperature Instability (≥ 100.4°F or < 97.5°F)  
   - Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O₂  
2. Two or more physiologic abnormalities lasting for ≥ 2 hrs  
   - Tachycardia (HR ≥ 160)  
   - Tachypnea (RR ≥ 60)  
   - Temperature Instability (≥ 100.4°F or < 97.5°F)  
   - Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O₂ |
| **Well Appearing** | No persistent physiologic abnormalities |

Note: abnormality can be intermittent