Neonatal Antibiotic Stewardship

Disclosure

- I do not have any financial arrangement or affiliations with a commercial entity.
- I will not be discussing the unlabeled use of a commercial product during the presentation.

Objectives

- Discuss the human micro-biome and the impact of antibiotic exposure on health outcomes
- Identify the problem of antimicrobial resistance and the importance of antibiotic stewardship
- Demonstrate strategies to track and implement antibiotic stewardship in neonates
- Review the results of the antibiotic stewardship program in the NICU at UPH-Meriter Hospital

Human Micro-biome

- The forgotten organ that has co-evolved with humans
- Trillions of organisms in the intestine
- 1000 species
- ~100 microbial genes for every human gene
- Innate and adaptive immunity evolved to require microbial interactions during development

Human Micro-biome

Normal Immune Development

A micro-biome is born

- Major colonization event at birth
- Vaginal microbiome shifts during pregnancy to become dominated by Lactobacillus<sup>1</sup>
- Human milk oligosaccharides promote the proliferation of Bifidobacterium infantis in infant intestinal tract<sup>2</sup>
- First weeks: facultative anaerobes (<i>Enterococcus, Streptococcus, Rothia</i>)
- First months: Bifidobacterium, Lactobacillus, Veillonella as transitioned to more anaerobic
- Then environmental bacteria, solid diet, cessation of breastfeeding

<sup>1</sup>Aagaard et al. 2012
<sup>2</sup>Vangay P et al, Cell Host & Microbe 2015
Timeline of Factors

- Initial colonization
- Maternal influence
- Delivery mode
- Microbial diversity

Yang et al., 2016

Delivery Mode

- Prime influence in shaping gut microbiome
- Strain-specific links between maternal fecal microbiome and infant microbiome
- Vaginal delivery
  - Bacteroides
  - Bifidobacterium
  - Parabacteroides
  - Escherichia/Shigella

Operative Delivery

- Fecal and vaginal maternal microbes less evident in children delivered by C-section
- Dominated by skin, oral, environmental microbes:
  - Enterobacter
  - Haemophilus
  - Staphylococcus
  - Streptococcus
- Microbiome more heterogeneous
- Differences persisted at 12 months, especially paucity of Bacteroides

Dominguez-Bello 2010

Primary feeding

Factors affecting the development of the microbiome and disease risk

Madden J et al, JAMA Pediatrics 2016
Perinatal antibiotics

- 33.39% of newborns are exposed to antibiotics during delivery
- IAP infants reduced microbial richness and biodiversity
- Predominance of Enterobacteriaceae and Proteobacteria
- Significant reduction in Bifidobacterium strains, Actinobacteria and Bacteroidetes

Newborn Antibiotic Exposure

- >5% term infants receive postnatal antibiotics
- Early infants differences noted at 3 & 12 mos., with Bifidobacterium underrepresented
- Premature infants: Consistent with overabundance of single species
- The impact of antibiotics on infants during development has implications for immune and metabolic function

Infant Microbiome recovery after initial antibiotic exposure

Antibiotics and child health

- Increased susceptibility to infection after antibiotics
- Critical window during infancy relating to obesity risk is being elucidated

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Long-term Implications for the Microbiome

- Neurodevelopment
- Allergies and asthma
- Obesity
- Inflammatory bowel disease, celiac disease
- Type 1 diabetes mellitus
- Mental health
The Threat of Antibiotic Resistance

- Antibiotic resistance is increasingly being recognized as one of the most serious threats to public health.
- What is antibiotic resistance?
- Quite simply it means that a bacteria can’t be killed by the antibiotic that clinicians would normally use.
- Patients with infections caused by resistant bacteria have to be treated with 2nd, or 3rd line choices. In some cases, there are no choices at all.
- The urgent need to address antibiotic resistance has been emphasized by many groups around the world.

The Human Cost of Antibiotic Resistance

- Increase in antibiotic-resistant organisms in the NICU from 1993-2013.

Driving Factors of Antibiotic Resistance

- Some are out of our control.
- The ability of bacteria to mutate to resistant antibiotics.
- BUT some of the most important ones are very much in our control.
- Overuse of antibiotics.
- Spread of resistant organisms in healthcare settings through poor infection control practices.

Antibiotic Overuse

- Well documented in all healthcare settings.
- Unnecessary antibiotic use has been estimated to be:
  - ~30% in hospitals
  - ~50% in outpatient clinics
  - ~70% in long term care facilities (nursing homes)
- Antibiotics are also used inappropriately in agriculture.

Neonatal Intensive Care Unit Antibiotic Use Varies Widely, and is Unrelated to Proven Infection Rates

Antibiotic Utilization Rate (AUR)

- Total # patient-days that infants were exposed to one or more antibacterial or antifungal agents administered intravenously or intramuscularly per 100 patient-days in the reporting NICU, expressed as a percentage

Results

- 127 NICUs in the analytic dataset
- 53,061 infants
- 746,051 patient-days
- 214,323 entailed antibiotic exposure
- Overall, antibiotic use rate varied 40-fold
  - 2.4% to 97.1%
  - median = 24.5%; quartile 1 ≤ 17.5%, quartile 4 ≥ 33.5%

Results

- In either overall or stratified analysis, NO correlation between AUR and
  - Proven infection
  - NEC
  - Surgical case volume
  - NICU mortality
- Comparing NICUs in lowest AUR quartile with NICUs in highest quartile revealed NO difference in
  - Proven infection
  - NEC
  - Surgical case volume
  - NICU mortality

Results

- Examining AUR and other resource use:
  - No correlation between AUR and AvLOS overall; however,
    - Positively correlated among Regional-level NICUs (Pearson’s correlation coefficient = 0.78, p < 0.001)
  - Compared with Regional NICUs in lowest AUR quartile, Regional NICUs in highest AUR quartile reported AvLOS 35% longer (90.2 days versus 66.9 days, p = 0.03)
- No correlation between AUR and inborn admission rate overall; however,
  - Positively correlated among both Regional (Pearson’s) and Spearman’s correlation coefficient = 0.68; p = 0.005) and Intermediate NICUs (Pearson’s correlation coefficient = 0.68; p = 0.005)
  - Compared with Regional NICUs in lowest AUR quartile, inborn admission rate among Regional NICUs in highest AUR quartile was 218% higher (0.24 versus 0.11, p = 0.03)
Discussion

- NICUs appear to differ only in rates of suspected infection NOT proven infection
- Practice variation appears to hinge on how practitioners interpret and respond to clinical situations ultimately considered unproven infection
- Unwarranted variation exists in antibiotic use
- In some NICUs, antibiotics are overused

Adverse Effects of Antibiotic Exposure in Neonates

- Increased risk of Candida bacteremia.
- Increased risk of infection with resistant organisms.
- Increased risk of late-onset sepsis.
- Alterations in the microbiome—potentially long-term increased risk of NEC?

Impact of Potentially Inappropriate Antibiotic Use in NICUs

- 5693 ELBW infants in 19 centers (NICHD NRN) Cotton et al 2009
  - 35 d of initial empiric therapy despite sterile cultures
    - NEC or death 1.30 (1.22–1.38)
    - NEC 1.34 (1.04–1.73)
    - Death 1.86 (1.45–2.39)
  - 365 infants, 33% who received prolonged antibiotics Kuppala VS et al 2011
  - 35 d of initial empiric therapy despite sterile cultures
    - NEC, LOS, or death 2.66 (1.12–6.30)
    - LOS 2.45 (1.28–4.67)

Antibiotic Stewardship is Now Required

- The Joint Commission accreditation standard for antibiotic stewardship became effective on Jan 1, 2017

Core Elements for Antibiotic Stewardship Programs

- Leadership commitment from administration
- Single leader responsible for outcomes
- Single pharmacy leader
- Antibiotic use tracking
- Regular reporting on antibiotic use and resistance
- Educating providers on use and resistance
- Specific improvement interventions
Key components

- Use of evidence
- Written unit procedures/protocols/guidelines
- Education about the practice
- Auditing compliance and understanding
- Auditing primary outcomes

Principles for Stewardship

- Identifying patients who need antibiotics
- Using local data to determine empiric therapy
- Avoiding agents with overlapping activity
- Adjusting antibiotics for culture results
- Monitoring for toxicity
- Optimizing dose, route, and duration

Strategies for Stewardship

- Interdisciplinary antibiotic stewardship teams
- Prescriber audit and feedback
- Preauthorization and formulary restrictions
- Education
- Information communication technologies
- Metrics to evaluate program, e.g., rates of adverse drug events, dosing and timing of antibiotics

Antibiotic Stewardship Team

- Physician
- Infectious diseases (ID) physician
- Pharmacist
- Infection preventionists
- Bioinformatician
- Nurses
- Patients/Families

- At minimum a physician, a pharmacist and a nurse or nurse practitioner

Changes in resistance patterns after initiation of stewardship

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Metrics of Measurement

- **AUR**
- **Days of therapy**

**AUR**
- Total # patient-days that infants were exposed to one or more antibacterial or antifungal agents administered intravenously or intramuscularly per 100 patient-days in the reporting NICU, expressed as a percentage

<table>
<thead>
<tr>
<th>Date</th>
<th># infants on abx</th>
<th># infants in NICU</th>
<th>AUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/1/17</td>
<td>2</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>4/2/17</td>
<td>4</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Days of Therapy

- Aggregate sum of days for which any antibiotic agent was administered to a patient divided by a standardized denominator (patient days, days present or admissions)
- (days of therapy)/(1000 patient days)

Other measures

- Baseline infection rate (number of positive cultures/number of cultures)
- Length of time for cultures to turn positive
- Antibiotic sensitivity profiles

Balancing Measures

- Are changes designed to improve one part of the system causing new problems in other parts of the system?
- Examples:
  - Late onset sepsis
  - Readmissions
  - Bacterial resistance

Potential better practices

- Antibiotic timeout
- Automatic Stop Orders for antibiotics
- Kaiser Sepsis Risk Calculator
Antibiotic Timeout

- Captures and controls attention
- Enhances informed and deliberative reasoning
- Redirects decision direction
- Fosters autonomy and improves team empowerment
- Limits use of emotion-based decisions

Automatic Stop in the NICU Admit Order Set Decreases Antibiotic Exposure

- 48-hr automatic antibiotic stop was placed into the electronic admit order
  - Placed in admit order set for Ampicillin & Gentamicin only.
  - Coverage duration was exactly 48-hr.
  - Decision to prolong course was an active, not passive, decision.

Antibiotic Does Pre and Post-Intervention

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Total</th>
<th>Ampicillin</th>
<th>Cefotaxime</th>
<th>Gentamicin</th>
<th>Metronidazole</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre (12 mo)</td>
<td>28,613</td>
<td>7370</td>
<td>4944</td>
<td>5913</td>
<td>5000</td>
<td>5488</td>
</tr>
<tr>
<td>Post (13 mo)</td>
<td>19,191</td>
<td>5101</td>
<td>3249</td>
<td>4051</td>
<td>3318</td>
<td>3472</td>
</tr>
<tr>
<td>Dose Reduction</td>
<td>30.8%</td>
<td>32.9%</td>
<td>31.5%</td>
<td>33.6%</td>
<td>36.7%</td>
<td></td>
</tr>
</tbody>
</table>

Antibiotic Doses/Patient Days

How the Calculator Can Help: Difficult Decisions

1. Should I do a sepsis work up on a neonate who was delivered?
2. Are the risk factors for early onset sepsis enough to start antibiotic treatment?

Kaiser Sepsis Risk Calculator

- The purpose of the calculator is to enhance the appropriate use and avoidance of antimicrobial treatment for newborns.
- The goal is to reduce the risks associated with unnecessary exposure of newborns to antimicrobials while ensuring that newborns who require antimicrobial treatment are treated promptly.
- The calculator determines the probability of early onset sepsis for a newborn by combining the known associations between risk factors and early onset sepsis.
- The calculator is intended for newborns who were born at 34 weeks or more of gestation.
What the Calculator Does

- Uses **objective** data to account for the changing clinical condition of the newborn during the first 12 hours after birth.
- Combines the objective maternal data with the objective neonatal clinical findings to increase the predictive power of the risk stratification model.

Where do you find it?

- Search for: sepsis calculator Kaiser

Information Needed for the Calculator:

- Gestation age of the newborn
- Highest maternal amniotic fluid temperature
- Duration of rupture of membranes in hours
- Maternal GBS status
- Type of antibiotics administered to the mother
- Clinical exam of the newborn

Risk Stratification Model

The risk stratification permits placement of the newborn into one of 3 care pathways:
1. Treat empirically with antibiotics.
2. Evaluate with treatment conditional upon further information.
3. Continued observation.

The Sepsis Calculator: Instructions

Instructions are near the top. Be sure to click the button to display the instructions.

The Sepsis Calculator: Data Entry

1. Choose incidence of EOS from the pull-down menu. There are 4 choices:
   a. 0.3/1000 live births (KPNC incidence)
   b. 0.4/1000 live births
   c. 0.5/1000 live births (CDC national incidence)
   d. 0.6/1000 live births
2. Enter the gestational age in weeks and days.

3. Enter the highest maternal temperature.

4. Enter the duration of rupture of membranes in hours.

5. Insert maternal GBS status.

6. Insert type of antibiotics administered to mother.
The Sepsis Calculator:
Case 1

- 37 weeks 5 days of gestation.
- Highest maternal temperature of 100.3 F.
- Rupture of membranes 12 hours before delivery.
- Mother GBS positive.
- GBS specific antibiotic given to mother starting 12 hours before delivery.
- Newborn has equivocal findings.

Case 1 Data Entered

Case 1: Calculation Result and Clinical Interpretation

- The incidence of early onset sepsis (for all newborns with similar risk factors) is 0.53 cases per 1000 births.
- For newborns with similar risk factors who have equivocal findings on clinical exam, the incidence is 2.65 cases per 1000 births.
- The clinical recommendation is to obtain a blood culture specimen and monitor vital signs every 4 hours for 24 hours.

The Sepsis Calculator:
Case 2

- 36 weeks 2 days of gestation.
- Highest maternal temperature of 101.6 F.
- Rupture of membranes 18 hours before delivery.
- Mother GBS negative.
- Broad spectrum antibiotics given to mother 2 hours before delivery.
- Newborn has findings of clinical illness.

Case 2 Data Entered

Case 2: Calculation Result and Clinical Interpretation

- The incidence of early onset sepsis (for all newborns with similar risk factors) is 2.04 cases per 1000 births.
- For newborns with similar risk factors who have findings of clinical illness on exam, the incidence is 41.60 cases per 1000 births.
- The clinical recommendation is to start empiric antibiotics (after obtaining appropriate specimens for culture).
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Implementation of a Neonatal Antibiotic Stewardship Program at UnityPoint Meriter NICU

Setting

- Unity Point Health-Meriter Hospital is a 36 bed level III NICU, with approximately 700 admissions a year, 20-30 (3.5%) of which are ELBW infants. Average daily census is approximately 27, with 20-25% of infants on antibiotics. There are approximately 3800 deliveries per year.

Problem Description

- Retrospective review of antibiotic use from October, 2015 to December, 2015 revealed the AUR was consistently higher than similar institutions.
- Audit in February, 2016 demonstrated our antibiotic usage to be in the highest quartile when compared to 143 other NICUs worldwide.
- Examination of the incidence of bacterial infections showed UPH-Meriter to be in the lowest quartile in the VON Network.
- This discrepancy represents a clear opportunity for improvement in judicious use of antimicrobial agents.

Aim

- By December, 2016 we aim to decrease our antibiotic utilization rate from 24.3% to 19.4%, to achieve a 20% reduction in overall use.

Measurement

- **Antibiotic Utilization Rate**
  - Total # patient-days that infants were exposed to one or more antibacterial or antifungal agents administered intravenously or intramuscularly per 100 patient-days in the reporting NICU, expressed as a percentage.
Interventions

- **PDSA #1 (01/16/2016)**
  - Literature review performed and protocol for the diagnosis and treatment of meningitis was refined. This included the use of sepsis criteria and imaging to assist in diagnosing true meningitis.

- **PDSA #2 (04/15/2016)**
  - (1) Assignment of Kaiser Score for risk assessment for early-onset sepsis for all infants born at >34 weeks, prior to starting antibiotics
  - (2) Time-out for review of antibiotics at 24-36 hours of treatment
  - (3) 100% compliance with documentation of antibiotic therapy assessment > 36 hours, including indications, length, and site of administration

- **PDSA #3 (06/08/2016)**
  - Revised guideline to limit the use of prophylactic fluconazole to infants less than 1000 grams on >7 days of broad-spectrum antibiotics.

- **PDSA #4 (06/15/2016)**
  - Implementation of a protocol for well-appearing infants in the newborn nursery with suspected chorioamnionitis utilizing the Kaiser sepsis score.

- **PDSA #5 (07/06/2016)**
  - (1) Update UTI prophylaxis guidelines to discontinue use of prophylactic amoxicillin for mild hydronephrosis
  - (2) Individualized antibiotic usage reports for the second quarter of 2016.

Results

- **2016 Results**
  - Oct 2015-Dec 2015: AUR 24.3%
  - April 2016-Dec 2016: AUR 13.6%
  - 44% reduction in antibiotic usage!!!!

Future Directions

- Informational handouts for parents
- 48 hour stop order on all antibiotic orders
- CSF PCR panel

Recommendations/Strategies

- Antibiotic stewardship team
- Guidelines for antibiotic use and discontinuation
- Data collection
- Audits and feedback

How can you incorporate these into your practice?

Questions/Comments?