Antimicrobial Stewardship in the NICU: A Big Idea for our Smallest Patients

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Disclosures

• None
Objectives

• Describe the barriers to appropriate use of antimicrobials in neonates
• Identify methods to improve utilization of antimicrobials in the NICU
• Discuss key concepts of antibiotic prescribing in the NICU
• Apply antibiotic prescribing rules to common NICU cases
CASE #1

• 10 week old ex 39 week GA with congenital surfactant deficiency, interstitial lung disease
• Multiple chest tubes placed due to pneumothoracies, hypoalbuminemia and extensive pulm edema
• Received Amp/Gent x7 d post birth (PROM, elevated CRP, neg cx and mom GBS neg when tested prenatally)
• Fever 6 weeks earlier - cultures obtained, started on ampicillin x2 days
• Developed hypotension placed on norepi, hydrocortisone, s/p volume boluses x2, diuretics discontinued, ART line placed.
• Blood cx (peripheral and PICC), urine Cx x2, ETT Cx sent and antimicrobials started.
CASE #1

• What antimicrobials would you start?

   a) Vancomycin and gentamicin
   b) Vancomycin and cefotaxime
   c) Ampicillin and gentamicin
   d) Vancomycin and zosyn
   e) Vancomycin, meropenem, amphotericin B
ANTIBIOTIC RESISTANCE: THE GLOBAL THREAT

Severe antibiotic resistance – when bacteria change and cause antibiotics to fail – is happening RIGHT NOW, across the world.

The full impact is unknown. There is no system in place to track antibiotic resistance globally.

Without urgent action, modern medicine will be obsolete and minor injuries will once again be deadly.

SUPER RESISTANT BACTERIA: PROBLEM TODAY, CRISIS TOMORROW

In INDIA, over 58,000 babies died in one year as a result of infection with super-resistant bacteria usually passed on from their mothers.

In the EUROPEAN UNION, antibiotic resistance causes 25,000 deaths per year and 2.5m extra hospital days.

In THAILAND, antibiotic resistance causes 38,000+ deaths per year and 3.2m hospital days.

In the UNITED STATES, antibiotic resistance causes 23,000+ deaths per year and >2.0m illnesses.
Cantey JB and Milstone AM Clin Perinatol, 2015
Antimicrobial Resistance Key Concepts

• Poor antibiotic use means the survival of resistant bacteria

• Resistant bacteria accumulate and spread

• Resistance increases clinical complications, lengthens hospital stay, adds cost

• Development of new antimicrobials is slow, expensive and cannot be guaranteed
Definition of Antimicrobial Stewardship

- A practice that ensures the optimal selection, dose, and duration of an antimicrobial therapy that leads to the best clinical outcome for the treatment or prevention of infection while producing the fewest toxic effects and the lowest risk for subsequent resistance

(Gerding et al., ICHE 2001)
Goals of Antimicrobial Stewardship

• Improve patient outcomes (LOS, ICU, procedures, mortality)

• ↓ Antibiotic resistance

• ↓ Adverse effects

• ↓ Cost of healthcare associated infections
Stewardship Principles

• Know local susceptibility patterns
• Know the patient’s history of culture results
• Know spectrum of coverage and appropriate dose
• Obtain appropriate cultures before starting
• Start antimicrobials at appropriate time
• Take a 48-72 hr antimicrobial “time out”
• De-escalate and stop therapy when appropriate
Challenges of Antimicrobial Stewardship in the NICU

• Non-specific signs of sepsis
• Culture-negative sepsis
• Necrotizing enterocolitis
• Colonization vs infection with coagulase-negative Staph
• Limited pharmacokinetic studies of antibiotics
• Knowledge gaps in antimicrobial utilization, optimal antimicrobials for specific disease states

Variability in practice and prescribing
Antibiotic Use in the NICU

• Antibiotics are among the most frequently prescribed medications in the NICU

• In a point prevalence study of 29 NICUs 47% of infants were receiving at least one antibiotic

• Forty-fold variation in NICU antibiotic prescribing practice across 127 NICUs with similar burdens of proven infection
Unique Risks of Antibiotics in Neonates

• Broad spectrum antibiotic use and emergence of Multi Drug Resistant Organisms (MDROs)

• Antibiotic use is associated with development of invasive candidiasis

• Prolonged duration of empiric antibiotic therapy in ELBW infants is associated with increased risk of death and NEC
Antimicrobial Stewardship Strategies in the NICU

• Prescriber audit and feedback
• Formulary restriction and prior authorization
• Education
• Guidelines and clinical pathways
• Antimicrobial order forms
• Dose optimization
• Computer surveillance and decision support
A Collaborative Approach

- Neonatologist/APP
- Infectious diseases physician
- Obstetrician
- Nursing
- Clinical pharmacist
- Clinical microbiologist
- Infection prevention personnel
- Hospital epidemiologist
Applying CDC Stewardship Principles to NICU

<table>
<thead>
<tr>
<th>Get Smart Principles</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Accurately identify patients who need antibiotic therapy</td>
<td>Obtain 2 blood cultures for evaluation of late-onset sepsis before starting antibiotics</td>
</tr>
<tr>
<td>Use local and regional antibiograms</td>
<td>Avoid use of meropenem for empiric treatment of suspected late-onset sepsis if rates of</td>
</tr>
<tr>
<td>Avoid therapy with overlapping activity</td>
<td>multidrug-resistant gram-negative bacilli are low</td>
</tr>
<tr>
<td>Give the right dose and interval of drug</td>
<td>Avoid simultaneous use of metronidazole and meropenem to treat necrotizing enterocolitis</td>
</tr>
<tr>
<td>Review culture results and adjust antibiotics</td>
<td>Target vancomycin trough to 15-20 mg/L to treat pneumonia caused by MRSA</td>
</tr>
<tr>
<td>Monitor for toxicity and adjust therapy accordingly</td>
<td>Review microbiology results at transitions of care (e.g., sign out, weekend cross-</td>
</tr>
<tr>
<td>Stop therapy promptly if indicated by culture results</td>
<td>coverage) and narrow antibiotic coverage promptly</td>
</tr>
<tr>
<td></td>
<td>Adjust antibiotic dose for patients with deteriorating renal function</td>
</tr>
<tr>
<td></td>
<td>Discontinue antibiotics after 48 hours if blood cultures are negative and ongoing</td>
</tr>
<tr>
<td></td>
<td>infection is not suspected</td>
</tr>
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Patel SJ and Saiman L Semin Perinatol 2012
Inappropriate Antibiotic Use Common in NICU

- Inappropriate use classified by CDC 12 Step Program
  - Target pathogen
  - Avoid redundant coverage
  - Treat infection, not colonization

<table>
<thead>
<tr>
<th></th>
<th>Overall Use</th>
<th>Inappropriate Use</th>
</tr>
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<tbody>
<tr>
<td>Courses</td>
<td>323</td>
<td>90 (28%)</td>
</tr>
<tr>
<td>Antibiotic-days</td>
<td>3,344</td>
<td>806 (24%)</td>
</tr>
<tr>
<td>Infants</td>
<td>200</td>
<td>70 (35%)</td>
</tr>
</tbody>
</table>

Collecting Samples Before Antibiotics

• Obtaining adequate volume of blood for cultures
  – Most infants have > 5 cfu/mL of blood
  – 1mL of blood can detect pathogens down to 4 cfu/mL
• Obtain 2 blood cultures to help distinguish infection vs colonization
• Urine and CSF should be sent to evaluate for LOS
• Interpret with caution:
  – Cultures obtained from non-sterile sites (ie endotracheal tubes, swabs from skin lesions)
  – Urine culture with normal urinalysis
QUESTION #1

- What organism is the most common cause of **late onset** blood stream infections (BSI) in the NICU?

  a) *Pseudomonas aeruginosa*
  b) *Escherichia coli*
  c) *Candida albicans*
  d) *Staphylococcus epidermidis*
  e) *Staphylococcus aureus*
Organisms Causing Late Onset BSI

Cantey JB and Milstone AM Clin Perinatol, 2015
Empiric Therapy for Neonatal Sepsis

• Early onset sepsis (<72 hrs)
  – GBS and E. coli
  – Ampicillin + Gentamicin
  – Cefotaxime → renal dysfunc, meningitis, gonorrhea

• Late onset sepsis (>72 hrs)
  – Multiple organisms (GP, GN, anaerobic, yeast)
  – Oxacillin/Vancomycin + Gentamicin
  – Pipercillin-Tazobactam if GN (outside CNS)
  – Carbapenems for ESBL GN organisms
Re-Evaluating Empiric Antibiotics (48-72 hrs)

• Consider discontinuation of therapy if no culture growth within 36-48 hrs

• Adjust to narrowest spectrum antibiotic that effectively targets the cultured pathogen in the affected body site (ie oxacillin for MSSA)

• Develop unit specific guidelines to treat “culture negative” sepsis and pneumonia
CASE #2

- A three week old ex 31 week GA neonate on enteral feeds develops respiratory distress and episodes of bradycardia. On exam the abdomen is more distended than the day before but is soft. Hypoactive bowel sounds are heard on auscultation. A KUB is ordered STAT and shows pneumatisosis with no peritoneal free air. You order blood cultures and start antibiotics.
CASE #2

• What antibiotics would you start?

a) Ampicillin, gentamicin, and metronidazole
b) Vancomycin and gentamicin
c) Vancomycin, gentamicin, and metronidazole
d) Vancomycin and pipercillin-tazobactam
e) Vancomycin and meropenem
f) None of the above
## NEC Treatment Variability

<table>
<thead>
<tr>
<th>Most Common Antibiotic Regimen</th>
<th>Total N (%)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin and gentamicin</td>
<td>30 (21%)</td>
<td>21</td>
<td>6</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Vancomycin + piperacillin/tazobactam</td>
<td>16 (11%)</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vancomycin + cefepime</td>
<td>4 (3%)</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Piperacillin/tazobactam + gentamicin</td>
<td>15 (10%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Vancomycin, gentamicin, metronidazole</td>
<td>17 (12%)</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Ampicillin, gentamicin, metronidazole</td>
<td>6 (4%)</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Brachio S et al. PAS 2013
Using Agents with Overlapping Spectrum

- Meropenem or pipercillin-tazobactam and metronidazole for anaerobic coverage
- Use of dual beta lactams (ie oxacillin and cefotaxime, oxacillin and meropenem)
- Dual agent Gram negative coverage
  - Combination therapy does not reduce morbidity or mortality in peds
  - Combination therapy does not protect against development of resistance
  - Combination therapy group with twice the odds of nephrotoxicity
Surgical Prophylaxis

• Institutional guidelines to reduce practice variability

• Surgical Care Improvement Project (SCIP)
  – One antibiotic agent should be used
  – Duration should be less than 24 hrs
  – Up to 48 hrs for cardiac procedures

• ECMO cannulation

• Chest tube insertion
Impact of NICU Antimicrobial Resistance (Clock et al. 2016)

• Multicenter study 1,320 infants hospitalized ≥14 days

• Rectal surveillance cultures obtained at discharge

• Factors associated with colonization with resistant GNB
  – 9% of infants colonized with ≥1 resistant GNB
  – Treatment with ≥10 days of meropenem
  – Treatment with ≥5 days of third/fourth gen cephalosporin, β-lactam/β-lactamase inhibitor (i.e. Zosyn) or metronidazole
Measuring Stewardship Success

- Episodes of ineffective empiric antibiotic therapy
  → Bug/Drug mismatch
- Proportion of infants receiving appropriate dosing and timing of perioperative prophylaxis
- Rates of infections with MDR Gram – organisms
- Episodes of antibiotic-associated adverse events
- Duration of treatment for culture-negative presumed late onset sepsis