ANTIMICROBIAL STEWARDSHIP IN NICU

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Drug Use in NICUs

- 253,651 NICU patients, 1996 to 2005
- What were the most-prescribed drugs?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>186,799</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>171,388</td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>90,152</td>
</tr>
<tr>
<td>Multivitamins</td>
<td>64,329</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>55,455</td>
</tr>
<tr>
<td>Caffeine citrate</td>
<td>48,814</td>
</tr>
<tr>
<td>Furosemide</td>
<td>47,278</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>44,218</td>
</tr>
</tbody>
</table>

“ANTIBIOTIC”

Definition:

- Chemical substance produced by various microorganisms or made synthetically that is capable of destroying or inhibiting the growth of other organisms, and, in particular, bacteria

- Webster dictionary: antibiotics prevent, inhibit, or destroy life

Coined in 1889 by Louis Pasteur’s pupil, Paul Vuillemin, that means a process by which life could be used to destroy life
Antibiotics in the NICU

- Antibiotic exposure impacts the neonatal microbiome:
  - Less diversity
  - Less commensal anaerobes
  - More Enterobacteriaceae

Antimicrobial utilization practices in NICUs impact on the types of microorganisms responsible for neonatal sepsis and their antibiotic resistance patterns!
EMPIRIC ANTIBIOTIC THERAPY AND RESISTANT BACILLI

- Prospective cross-over trial, 6-month intervals (12/96-12/97): 2 NICUs (Netherlands)

- Empiric antibiotic regimens:
  - Penicillin / tobramycin (EOS);
    flucloxacillin / tobramycin (LOS)
  - Amoxicillin IV / cefotaxime (EOS);
    flucloxacillin / cefotaxime (LOS)

- Weekly rectal, respiratory aspirate cultures; clinical isolates monitored

de Man et al, Lancet 2000;355:973
EMPIRIC ANTIBIOTIC THERAPY AND RESISTANT BACILLI

◆ Penicillin (flucloxacillin) / tobramycin regimen:
  – *E. coli* predominant Gram-neg isolate (53%)

◆ Amoxicillin (flucloxacillin) / cefotaxime regimen:
  – *Enterobacter* sp. predominant Gram-neg (77%)
  – Emergence of resistance higher:
    • Cefotaxime-R Gram-neg: RR 3
    • Cefotaxime-R *Enterobacter* sp.: RR 3
    • Gram-neg bacilli resistant to empiric rx: 41 vs 3 infants (p<0.001); RR 18
EMPIRIC ANTIBIOTIC THERAPY AND RESISTANT BACILLI

- Penicillin (flucloxacillin) / tobramycin regimen:
  - Shorter hospital stay, less CVLs

- Amoxicillin (flucloxacillin) / cefotaxime group:
  - Higher vancomycin use

- No significant differences in deaths

- CoNS predominant pathogen in both groups!

* de Man et al, Lancet 2000;355:973
Prolonged Initial Antibiotic Treatment in ELBW Infants

Cotten et al. *Pediatrics* 2009;123;58

- Multicenter (NICHD NRN), retrospective study of 4039 extremely-low-birth-weight infants (BW, <1000 g) and sterile cultures in 1st 3 days of age

- Infants who received ≥5 days of therapy:
  - Higher risk of necrotizing enterocolitis (OR 1.3 [1.10-1.54])
  - Higher mortality (OR 1.46 [1.19 – 1.78])
Prolonged Initial Antibiotic Treatment in Preterm Infants

Kuppula et al. *J Pediatr* 2011;159;720

- Retrospective cohort study; 2000-2004
- 365 infants (≤32 wks, ≤1500 g) infants who survived free of sepsis and NEC for 7 days
- 36% received prolonged initial empiric antibiotics (≥5 days)
- Multivariate logistic regression:
  - LOS (OR, 2.45; 95% CI, 1.3-4.7)
  - LOS/NEC, or death (OR 2.7; 95% CI, 1.1-6.3)
Antibiotic Exposure and NEC
Alexander et al. J Pediatr 2011;159;392

- Retrospective, 2:1 control-case study: 2000-2008
- 124 NEC cases matched to 248 control subjects: gestational age, birth weight, birth year
- After removal of neonates with sepsis from cohort, risk of NEC increased significantly with duration of antibiotic exposure
- Exposure for >10 days resulted in a nearly threefold increase in risk of NEC
Antibiotic Exposure: Adverse Effects

◆ Cohort study of all infants:
  • Parkland NICU (Dallas): 9/10 - 6/14
  • ≤32 weeks and ≤1500 grams birth weight

◆ Antibiotic exposure during the first 14 days of age was quantified two ways:
  • Days of therapy (DOT, calculated by multiplying the number of doses by the dosing interval, then dividing by 24 hours)
  • Length of therapy (LOT, calendar days that infant was on at least one antibiotic)

Cantey et al. Antimicrobial Stewardship Mtg, Kansas City, 2015
# Results – Primary Outcome*

<table>
<thead>
<tr>
<th>Number</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of infants (total)</td>
<td>374</td>
</tr>
<tr>
<td>Composite outcome</td>
<td>18%</td>
</tr>
<tr>
<td>Late-onset sepsis</td>
<td>14%</td>
</tr>
<tr>
<td>NEC</td>
<td>6%</td>
</tr>
<tr>
<td>Death</td>
<td>3%</td>
</tr>
</tbody>
</table>

* Composite of late-onset sepsis, NEC, or death after 14 days of age.
### Results – Multivariate Analysis

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>95% C.I. for OR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of therapy</td>
<td>1.25</td>
<td>1.18</td>
<td>1.32</td>
</tr>
<tr>
<td>Length of therapy</td>
<td>1.49</td>
<td>1.34</td>
<td>1.67</td>
</tr>
</tbody>
</table>

- **Each additional day** of antibiotic therapy increased the risk of the composite outcome (NEC, LOS or death) even after controlling for initial severity of illness.
- Once initial severity of illness was controlled for in multivariate analysis, antibiotic exposure was the **only factor** associated with the composite outcome.
ANTIMICROBIAL STEWARDSHIP

“Selection, dose, and duration of antibiotic treatment resulting in best clinical outcome... minimal toxicity... minimal subsequent resistance.”

Goal: to improve the quality of antibiotic prescribing

Owens RC, Pharmacotherapy 2004
1. Measure antimicrobial usage to know if an intervention was effective in changing antimicrobial use

2. Measure an outcome related to the change in use

Ibrahim and Polk, Infect Dis N Am, 2014
Objectives

1. Quantify all antibiotic use in the NICU and qualify the reasons for their use
2. Identify scenarios where antimicrobial use could be reduced
3. Implement interventions targeting those areas

Cantey et al, Ped Inf Dis J 2014
Parkland Memorial Hospital: One Year Prospective Surveillance

- 1607 infants admitted to NICU; all inborn

7570 antibiotic days (4.7 per infant)

*Gerber Foundation

Cantey et al, Ped Inf Dis J 2014
% coag neg staph before, after: 48%, 59%
No. deaths/100 patient days admit before, after: 0.28, 0.31 (p=0.6)
VANCOMYCIN REDUCTION: 2 NICUs in BOSTON

NICU #1
Vancomycin
- Pre-intervention: 35%*
- Post-intervention: 62%*

NICU #2
Vancomycin
- Pre-intervention: 40%*
- Post-intervention: 49%*

* p<0.05

Ox/Naf; no change in mortality

Chiu et al. PIDJ 2011;30:273
GRAM-NEGATIVE BLOODSTREAM INFECTION: RISK FACTORS (VLBW)

Smith et al. PIDJ, 2010

- 2004-2007: prospective study in 2 NICUs (NYC)
- 51 (7%) cases of GN BSIs in 698 VLBW infants:
  - Vaginal delivery: OR 4
  - Birth weight: ≤750 g, OR 6; 751-1000 g, OR 4
  - Gastrointestinal tract pathology: OR 6
  - Vancomycin use: OR 6
  - H₂ blocker/proton pump inhibitor use: OR 7
  - Mechanical ventilation: OR 4
  - CVC days: OR 1.1
NICU - Park and Hospital, Dallas: Baseline Surveillance

1607 infants
343.2 DOT/1000 PD

Empiric therapy for suspected sepsis
94% 323 DOT/1000 PD

Culture-proven infection
5% (17.4 DOT/1000 PD)

Sterile cultures
89% (305.6 DOT/1000 PD)

GBS prophylaxis
5% (16.6 DOT/1000 PD)

Surgical prophylaxis
1% (3.5 DOT/1000 PD)
Results – Baseline Surveillance

Sterile cultures
89% (305.6 DOT/1000 PD)

≥ 5 days of therapy
26% (89.4 DOT/1000 PD)

“Ruled-out” sepsis
63% (216.2 DOT/1000 PD)

Pneumonia
16% (54.3 DOT/1000 PD)

“Culture-negative” sepsis
8% (28.4 DOT/1000 PD)

Necrotizing Enterocolitis
2% (6.2 DOT/1000 PD)

Congenital syphilis
<1% (0.4 DOT/1000 PD)

Cellulitis
<1% (0.3 DOT/1000 PD)
Results – Baseline

• **Ruled-out sepsis** accounted for **63%** of all antibiotic use
  – 32% of courses were stopped at ≤ 48 hours
  – 68% of courses were extended beyond 48 hours
  – This resulted in **40.8 “extra” DOT/1000 PD** (12% of all antibiotic use).
Results – Baseline

• Treatment for $\geq 5$ days for a presumed infection despite sterile cultures accounted for 26% of all antibiotic use:
  – Pneumonia, 16%
  – “Culture-negative” sepsis, 8%
  – Two-thirds of courses for these indications were $\geq 7$ days duration
Results – Baseline

• Interventions:

1. Limiting empiric therapy to 48 hours by means of an electronic hard stop
2. Limit treatment of suspected pneumonia to 5 days
3. Limit treatment of “culture-negative” sepsis to 5 days
<table>
<thead>
<tr>
<th>Target</th>
<th>Intervention</th>
<th>Period</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>“48 hour” rule-out sepsis courses</td>
<td>Electronic hard stop at 48 hours</td>
<td>Baseline</td>
<td>32%</td>
<td>Intervention</td>
</tr>
<tr>
<td>Pneumonia courses</td>
<td>Limit to 5 days</td>
<td>Baseline</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>“Culture-negative” sepsis courses</td>
<td>Limit to 5 days</td>
<td>Baseline</td>
<td>31%</td>
<td></td>
</tr>
</tbody>
</table>
Results

27% reduction
RESPIRATORY VIRUSES IN NICU: THE VIRION-I Study
Ronchi et al, J Pediatrics 2014

- Prospective cohort study performed at Parkland Hospital (Dallas) and Women & Infants Hospital (Rhode Island – Michelow): 1/15/12 – 1/31/13

- OBJECTIVE: To determine the incidence of respiratory viral infections among infants who are >72 hours of age, evaluated for possible sepsis and antibiotics started while in NICU

- NP specimen for respiratory viral PCR (Luminex; Genmark)
Respiratory Viruses in NICU: THE VIRION-I Study
Ronchi et al. J Pediatrics 2014

◆ 8 (8%) of 100 infants: positive respiratory viral PCR:
  – 7% (6/86) at PMH
  – 14% (2/14) at W&I

◆ 8 (6%) of 135 sepsis evaluations was associated with a positive respiratory viral PCR test
  – None had a positive bacterial or fungal blood/CSF culture.
Respiratory Viruses in NICU: THE VIRION-I Study

- 8 infants (GA: 25-34 wk; BW 420-2705 g):
  - Rhino/entero: 4
  - Parainfluenza-3: 2
  - Coronavirus: 2
- Hypothermia (7), fever (1), tachypnea (7), apnea (6), congestion/rhinorhrea (2), bloody stool (2); 2 required mechanical ventilation
- 3 received antibiotics ≥5 days
- Clinical suspicion (75% of PCR-pos infants)
Prospective, 1 year surveillance in 2 NICUs

Preterm infants <33 wks GA (NICU since birth) had nasopharyngeal swabs for detection of respiratory viruses by multiplex PCR twice weekly within 3 days of birth until discharge.

Respiratory viral panel (Luminex): 17 different respiratory viruses (influenza A/B; RSV A/B; parainfluenza 1-4; coronavirus; adenovirus; rhinovirus/enterovirus; metapneumovirus)
52% (26/50) of infants tested positive for a respiratory virus at least once during the NICU stay (708 specimens obtained)
Respiratory Viruses Detected in 26 (52%) Preterm Infants in NICU

- PIV-3: 25%
- RSV-A: 14%
- RSV-B: 16%
- Entero-rhino: 14%
- hMPV: 18%
- PIV-2: 14%

n=55

*Luminex

Virus-positive infants:
- Longer length of stay (70 d vs 35 d, p=0.002)
- Need for intubation (65% vs 29%, p=0.01)
- Duration of intubation (19 vs 5 days, p=0.03)
- Duration of oxygen requirement (51 vs 13 d, p=0.002)
- BPD (46% vs 21%, p=0.05)
- More desaturation (p<0.0001) and clinical deterioration episodes (p=0.0001)
NICU Antimicrobial Stewardship Team

◆ Multidisciplinary/interprofessional:
  – Neonatologist
  – Pediatric infectious diseases specialist
  – Neonatal or ID-trained pharmacist
  – Infection preventionist
  – Bioinformatician - information technologist
  – Neonatal nurse
NICU Antimicrobial Stewardship Program

- Diagnosis: full evaluation
- Empiric therapy: NICU-specific antibiogram, surveillance of culture results
- Dose optimization: avoid redundant use
- Prescriber audit and feedback
- Duration of therapy

NICU Antimicrobial Stewardship Program

- Improving antimicrobial use in the NICU requires generating local data and engaging key stakeholders.
- Use variability in treatment to gain consensus.
- Start with low hanging fruit to achieve success!
- Assessment needs to include safety.
- Disseminate outcomes widely within your organization and publish your results!!!