Neonatal Sepsis & Overview of Current NICU QI Projects

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Premature infants & Health Care Dollars - 2013

• Estimated expenditures: First Year
  - Employer Sponsored Health Plans: $6 billion to $14 billion
  • $78,000 per preterm infant @ the high end.

Nosocomial Infection (HAC)

- Huge burden of morbidity and mortality

  - Causes
    - Antibiotic Overuse
    - Formula Feeding
    - Use of H2 Blockers
    - Poor Central Catheter Care
    - Handwashing

Antibiotic Overuse
Bacterial Resistance

• Multiple etiologies

- Acquisition of enzymes that alter antibiotic structure and function (e.g., β-lactamases);
- Mutations in bacterial targets such as penicillin-binding proteins,
- Changes in efflux pumps: allow removal of antibiotics from bacteria or decreased entry sites (porins) which prevent antibiotics from entering bacteria.
Bacterial Resistance

• Mechanisms
  - Underdosing
  - Use of specific antibiotics (i.e., 3rd generation cephalosporin)
    • Cephalosporin use also associated with increased candida infection*, NEC^ & mortality^^
  - Overuse/prolonged use

Antibiotic Overuse

- Bacterial Interference: The More Different Species of Bacteria = Less Risk of Infection
  - S. pneumoniae produces NanA – strips sialic acid from LPS of H influenzae & N. meningitidis (destroys biofilm capacity)
  - H influenzae may promote local inflammation – recruits neutrophils that selectively eliminate S. pneumoniae
Antibiotic Overuse

• Translocation of bacteria from the GI tract 2° to changes in the intestinal microbiome.
  - Early postnatal as well as prenatal antibiotic exposure for GBS prophylaxis: Associated with alterations of the microbiome
  - Shorter courses of antibiotics (1–3 days vs. 5–7 days)
    • Associated with suppression and alteration of the microbiome for several weeks
    • Recovery occurred after the third postnatal week.
    • The CDC estimates that nearly 50% of antibiotics are unnecessary or suboptimally effective as prescribed
Antibiotic Overuse

• > 5 days of antibiotics associated with increased incidence of LOS, NEC & death*
  - ~7% increase in the odds of developing NEC for each additional day of empiric antibiotics beyond 5 days^


Antibiotic Overuse

• Antibiotic Stewardship

  - Who to treat: Maternal chorioamnionitis
    • On line “risk tool” for EOS: ≥34 weeks’ gestation
      • Reduced number of patients treated (99.7% to 2.5%)*
      • Missed asymptomatic infants with positive blood culture

Antibiotic Overuse

• Antibiotic Stewardship
  - How long to treat: DUE
    • EOS: if patient is not symptomatic of infection < 48 hours*
    • LOS: no recommendations
      • Use of an algorithm to reduce antibiotic use to <48 hours has been successful
      • Questionable duration when treating NEC
  - Avoid overly broad spectrum antibiotics (e.g., 3rd generation cephalosporin)

Antibiotic Stewardship

• Methodology:
  - Prescriber audit and feedback
  - Preauthorization and formulary restriction of selected antibiotics
  - Education and computerized decision support.
  - Metrics to evaluate antimicrobial stewardship programs include
    • Measurements of patient safety and quality:
      • Rates of adverse drug events,
      • Appropriate dosing and timing of perioperative prophylaxis.
Figure 8–2. Late-onset Sepsis in Newborn Center Patients, Level 2 and 3

Begin

Called to evaluate > 72-h-old infant with possible sepsis

Yes

GI symptoms and pt at risk for NEC -

Yes

Follow NEC algorithm, which should include workup for sepsis

No

High index of suspicion for sepsis #

No, vague symptoms *

Monitor clinical status, VS, urine output

Yes

Change in clinical status suggestive of sepsis

No

 AFTER 24-hr evaluate:
 1. CRP
 2. Culture
 3. Pt status

Yes

Pt clinically ill OR cultures (+)

CRP ≥ 1 mg/dL ^

No

Discontinue vanc and gent

Discontinue gent, continue vanc another 24 hr

Continue antibiotics another 24 hr

- Monitor cultures
- Closely monitor clinical status, VS
- Consider repeat CRP at ~44 hrs

Culture (+) at 48 hr

Yes

No

Discontinue abx unless clinical suspicion for sepsis remains. If abx continued, document reason in chart.

KEY
- Bilious emesis, abdominal distention, absent/hypoactive bowel sounds, abdominal discoloration, bloody stools
# High index of suspicion for sepsis (clinical correlation needed): central line, poor nutritional status, < 32 wks PMA, conditions w/ ↓ host immune defenses (disruption of skin integrity, autoimmune disease, HIV); lethargy, ↓ O₂ or vent support, significant worsening of central apnea, signs of localized infection, abnormal glucose homeostasis, hypotension
* Vague sx include: temp instability, feeding intolerance, mild ↓ in apnea-bradycardia episodes but consistent with prematurity
** GU risk factors: suspected fungal infection, known renal anomalies, history of > 1 episode of Gram (+) bacteremia w/o an identified source
^ CRP may be false (-) in case of leukopenia

CBC w/diff, blood culture x 2 (central and peripheral, ≥ 1 ml/bottle preferred but at least 0.5 ml/bottle, LP
For infants > 1 kg and those susceptible to GU infection, check cath urine culture **; for infants < 1 kg consider suprapubic tap
Start antibiotics (usually Vanc/Gent unless indicated otherwise by history)
Obtain CRP 18–22 hrs after initial antibiotic order

If blood culture positive provide appropriate abx coverage
Check gent peak and trough with 3rd dose
If one of two blood cultures positive (+) for CONS, clinical picture inconsistent with infection, and CRP < 1, (+) culture may be contaminant. Consider DC abx. A repeat CRP < 1 may provide additional reassurance
Document decision/reason in chart.
Feeding
Relationship between mode of delivery and microbiome

• Cesarean section: Colonized by organisms in the environment

• Vaginal: Colonized by maternal organisms
Feeding and the Microbiome

• Breast Milk
  - Human milk oligosaccharides
    • Directly interact with the surface of pathogenic bacteria,
    • Inhibit the binding of pathogens and toxins to host cell receptors
  - Secretory IgA confers a protective effect against pathogens
  - Non-digestible carbohydrates ferment in the colon and promote further growth of probiotic *Bifidobacterium* and *Bacteroides* species
  - Lower gastric pH

Feeding and the Microbiome

• Differing microbiota

Major differences in neonatal gut colonization by type of feeding.

<table>
<thead>
<tr>
<th>Breast fed</th>
<th>Formula fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bifidobacteria</td>
<td>Bifidobacteria species</td>
</tr>
<tr>
<td>Enterobacteria</td>
<td>Escherichia coli</td>
</tr>
<tr>
<td></td>
<td>Clostridium difficile</td>
</tr>
<tr>
<td></td>
<td>Bacteroides species</td>
</tr>
<tr>
<td></td>
<td>Prevotella species</td>
</tr>
<tr>
<td></td>
<td>Lactobacillus species</td>
</tr>
</tbody>
</table>
**Type of Feeding and NEC**

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross $^{12}$</td>
<td>0.21 (0.02 to 1.93)</td>
</tr>
<tr>
<td>Lucas and Cole $^{3}$</td>
<td>0.23 (0.03 to 2.00)</td>
</tr>
<tr>
<td>Svenningsen <em>et al</em> $^{10}$</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Tyson <em>et al</em> $^{11}$</td>
<td>0.39 (0.01 to 9.41)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>0.25 (0.06 to 0.98)</strong></td>
</tr>
</tbody>
</table>

- Donor breast milk vs. formula & confirmed NEC

Incidence of NEC

Type of feeding and NEC

- Estimated number needed to treat with breast milk to prevent 1 case of NEC: 10

H2 Blockers
Infection & H2 Blockers

• Two Observational Studies

1. National Institute of Child Health and Human Development Neonatal Research Network*:
   • BW: 401 – 1500 gms
   • Case-control methodology
   • 11,072 Infants
   • H2-blocker use was associated with an increased incidence of NEC (odds ratio [OR]: 1.71; 95% confidence interval [CI]: 1.34–2.19; P < .0001

Infection & H2 Blockers

• Two Observational Studies

2. Multicenter, observational study
• BW: 401 – 1500 gms or GA between 24 & 32 weeks
• Rates of infectious diseases, NEC, and death
• 274 VLBW infants: 91 received ranitidine and 183 had not
• Results:
  • Increased rate of infection (odds ratio 5.5, 95% confidence interval 2.9-10.4, P < .001); 6.6 fold increase in NEC
  • Increased mortality x 6

CLABSI
(Central Line Associated Bloodstream Infection)
CLABSI Impact

• CDC Estimate: 2002, ~250,000 CLABSI in US hospitals
  -> 30,000 deaths

• Risk Factors (Neonatal)
  - Catheter hub and exit site colonization
  - ELBW (< 1000 g)
  - Duration of parenteral nutrition (Dwell time)*
  - Catheter insertion after first week of life

Dwell Time

- Retrospective cohort study of 13,327 infants with 15,567 catheters (93% peripherally inserted central catheters [PICCs], 7% tunneled catheters) and 256,088 catheter days cared for in 141 NICUs.
  - Incidence of CLABSI was 0.93 per 1000 catheter days.
  - No relationship to dwell time for PICC.

Central Line Care Bundles

• 2008, all 18 regional referral NICUs in New York state
  - Prospective cohort study
  - Pre-intervention (January to December 2007) versus the post-intervention (March to December 2009)
  - Each study period: >55,000 central-line days and >200,000 patient-days

Central Line Care Bundles

• Results
  - 40% decrease over all (RR: 0.60 [95% CI: 0.48-0.75]; P < .0005)
  - Use of Check-lists with the Bundles improved outcome
  - Large interfacility variation
    - incidence rate ratio: 0.044 to 2.87

Central Line Bundles

Newborn Center CLABSIs

FY18 rate: 1.02 infections per 1000 line days
HANDWASHING
Handwashing

• Soaps with no Residual Antimicrobial Activity
  - Iodophores: water-soluble material that releases free iodine when in solution.

• Soaps with residual antibacterial activity
  - ≤ 3% Hexachlorophene
  - 4% Chlorhexidine gluconate
Hand Hygiene

• 60% - 70% Alcohol/water: As effective or more effective than hand washing in normal circumstances
  - If hands are soiled, use soap and water
  - Ineffective against C. difficile and other spore producing pathogens as well as human norovirus (i.e., Norwalk virus)

https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5116a1.htm