The PRObiotics of NEC: Necrotizing Enterocolitis in the NICU

Laura Steinauer, PharmD
PGY1 Pediatric Pharmacy Resident
Mayo Eugenio Litta Children’s Hospital
Objectives

- Review the proposed pathogenesis and risk factors associated with necrotizing enterocolitis (NEC)
- Identify preventative measures and treatment available
- Discuss the literature available for utilization of probiotics in NEC prevention
Definitions

- Neonate
  - Time of birth - 28 days of life (DOL)

- Premature
  - Born before 37 weeks gestation (259 days)

- Extremely low birth weight (ELBW)
  - <1000 grams (1 kg or ~0.5 lb)

- Very low birth weight (VLBW)
  - <1500 grams (1.5 kg or ~0.7 lb)

- Low birth weight
  - < 2500 grams (~1.1 lb)
Necrotizing Enterocolitis (NEC)

- Gastrointestinal (GI) syndrome characterized by inflammation and necrosis of the large or small bowel and subsequent translocation of gas-forming bacteria into the intestinal wall with potential for bacterial invasion

- Complications
  - Sepsis
  - Bowel necrosis or perforation
  - Neurodevelopmental impairment
  - Strictures
  - Short gut syndrome
  - Death

Sawh et al. PeerJ. 2016.4:e2429
Thompson AM, Bizzarro. Drugs. 2008; 68(9): 1227-1238
Sawh et al. PeerJ. 2016.4:e2429
Question #1

• True or False: Necrotizing enterocolitis rates are decreasing due to modern technology and advances in clinical care

• True

• False
Epidemiology

- Most common
  - Gastrointestinal emergency in neonates
  - Cause of GI-related morbidity and mortality in the NICU
- Second most common cause of mortality in NICU
- Incidence
  - 1-5% of ALL NICU admissions
  - 90-95% cases occur in babies < 36 weeks GA
  - Inversely correlated to gestational age/birth weight
  - Increased due to survival of smaller, more premature babies

Thompson AM, Bizzarro. *Drugs*. 2008; 68(9): 1227-1238


Pathogenesis

• Multifactorial
  • Ischemic insult
  • Infection
  • Overactive immune response
    • → inflammation and leaky gut
  • Translocation of normal gut bacteria into the blood
    • → SEPSIS

Sawh et al. PeerJ. 2016;4:e2429
Thompson AM, Bizzarro. Drugs. 2008; 68(9): 1227-1238
<table>
<thead>
<tr>
<th>Bell's Staging Criteria for NEC</th>
<th>Systemic Signs</th>
<th>Intestinal Signs</th>
<th>Radiologic Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Suspected</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Temperature instability, apnea, bradycardia (same as IA)</td>
<td>Elevated pregavage residuals, abdominal distension, blood in stool, plus absent bowel sounds, abdominal tenderness</td>
<td>Ileus, pneumatosis intestinalis</td>
<td></td>
</tr>
<tr>
<td>B. Same as IA</td>
<td>Same as IA, plus gross blood in stool</td>
<td>Same as IA</td>
<td></td>
</tr>
<tr>
<td><strong>II. Definite</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Mildly ill</td>
<td>Same as above, plus mild metabolic acidosis, mild thrombocytopenia</td>
<td>Same as above, plus absent bowel sounds, definite abdominal tenderness, abdominal cellulitis, RLQ mass</td>
<td>Same as IIA, plus portal vein gas with or without ascites</td>
</tr>
<tr>
<td>B. Moderately ill</td>
<td>Same as above, plus mild metabolic acidosis, mild thrombocytopenia</td>
<td>Same as above, plus absent bowel sounds, definite abdominal tenderness, abdominal cellulitis, RLQ mass</td>
<td>Same as IIA, plus portal vein gas with or without ascites</td>
</tr>
<tr>
<td><strong>III. Advanced</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Severely ill: bowel intact</td>
<td>Same as IIB, plus hypotension, bradycardia, respiratory acidosis, metabolic acidosis, disseminated intravascular coagulation, neutropenia</td>
<td>Same as above, plus signs of generalized peritonitis, marked tenderness and distension of abdomen</td>
<td>Same as IIB, plus definite ascites</td>
</tr>
<tr>
<td>B. Severely ill: bowel perforated</td>
<td>Same as IIA</td>
<td>Same as IIA</td>
<td>Same as IIB, plus pneumoperitoneum</td>
</tr>
</tbody>
</table>

Thompson AM, Bizzarro. Drugs. 2008; 68(9): 1227-1238
Risk Factors

- Prematurity
- Hypoxia
- Feeding
- Sepsis
- Drug exposure
- Abnormal colonization of the bowel
- Inflammatory cascade

Thompson AM, Bizzarro. Drugs. 2008; 68(9): 1227-1238
Prenatal Risk Factors

• Maternal
  • Drug use
  • Hypertensive disease
  • Infections
    • HIV
  • Problems related to placental blood flow

Intrapartum Risk Factors

- Hypoxic-ischemic compromise
  - Maternal cardiac arrest
  - Umbilical cord prolapse
  - Placental abruption
- Bacterial exposure
  - Chorioamnionitis
  - Cesarean section

Clinical Course Risk Factors

• Patent Ductus Arteriosus (PDA)
  • Indomethacin vs. ibuprofen
  • Concurrent steroid use for bronchopulmonary dysplasia/adrenal insufficiency
• Antibiotics
• Enteral feeding
  • Histamine type 2 (H2) antagonists
• Mechanical ventilation

Question #2
• What is the baby's biggest independent risk factor for developing necrotizing enterocolitis?
  • A. Maternal diseases
  • B. Prematurity
  • C. Hypoxia
  • D. Drug exposure
Treatment of NEC

- Stop feeds, bowel rest, decompression
- Broad spectrum antibiotics
- IV fluids
- IV nutrition
- Surgery

Thompson AM, Bizzarro. Drugs. 2008; 68(9): 1227-1238
Prevention of NEC

- Antenatal steroids
  - Mixed evidence
- Human milk feeding
- Probiotics

Microbiome: What is it?

• Totality of the microbes in an environment, including bacteria, protozoa, viruses, fungi, and their genetic elements

• Dysbiosis

• Growing evidence supports that a functional communication exists between the CNS and GI tract (brain-gut axis)

Sawh et al. PeerJ. 2016;4:e2429
Gut Microbiome: Importance

• Profound impact on GI tract development
• Maintenance of mucosal surface integrity
• Contributes to the nutritional status of the host
• Distortion of the gut microbiota found to correlate with fatal diseases in preterm infants

Sawh et al. PeerJ. 2016.4:e2429
Probiotics

- Live microorganisms, which when administered in adequate amounts confer a benefit to the host

- Beneficial mechanisms:
  - Changes in intestinal permeability
  - Enhanced mucosal IgA response
  - Increased production of anti-inflammatory cytokines
  - Populate intestine with normal flora → prevent an overgrowth of pathogenic bacteria

Sawh et al. PeerJ. 2016;4:e2429
Systematic Review and Meta Analysis of Observational Studies-2016

Objective: Evaluate the efficacy of probiotic supplementation outside strictly controlled settings

<table>
<thead>
<tr>
<th>Study Selection</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• &lt;37 weeks GA or birth weight &lt;2500g</td>
<td>• Incidence of NEC</td>
<td>• Probiotic supplementation reduces the risk of NEC and mortality in preterm infants</td>
</tr>
<tr>
<td>• Prophylactic probiotics vs. standard regimen</td>
<td>• RR 0.55 [0.39-0.78]</td>
<td>• Optimal strain, dose, and timing need further investigation</td>
</tr>
<tr>
<td>• 12 studies</td>
<td>• p 0.0006</td>
<td></td>
</tr>
<tr>
<td>• n = 10,800</td>
<td>• All trials</td>
<td></td>
</tr>
<tr>
<td>• 5,144 probiotics</td>
<td>• Incidence of mortality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RR 0.72 [0.61-0.85]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• p &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 9 trials</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Incidence of sepsis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• RR 0.86 [0.74-1.00]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• P 0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 7 trials</td>
<td></td>
</tr>
</tbody>
</table>

Olsen et al. 2016 (Observational Studies)

**NEC**

- **Prophylactic Probiotics:** 3.3% (169/5,144)
- **Control:** 5.7% (325/5,656)

**Mortality**

- **Prophylactic Probiotics:** 7.6% (354/4,629)
- **Control:** 10% (353/3,510)

Olsen et al 2016: Forest Plot

Effects of probiotics on NEC

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Probiotics events</th>
<th>Control events</th>
<th>Weight, %</th>
<th>RR M-H, random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonsante [15], 2013</td>
<td>4</td>
<td>42</td>
<td>6.7</td>
<td>0.21 (0.08-0.59)</td>
</tr>
<tr>
<td>Dang [16], 2015</td>
<td>2</td>
<td>8</td>
<td>3.8</td>
<td>0.26 (0.06-1.22)</td>
</tr>
<tr>
<td>Hoyos [18], 1999</td>
<td>10</td>
<td>26</td>
<td>10.2</td>
<td>0.39 (0.20-0.76)</td>
</tr>
<tr>
<td>Hunter [19], 2012</td>
<td>2</td>
<td>35</td>
<td>4.4</td>
<td>0.17 (0.04-0.68)</td>
</tr>
<tr>
<td>Härtel [17], 2014</td>
<td>67</td>
<td>44</td>
<td>14.1</td>
<td>0.62 (0.43-0.90)</td>
</tr>
<tr>
<td>Janvier [20], 2014</td>
<td>16</td>
<td>31</td>
<td>11.4</td>
<td>0.56 (0.31-1.00)</td>
</tr>
<tr>
<td>Lambæk [21], submitted</td>
<td>23</td>
<td>34</td>
<td>12.3</td>
<td>0.77 (0.47-1.29)</td>
</tr>
<tr>
<td>Li [22], 2013</td>
<td>7</td>
<td>8</td>
<td>6.9</td>
<td>0.87 (0.32-2.37)</td>
</tr>
<tr>
<td>Luoto [23], 2010</td>
<td>19</td>
<td>61</td>
<td>12.4</td>
<td>0.42 (0.86-2.34)</td>
</tr>
<tr>
<td>Repa [24], 2014</td>
<td>16</td>
<td>24</td>
<td>11.1</td>
<td>0.68 (0.37-1.24)</td>
</tr>
<tr>
<td>Yamashiro [25], 2010</td>
<td>0</td>
<td>6</td>
<td>1.3</td>
<td>0.05 (0.00-0.91)</td>
</tr>
<tr>
<td>Zampieri [26], 2013</td>
<td>3</td>
<td>6</td>
<td>5.5</td>
<td>0.39 (0.12-1.29)</td>
</tr>
</tbody>
</table>

Total (95% CI) 169 325 100.0 0.55 (0.39-0.78)

Heterogeneity: τ² = 0.18, χ² = 26.34, d.f. = 11 (p = 0.006), I² = 58%
Test for overall effect: Z = 3.43 (p = 0.0006)
Observational Study Discussion

• Large number of preterm infants included
• Large geographical area
• Newer studies included
• Limitations: observational, heterogeneity
• My thoughts
  • Positive results + low cost = reasonable to consider this intervention
  • Beneficial in VLBW and LBW

Systematic Review and Meta Analysis of RCT- 2016

Objective: Assess the efficacy & safety of probiotics for prevention of NEC and update previous systematic reviews

<table>
<thead>
<tr>
<th>Study Selection</th>
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<th>Conclusions</th>
</tr>
</thead>
</table>
| • <37 wks GA or <2,500g  
  • Probiotic vs. standard therapy/ placebo  
  • 2013-2015  
  • 13 “new” trials  
  • n=5,033 | • Incidence of severe NEC  
  • RR 0.53  
  • [0.42-0.66]  
  • Incidence of all-cause mortality  
  • RR 0.79  
  • [0.68-0.93]  
  • Culture proven sepsis  
  • RR 0.88  
  • [0.77-1.00] | • Heterogeneity of organisms and dosing regimens studied prevent a species-specific treatment recommendation from being made  
  • Preterm infants benefit from probiotics to prevent severe NEC and death |

*Other statistically significant findings: shorter duration of hospitalization, increased weight gain (g/day), and reduced time to reach full enteral feeds

Sawh et al. PeerJ. 2016.4:e2429
Sawh et al. 2016: RCT Patient Characteristics

**Probiotic**
- Multiple species
- Single species

**Timing**
- First feed
- "More than 48hr"
- 48hr of birth/72hr of birth
- First week

**Duration**
- 14 days or until discharge

Comparison of Observational vs. RCT

- **NEC Mortality**: Relative Risk
  - **RCT**: 0.53
  - **Observational**: 0.55

- **Mortality**: Relative Risk
  - **RCT**: 0.79
  - **Observational**: 0.72

Sawh et al. PeerJ. 2016;4:e2429
Probiotic Supplementation and Late Onset Sepsis (LOS) 2016

<table>
<thead>
<tr>
<th>Study Selection</th>
<th>Outcome Measured</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>• RCTs</td>
<td>• LOS: presence of positive blood or cerebrospinal fluid culture on a sample collected 48-72 hours after birth</td>
<td>Incidence of LOS 13.9% vs. 16.3% RR 0.86 [0.78-0.94] p= 0.0007 NNT= 44</td>
</tr>
<tr>
<td>• 37 studies</td>
<td>• Primary outcome: 9 studies</td>
<td></td>
</tr>
<tr>
<td>• n= 9416 patients</td>
<td>• Secondary outcome: 28 studies</td>
<td></td>
</tr>
<tr>
<td>• &lt;37 weeks GA, &lt;2500g, or both</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Probiotic supplement vs. placebo or control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subgroup analysis</td>
<td>• Same as above</td>
<td>• No significant benefits in reducing LOS</td>
</tr>
<tr>
<td>• &lt;28 weeks or &lt;1000g</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Question #3

Which of the following statements is true?

• Probiotic use increases the risk of sepsis
• Probiotic use has not been shown to decrease mortality
• Probiotic use has been shown to decrease incidence of NEC
• None of the above
Our Practice

• No routine use of probiotics
• Introduce early trophic feeds

• Concern:
  • Introducing foreign bacteria into a susceptible host
  • Bacteria are **NOT** FDA regulated
Considerations

- No neonatal formula available
- Unregulated by FDA
- Optimal dose, strain, timing
  - Protocol/guideline
- Clinical trials are ongoing
  - Head-to-head comparisons needed
Question 4: I would consider using a probiotic for prophylaxis in a neonate?

- Yes
- No
Summary

• Use probiotics
  • <37 weeks GA, <2500g
  • Multi-species formulation
  • Start with first feed or after 48 hours
  • Continue for at least 2 weeks or till discharge

• Probiotic use does not cause an increase in sepsis

• More research needed

Sawh et al. PeerJ. 2016.4:e2429
“If a simple intervention such as probiotic supplementation can reduce the risk of TWO of the most devastating conditions that affect preterm infants, it is worth paying attention.”

Questions?
Steinauer.Laura@mayo.edu
<table>
<thead>
<tr>
<th>Study</th>
<th>Neonates on probiotics (n=)</th>
<th>Probiotic agent</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dang 2015</td>
<td>128</td>
<td>Lactobacillus rhamnosus GG, Bifidobacterium infantis</td>
<td>NEC, mortality, sepsis</td>
</tr>
<tr>
<td>Hunter 2012</td>
<td>79</td>
<td>Lactobacillus reuteri</td>
<td>NEC, sepsis</td>
</tr>
<tr>
<td>Li 2013</td>
<td>291</td>
<td>Mixture of streptococcus and Bifidobacterium</td>
<td>NEC, mortality</td>
</tr>
</tbody>
</table>

- **VLBW**
  - n=6,587 patients
  - Incidence of NEC
    - RR 0.47 [0.36-0.61]
  - Incidence of mortality
    - RR 0.74 [0.61-0.90]

- **ELBW**
  - 8 trials
    - 1 exclusively
  - Significant
    - Shorter duration of hospitalization
    - Full enteral feeds sooner
  - No statistical significance for incidence of NEC, mortality, sepsis