Necrotizing Enterocolitis: What is it and what can we do about it?

Christine Culpepper, MD
Objectives

• Describe the pathophysiology of Necrotizing Enterocolitis (NEC)
• Discuss presentation, diagnosis and management of NEC
• Identify infants at risk for NEC in the NICU
• Apply preventative measures in own units to reduce the incidence of NEC
Acute inflammatory necrosis of the bowel

NECROTIZING ENTEROCOLITIS (NEC)
NEC

- Most common severe neonatal gastrointestinal emergency
- Occurs in 1-3 per 1000 live births
  - VLBW infants
  - Term infants with CHD
- Morbidity
  - Intestinal stricture
  - Short bowel syndrome
  - Neurodevelopmental impairment
- Mortality ranges from 25-50%
History

• Pathology was described in 1952, when Schmidt and Quaiser labeled it as *enterocolitis ulcerosa necroticans*.

*Figure 1. Number of articles published per year on PubMed since 1952 to 2015 (July).*
Pathophysiology

Genetic predisposition

Microbial imbalance

Intestinal immaturity

NEC
Intestinal Immaturity

• Premature infants have immature:
  – Intestinal motility
  – Digestion
  – Absorption
  – Immune defenses
  – Barrier function

• Increased risk for intestinal injury
Microbes

- **Culture**
  - No single organism consistently implicated
- **Gas-forming organisms** → pneumatosis
- **“Outbreaks”**
- **Molecular methods**
  - Proteobacteria
  - Lower diversity of microbiota
Exaggerated Inflammation

- Altered microbiota (low diversity caused by antibiotics)
- Intact intercellular junction
- Immature intestinal barrier
  - Decreased mucus
  - Decreased IgA
  - Low intercellular junction integrity and increased permeability
- Exaggerated inflammation and tissue injury

Genetics
- Polymorphisms in TLRs

Intestinal necrosis

TLR

IgA

Commensals

Intestinal epithelium

Mucus

Neu 2011
Necrotizing enterocolitis: Susceptibility of premature infants

Immaturity of the intestinal epithelial barrier and the neonatal mucosal immune system predispose the premature infant to microbial invasion, which triggers the sequence of events leading to necrotizing enterocolitis (NEC). Stimulation of pro-inflammatory cytokines compromises intestinal defenses. An imbalance between epithelial cell injury and repair leads to a cycle of bacterial invasion, immune activation, uncontrolled inflammation, and gut barrier failure.

NO: nitric oxide; TNF-α: tumor necrosis factor - alpha.


www.nature.com/pr
Presentation

• Age at onset inversely related to GA

• Clinical Presentation
  – Abdominal distension
  – Feeding intolerance
  – Hematochezia
  – Non-specific systemic signs
Labs

- Anemia
- L shift neutrophils
- Neutropenia
- Thrombocytopenia
- Raised C-reactive protein (CRP)
- Metabolic acidosis
- Hyponatremia
- Hyperkalemia
- Glucose instability
- Positive blood culture (<40%)
Differential Diagnosis

• Septic ileus
• Hirschsprung disease
• Spontaneous intestinal perforation
• Anal fissure
• Milk protein allergy
Diagnosis

- Pneumatosis intestinalis
- Portal venous gas
- Pneumoperitoneum
Submucosal and Subserosal Pneumatosis
Portal Venous Gas
Pneumoperitoneum
Figure 7(A,B). A: Abdominal plain x-ray obtained in dorsal decubitus with horizontal x-ray beam. Free air movement is observed anteriorly within the abdominal cavity. B: Scheme demonstrating the NN positioning to be adopted for study in dorsal decubitus with horizontal beam to demonstrate pneumoperitoneum (reference 16).

Figure 8(A,B). A: Abdominal x-ray film obtained in left lateral decubitus with horizontal x-ray beams, left lateral decubitus with horizontal x-ray beams, where pneumoperitoneum is demonstrated between the liver and the right abdominal wall. B: Scheme demonstrating the NN positioning to be adopted for study in left lateral decubitus with horizontal beam to demonstrate pneumoperitoneum (reference 16).
Cross table lateral

Left lateral decubitus
Ultrasound

a. Portal venous gas in liver  
b. Thickening of bowel wall  
c. Intramural gas and no blood flow to bowel
### Modified Bell’s Staging Criteria

<table>
<thead>
<tr>
<th>Staging</th>
<th>Systemic Signs</th>
<th>Intestinal Signs</th>
<th>Radiologic Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected</td>
<td><strong>IA</strong> Temperature instability, apnea,</td>
<td>Occult blood in stool, mild abdominal distension</td>
<td>Normal or mild ileus</td>
</tr>
<tr>
<td></td>
<td>bradycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>IB</strong></td>
<td>+ Gross blood in stool</td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td><strong>IIA</strong></td>
<td>+ Absent bowel sounds</td>
<td>+ Pneumatosis</td>
</tr>
<tr>
<td></td>
<td>+ mild metabolic acidosis, mild</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>IIB</strong></td>
<td>+ Definite abdominal tenderness, abdominal cellulitis</td>
<td>+ Portal venous gas</td>
</tr>
<tr>
<td></td>
<td>+ hypotension, respiratory acidosis,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DIC, neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td><strong>IIIA</strong></td>
<td>+ Generalized peritonitis</td>
<td>+ Ascites</td>
</tr>
<tr>
<td></td>
<td>+ pneumoperitoneum</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>IIIB</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Walsh and Kleigman 1986*
Management

**Medical**
- Supportive care
- Bowel rest
- Abdominal decompression
- Broad spectrum antibiotics

**Surgical**
- Exploratory laparotomy
- Primary peritoneal drainage
Infants at Risk

- PREMATURITY
- Lower gestational age
- Lower birth weight
- Enteral feedings
- Intrauterine growth restriction
Summary

• NEC is most common severe neonatal gastrointestinal emergency

• Pathophysiology of NEC is multifactorial (intestinal immaturity, microbial imbalance, exaggerated inflammation)

• Diagnose with clinical symptoms and xray/ultrasound

• Management is supportive

• Prematurity is greatest risk factor for NEC
Can we change our practice to prevent NEC?

CONTRIBUTING FACTORS
Contributing Factors

• Treatment with H2 blockers
• Treatment with antibiotics
• Prolonged NPO
• Transfusion with packed red blood cells
Limited gastric acid secretion

Administration of H2 blocker

Gastric bacterial overgrowth

NEC
Case control study of VLBW infants with NEC

- Received Zantac, Pepcid or Tagament (IV/PO) > 1 day before diagnosis

- Median 14 days
Antibiotics

• Most commonly prescribed medication in NICU

• Exposure
  → Reduce biodiversity
  → Delay beneficial colonization
  → Promote pathogenic and/or resistant organisms
Figure 1. Pie graphs depicting relative abundance of bacterial genera detected in stool specimens from study infants as a function of antibiotic exposure over the first 3 weeks of life.
Antibiotics, NEC and ELBW Infants

- ELBW infants with $\geq 1$ antibiotic in first 3 days of life
- $\sim 4000$ infants
- Prolonged treatment: $\geq 5$ days with sterile culture results
- $\sim 4\%$ increase in odds of NEC or death with each additional day of treatment
Prolonged NPO

Lack of trophic hormones

Mucosal Atrophy

Decreased levels of mucosal IgA

NEC?
NPO and NEC

- Cochrane Review 2013
  - Nine trials with VLBW infants
    - No difference in NEC
- Am J Perinatol 2015
  - Infants <29 weeks
    - 467 without NEC
      - NPO 3.7 days
    - 234 with NEC
      - NPO 5.6 days
TANEC (Transfusion Associated NEC)

- Meta-analysis published in Pediatrics 2012
- Feeding during transfusion?
- Severe Anemia? (<8 g/dL)
- JAMA 2016
Choosing Wisely in Newborn Medicine

1. Avoid routine use of antireflux medications for treatment of symptomatic gastroesophageal reflux disease or for treatment of apnea and desaturation in preterm infants

2. Avoid routine continuation of antibiotic therapy beyond 48 hours for initially asymptomatic infants without evidence of bacterial infection
 Potential Changes

• Reflux
  – Reflux precautions
  – If trial medication STOP use if no documented change

• Antibiotics
  – Consider monitoring (with or without blood culture)
  – STOP antibiotics after 48 hours with stable infant and negative culture
Potential Changes

- NPO
  - Minimal enteral feeding, gut priming, or trophic feeding
  - ≤ 24 mL/kg/day
  - SAFE
    - Treatment indomethacin
Potential Changes

• Anemia
  – Threshold for transfusion (asymptomatic)
    • 11.5/34.5 young, sick babies
    • 9.5/28.5 for low FiO2 with NC
    • 7.5/22.5 older, stable babies
Potential Changes

Practice Change to Potentially Reduce TANEC

1. Evaluate unit-specific NEC rate and benchmark unit performance against other unit NEC rates because the rate may be reducible.
2. Communicate the unit-specific NEC rate with every physician, neonatal nurse practitioner, bedside nurse, dietitian and lactation consultant.
3. Encourage mothers to provide human milk as soon as possible by initiating early pumping.[17]
4. Consider feeding pasteurized donor milk if mother’s milk is not available.[17]
5. Evaluate unit-specific transfusion practices
   - Are they standardized? [4,5]
   - How are feedings handled before, during and after transfusion?
   - Do most infants < 1500 grams receive > 1 transfusion? [5]
   - Consider developing and implementing a standardized transfusion guideline
5. Consider changing practice to exclusive human milk or nothing by mouth during transfusion and measure the impact on unit-specific NEC rate [14,15]
What else can we do?

PREVENTATIVE STRATEGIES
Prevention of NEC

• Antenatal corticosteroids
• Mother’s own milk (MOM)
• Donor breastmilk
• Standardized feeding protocols
• Probiotics
• Future directions
Antenatal Corticosteroids

Reduces the incidence of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and neonatal mortality.
Feeding preterm infants human milk is associated with a significant reduction in the incidence of NEC.
Liquid Gold

• Bioactive components
  – Anti-infectious
    • Immunoglobulins
    • Oligosaccharides
  – Trophic effects
    • Epidermal growth factor
    • Lactoferrin
  – Hormones
    • Pituitary
    • Thyroid
    • Steroid
  – Cells
    • Neutrophils
    • Macrophages
    • T-lymphocytes
Got Breastmilk?

- Pumping within first hour
- Support for moms
- Breast pumps available through insurance
- Lactation consultants
Pasteurized Donor Human Milk (PDHM)

- Strict screening process
- Holder pasteurization
  - ↓ Secretory IgA
  - ↓ Lactoferrin
  - Inactivates lipase
Forest Plots

No effect
Formula versus donor breast milk for feeding preterm or low birth weight infants

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Formula milk</th>
<th>Donor breast milk</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.20.1 Term formula</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross 1983</td>
<td>3</td>
<td>26</td>
<td>1</td>
<td>41</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>26</td>
<td>41</td>
<td>7.4%</td>
<td>4.73 [0.52, 43.09]</td>
</tr>
<tr>
<td>Total events</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)

1.20.2 Preterm formula

<table>
<thead>
<tr>
<th>Study</th>
<th>Events</th>
<th>Total</th>
<th>Subtotal (95% CI)</th>
<th>Total (95% CI)</th>
<th>Total events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cristofalo 2013</td>
<td>5</td>
<td>24</td>
<td>1</td>
<td>29</td>
<td>8.8%</td>
</tr>
<tr>
<td>Lucas 1984a</td>
<td>4</td>
<td>76</td>
<td>1</td>
<td>83</td>
<td>9.1%</td>
</tr>
<tr>
<td>Lucas 1984b</td>
<td>5</td>
<td>173</td>
<td>2</td>
<td>170</td>
<td>19.2%</td>
</tr>
<tr>
<td>Schanler 2005</td>
<td>10</td>
<td>88</td>
<td>5</td>
<td>78</td>
<td>50.5%</td>
</tr>
<tr>
<td>Tyson 1963</td>
<td>1</td>
<td>44</td>
<td>0</td>
<td>37</td>
<td>5.2%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>405</td>
<td>397</td>
<td>92.6%</td>
<td>2.61 [1.27, 5.35]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>25</td>
<td>9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.39, df = 4 (P = 0.85); I² = 0%
Test for overall effect: Z = 2.62 (P = 0.009)

Total (95% CI) | 431      | 438 | 100.0% | 2.77 [1.40, 5.46] |
Total events | 28       | 10   |            |                  |
Heterogeneity: Chi² = 1.68, df = 5 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.94 (P = 0.003)
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Standardized Feeding Protocols

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.20 (0.01 to 4.20)</td>
<td>11.1</td>
</tr>
<tr>
<td>2</td>
<td>0.23 (0.09 to 0.60)</td>
<td>21.7</td>
</tr>
<tr>
<td>3</td>
<td>0.13 (0.02 to 1.02)</td>
<td>15.8</td>
</tr>
<tr>
<td>4</td>
<td>0.01 (0.00 to 0.15)</td>
<td>12.1</td>
</tr>
<tr>
<td>5</td>
<td>0.57 (0.32 to 1.01)</td>
<td>23.3</td>
</tr>
<tr>
<td>6</td>
<td>0.03 (0.00 to 0.23)</td>
<td>16.0</td>
</tr>
<tr>
<td>Overall</td>
<td>0.13 (0.03 to 0.50)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1  Meta-analysis of the six studies that used a random effects model: 1, Premji et al.; 2, Kamitsuka et al.; 3, Brown et al.; 4, Spritzer et al.; 5, Kuzma-O’Reilly et al.; 6, Patole et al. CI, Confidence interval.
ON THE BASIS OF THAT, STANDARDIZED FEEDING PROTOCOLS ARE SIMPLE, CHEAP, EFFECTIVE, AND TRANSMISSIBLE; FURTHERMORE, THEY REDUCE THE RISK OF NEC, IT IS TIME THAT ADOPTION OF STANDARDIZED FEEDING PROTOCOLS IS NO LONGER OPTIONAL BUT IMPERATIVE IN THE QUEST TO PREVENT NEC.”
Figure 1. Feeding Guidelines for Preterm Infants Born <1500 grams

<table>
<thead>
<tr>
<th>Weight (g)</th>
<th>DOF* 1</th>
<th>DOF 2</th>
<th>DOF 3</th>
<th>DOF 4</th>
<th>DOF 5</th>
<th>DOF 6</th>
<th>DOF 7</th>
<th>DOF 8</th>
<th>DOF 9</th>
<th>DOF 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤750</td>
<td>≤20</td>
<td>≤20</td>
<td>≤20</td>
<td>≤20</td>
<td>≤20</td>
<td>≤50</td>
<td>≤80 Fortify</td>
<td>≤110</td>
<td>≤140</td>
<td>160</td>
</tr>
<tr>
<td>750-1000</td>
<td>≤20</td>
<td>≤20</td>
<td>≤20</td>
<td>≤50</td>
<td>≤80 Fortify</td>
<td>≤110</td>
<td>≤140</td>
<td>160</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000-1500</td>
<td>≤20</td>
<td>≤20</td>
<td>≤50</td>
<td>≤80 Fortify</td>
<td>≤110</td>
<td>≤140</td>
<td>160</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*DOF = day of feed

Risk Factors supporting conservative advancement of feeds:

Perinatal:
1) Umbilical Cord Gas or infant’s first blood gas with metabolic acidosis: \( pH < 7 \) and base deficit \( \geq -15 \)
2) Asymmetric IUGR or IUGR with reversed or absent end-diastolic flow
3) Monochorionic twin gestation with Twin-Twin Transfusion Syndrome

Neonatal:
1) Significant cardiovascular instability: Chest compressions, vasoactive agent requirement, or multiple boluses of crystalloid or colloid.
2) Symptomatic patent ductus arteriosus
3) Prolonged NPO status greater than 7 days
Probiotics

- Live microorganisms
  - Protective barrier
  - Modulate inflammatory response
  - Improved intestinal motility
Probiotics for prevention of necrotizing enterocolitis in preterm infants

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Probiotics n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H fixed 95% CI</th>
<th>Risk Ratio M-H fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Hosni 2012</td>
<td>2/50</td>
<td>2/51</td>
<td>1.02 [0.15, 6.96]</td>
<td></td>
</tr>
<tr>
<td>Bin-Nun 2005</td>
<td>1/72</td>
<td>10/73</td>
<td>0.10 [0.01, 0.77]</td>
<td></td>
</tr>
<tr>
<td>Braga 2011</td>
<td>0/119</td>
<td>4/112</td>
<td>0.10 [0.01, 1.92]</td>
<td></td>
</tr>
<tr>
<td>Costales 2003</td>
<td>5/51</td>
<td>6/36</td>
<td>0.59 [0.19, 1.78]</td>
<td></td>
</tr>
<tr>
<td>Duni 2002</td>
<td>4/295</td>
<td>8/290</td>
<td>0.49 [0.15, 1.61]</td>
<td></td>
</tr>
<tr>
<td>Demirel 2013</td>
<td>6/135</td>
<td>7/136</td>
<td>0.86 [0.30, 2.50]</td>
<td></td>
</tr>
<tr>
<td>Ferrandez-Carriera 2013</td>
<td>6/75</td>
<td>12/75</td>
<td>0.50 [0.20, 1.26]</td>
<td></td>
</tr>
<tr>
<td>Kitisins 1997</td>
<td>0/45</td>
<td>0/46</td>
<td>0.0 [0.00, 0.00]</td>
<td></td>
</tr>
<tr>
<td>Lin 2005</td>
<td>2/180</td>
<td>10/187</td>
<td>0.21 [0.05, 0.94]</td>
<td></td>
</tr>
<tr>
<td>Lin 2008</td>
<td>4/217</td>
<td>14/217</td>
<td>0.29 [0.10, 0.85]</td>
<td></td>
</tr>
<tr>
<td>Marzioni 2006</td>
<td>1/39</td>
<td>3/41</td>
<td>0.35 [0.04, 3.23]</td>
<td></td>
</tr>
<tr>
<td>Marzioni 2009</td>
<td>0/151</td>
<td>10/168</td>
<td>0.05 [0.00, 0.90]</td>
<td></td>
</tr>
<tr>
<td>Minatsu 2010</td>
<td>2/91</td>
<td>4/89</td>
<td>0.49 [0.09, 2.60]</td>
<td></td>
</tr>
<tr>
<td>Mohan 2006</td>
<td>2/337</td>
<td>1/32</td>
<td>1.73 [0.16, 18.20]</td>
<td></td>
</tr>
<tr>
<td>ProPrensn 2013</td>
<td>11/548</td>
<td>24/551</td>
<td>0.46 [0.23, 0.93]</td>
<td></td>
</tr>
<tr>
<td>Rojas 2012</td>
<td>9/372</td>
<td>15/378</td>
<td>0.61 [0.27, 1.38]</td>
<td></td>
</tr>
<tr>
<td>Rougier et al 2009</td>
<td>2/45</td>
<td>1/49</td>
<td>2.18 [0.20, 23.21]</td>
<td></td>
</tr>
<tr>
<td>Samenta 2009</td>
<td>5/91</td>
<td>15/95</td>
<td>0.35 [0.13, 0.92]</td>
<td></td>
</tr>
<tr>
<td>Sari 2010</td>
<td>6/110</td>
<td>10/111</td>
<td>0.61 [0.23, 1.61]</td>
<td></td>
</tr>
<tr>
<td>Stratki 2007</td>
<td>0/38</td>
<td>3/31</td>
<td>0.12 [0.01, 2.19]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2761</strong></td>
<td><strong>2768</strong></td>
<td><strong>0.43 [0.33, 0.56]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 68 (Probiotics), 159 (Control)

Heterogeneity: Ch² = 14.67, df = 18 (P = 0.68; P > 0.05)

Test for overall effect: Z = 6.02 (P < 0.00001)

Test for subgroup differences: Not applicable

Evidence-Based Child Health: A Cochrane Review Journal
Why isn’t everyone on probiotics?

- Trend for higher incidence sepsis (infants <750g)
- Poor quality control
- Appropriate probiotic and dose?
Future Directions

• Stem cells in amniotic fluid as a protective agent against the development of NEC
Conclusion

• NEC is multifactorial

• Prevention is key!
  – Your unit’s incidence of NEC compared to other similar units
  – Quality Improvement Project
    • Feeding protocol
      – Use of MOM
      – Decrease days NPO
    • Decrease antibiotic and H2 blocker use
    • Transfusion practice
    • Probiotics
Thank You!
References

• Cotten, C.M. et al., 2009. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. PEDiATRICS, 123(1), pp.58–66.
• Guillet, R. et al., 2006. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. PEDiATRICS, 117(2), pp.e137–42.
• Morgan, J., Young, L. & McGuire, W., 2013. Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants. Cochrane database of systematic reviews (Online), 5, p.CD001970.