Recent Advances in Necrotizing Enterocolitis

Michael S. Caplan, MD
Northshore University Healthsystem
University of Chicago, Pritzker School of Medicine
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NEONATAL NEC:
- Epidemiology
- Clinical features
- Pathophysiology
- Targets for Intervention

Epidemiology of NEC
- Primarily a disease of prematurity: Inversely correlates with gestational age and birthweight
- Increased with IUGR
- Slightly increased risk in boys and African-American race
- Increased with monozygotic twinning
- Recurrent NEC with higher risk

EPIDEMIOLOGY: Geographic Variation
- U.S.: 7-10% premature infants < 1500 grams
- Hong Kong: 28% < 1500 grams (13% with preventive oral vancomycin)
- Argentina: 14% < 1500 grams (7% with preventive dexamethasone)
- Austria: 7% < 2000 grams (0 with enteral IgA supplementation)
- Japan: 1.5% < 1500, 3.1% < 1000 grams

NEC: Clinical symptoms
- Abdominal distention
- Bloody stools
- Emesis and/or gastric residuals
- Apnea and bradycardia
- Lethargy

Do gastric residuals predict the onset of NEC?

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Does fecal blood predict NEC?

Does thrombocytopenia correlate with NEC outcome?

NEC: Clinical Signs

- Abdominal tenderness and/or discoloration
- Metabolic acidosis
- Thrombocytopenia
- Neutropenia
- Hypotension
- Shock
- SIRS


**Portal venous gas by abdominal US in NEC**

**Staging criteria for NEC: modified Bell system**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Classification</th>
<th>Signs</th>
<th>Radiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Suspected NEC</td>
<td>Abdominal distention, bloody stools, nausea, hypotension, bradycardia</td>
<td>Doppler dilatation</td>
</tr>
<tr>
<td>II</td>
<td>Proven NEC</td>
<td>Above with: abdominal distention, hypotension, acute respiratory distress, thrombocytopenia</td>
<td>Pneumatosis intestinalis or portal venous gas</td>
</tr>
<tr>
<td>III</td>
<td>Advanced NEC</td>
<td>Above with: hypoproteinemia, anemia, acidosis, DIC, neutropenia</td>
<td>Above with pneumomediastinum</td>
</tr>
</tbody>
</table>

**NEC: Treatment**

- NPO
- Gastric decompression
- Antibiotics
- Fluids and blood pressure support
- Surgery: not a cure? Effect on outcome
- Laparotomy vs Drain: no diff in mortality or short term morbidity
  - Prospective: Moss et al, 2006, NEJM

**NEC: Outcome**

- 20-30% die
- 30-50% surgery
- Longer LOS
- Higher cost
- Complications:
  - Short Bowel Syndrome
  - Strictures
  - Compromised Neurodevelopmental Outcome

**Pathogenesis: Prematurity**

- Altered host defense
- Dysmotility
- Autoregulation of blood flow
- Inflammatory response
- Microbial flora
- Feeding patterns

**PATHOGENESIS: Multifactorial Theory**

- Prematurity
- Formula feeding
- Intestinal ischemia
- Bacterial colonization

"Final Common Pathway"
**Pathogenesis: Role of Feeding**
- Formula vs breast milk
- Early trophic vs delayed feeding
- Continuous vs bolus feeding
- Type and strength of formula
- Volume of feed
- Rate of increase

**Feeding Strategies for Premature Infants**
- Randomized trial: priming vs NPO x 14 d and continuous vs bolus
- 171 infants, avg 28 weeks and 1050 gms
- Findings: Similar attainment of full oral feeds, priming not harmful and improved bone mineral metabolism, bolus had less intolerance and greater weight gain
  
  Schanler et al, Pediatrics 1999;103:434

**Prolonged trophic feedings decreases NEC**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Advancing volume (20 cc/kg x 10 d)</th>
<th>Minimal volume (20 cc/kg x 10 d)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>70</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>NEC (%)</td>
<td>7 (10)</td>
<td>1 (1.4)</td>
<td>.03</td>
</tr>
<tr>
<td>discharge home (d)</td>
<td>64</td>
<td>76</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>days TPN</td>
<td>24</td>
<td>36</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Berseth et al, Pediatrics, 111:529-534, 2003

**Pathogenesis: Intestinal Ischemia**
- Animal models typically require reperfusion to produce significant bowel necrosis
- PDA ligation on day 1 in extremely premature infants reduces the incidence of NEC
- Altered autoregulation in preterm/newborn animals
- ? Cocaine, UAC’s, indocin

**Pathogenesis: Role of bacteria**
- Intestine sterile at birth
- Feeding promotes intestinal colonization
- Overgrowth of pathogenic bacteria may predispose to NEC
- Formula fed, NICU premature infants have different patterns of colonization compared to breast-fed term infants

**Stool microflora in ELBW infants**
- Paucity of bacterial species (< 3 at 10 days)
- Breast milk increases diversity
- Antibiotic exposure decreases number
- Only 1/29 colonized by Bifidobacteria or Lactobacilli
- ? Risk for overgrowth of pathogenic strains

Gewolb et al, Arch Dis Child 1999;80:F167
Reduced Microbial Diversity in NEC Patients compared to age-matched Controls

Wang, Claud et al. ISME J: 2009

Toll-like receptor signaling

EGF, TGF, EPO, IGF

EGF, TGF, IGF

Arginine

Thromboxane

Glutamine

ET-1

Mediators associated with NEC in animal studies and human trials

<table>
<thead>
<tr>
<th>Promote injury</th>
<th>Prevent injury</th>
</tr>
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<tbody>
<tr>
<td>PAF</td>
<td>eNOS</td>
</tr>
<tr>
<td>TNF</td>
<td>Prostacyclin</td>
</tr>
<tr>
<td>IL-1, IL-6, IL-8, IL-18</td>
<td>IL-10, IL-11, IL-12</td>
</tr>
<tr>
<td>LTC4</td>
<td>Erythropoietin</td>
</tr>
<tr>
<td>iNOS</td>
<td>(HB)EGF, TGF, IGF</td>
</tr>
<tr>
<td>ET-1</td>
<td>Glutamine</td>
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<td>Thromboxane</td>
<td>Arginine</td>
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Model for NEC pathogenesis: Role of PAF

Increased PAF production (PAF-AH, MyD88-IRAK-IκB-NFκB)

Inflammation

Role of PAF

NEC pathophysiology: working hypothesis

n Preterm infant with immature mucosal barrier,
  impaired host defense/inflammatory responses/growth factors
n Genetic predisposition/SNP's
n Abnormal bacterial colonization/responses
n Mucosal stress with feeding/ischemia
TARGETS FOR TREATMENT OR PREVENTION?

Is Breastmilk Effective for NEC Prevention?
- Many reports suggest a 2-5 fold reduction in NEC with breastmilk feeds; retrospective cohort trials
- No significant change in NEC incidence over time, bw < 1500 grams
- VON: 1998 - 6.5%, 2007 - 7.4%
- NICHD NRN: 1990 - 10.1%, 2007 - 8.0%
- Breast milk usage is increasing in NICU’s
- NEC-associated morbidity and mortality is not improving

PROTECTIVE FACTORS IN BREAST MILK
- Antibodies (IgA, IgM, IgG)
- Leukocytes
- Enzymes (lysozyme, PAF-AH)
- Lactoferrin
- Growth factors (EGF, TGF, EPO)
- Oligosaccharides
- Long-chain polyunsaturated fatty acids
- Caution!!! Fresh or frozen BM??

Prospective Trial: Human milk and NEC incidence

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<td>3%</td>
</tr>
<tr>
<td>31-33</td>
<td>4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>34-36</td>
<td>9%</td>
<td>0</td>
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Randomized patients: 5% formula vs 1% human milk; Odd’s ratio 4.7, p > 0.05. Lucas and Cole, Lancet 1990:336;1519

Exclusive Human Milk-based diet reduces NEC

Study powered to identify reduction in TPN time; no difference found in primary outcome

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Neonatal NEC: Targets for Intervention/Prevention: human trials
- Human Milk (many studies, few prospective)
- IgA (7% vs 0%, Eibl et al, NEJM, 1988)
- Prophylactic Antibiotics (28% vs 13% with oral vancomycin, Sin et al, Arch Dis Child, 1998)
- Dexamethasone (14% vs 7%, Fox et al, J Peds, 1990)
- Glutamine (no diff, Poindexter et al, Pediatrics, 2004)
- Arginine (↓ grade I but not grade II NEC, Amin et al, J Peds, 2002)
- PUFA (↓ NEC, Carlson et al, Peds Res, 1998; no diff in meta-analyses)

Sullivan et al, J Peds, 2010
**Preventive Probiotic Trials in Preterm Infants**

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<tbody>
<tr>
<td>Probiotic species</td>
<td>L. acidophilus, B. infantis (Infloran)</td>
<td>L. GG</td>
<td>L. acidophilus, B. infantis (Infloran)</td>
<td>L. acidophilus, B. infantis, B. bifidum (Infloran)</td>
<td>L. acidophilus, B. infantis, B. bifidum (Infloran)</td>
<td>L. acidophilus, B. infantis, B. bifidum (Infloran)</td>
</tr>
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<td>Effect</td>
<td>Decreased NEC vs historic controls</td>
<td>1.4% vs 2.7%, p &lt; 0.05</td>
<td>1.6% vs 3.3%, p &lt; 0.06</td>
<td>6% vs 18%, p &lt; 0.05</td>
<td>1.8% vs 0.2%, p &lt; 0.05</td>
<td>5.3% vs 15.8%, p &lt; 0.01</td>
</tr>
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Probiotics: 53/2093 (2.5%) vs Control: 142/2143 (6.6%) p < 0.01, NNT=24

**Safety of Probiotics in Neonates**

- No cases of probiotic sepsis in previous prevention trials, but cases reported in immunocompromised patients
- Theoretical risk of contamination in nursery environment
- Accuracy and quality control of the formulation requires consideration
- Unexpected outcomes in adults and children

**Probiotic prophylaxis in adult ICU patients with pancreatitis:** 298 patients total, no difference in infectious complications, but...


**Probiotics given during infancy associated with increased respiratory disease**

- At 2 years, Kopp et al, 2008
- At 7 years, Kalliomaki et al, 2007

**Effectiveness of Probiotics: are there rational biologic pathomechanisms?**

- Production of inflammatory mediators such as iNOS, IL-8 and TNF-α.
- Bacteriocins: secreted modulatory proteins
- Production of DNA-CpG activates TLR9

**Unanswered Questions:**

- Safety in large study with long-term follow-up
- Best strain(s) or species combination
- Dose
- Duration
- Live or heat-killed/DNA
- Appropriate quality control
- Do neonatologists have equipoise?
Conclusions

- Pathophysiology of NEC complex and unclear, but likely involves an unbalanced pro-inflammatory response.
- Prevention is more likely to be efficacious than treatment.
- Breast milk and cautious enteral feeding only proven factors that reduce risk.
- Probiotics and other approaches on the horizon.