New Concepts and Controversies in Necrotizing Enterocolitis

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NEONATAL NEC:

- Clinical features
- Pathophysiology
- Role of PAF and TLR4: research reflections
- Prevention based on biological plausability
## Clinical differences between NEC and SIP (spontaneous intestinal perforation)

<table>
<thead>
<tr>
<th></th>
<th>NEC</th>
<th>SIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence &lt; 1500 grams</td>
<td>7-10%</td>
<td>2-3%</td>
</tr>
<tr>
<td>Age of onset</td>
<td>2-6 weeks</td>
<td>0-14 days</td>
</tr>
<tr>
<td>Pneumatosis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Enteral feedings</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Histologic evidence of villus necrosis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Mortality</td>
<td>10-30% above baseline</td>
<td>5-10% above baseline</td>
</tr>
</tbody>
</table>
NEC: clinical observations

- Premature presentation different than FT infant
- No effective therapeutic intervention
- Mortality rate not improving
- Long term outcome complicated by GI morbidity and NDI (RR=1.8 vs control for surgical NEC)
SIP: clinical observations

- early dx (0-3 d) in ‘larger’ preterm infants much less common than later dx (4-14 d)
- Early hypothesis: reduced intestinal blood flow, but no clear evidence
- Associated with postnatal steroid use
- Hydrocortisone and indocin (12%) vs HC alone (2%), Watterberg et al, 2004
NEC: Surgical approach and effectiveness

- Surgery: not a cure; ?
  Effect on outcome

- Laparotomy vs Drain:
  no diff in mortality or short term morbidity
  - Prospective: Moss et al, 2006, NEJM

Does surgical intervention alter the course of disease?
PATHOGENESIS: Multifactorial Theory

- Prematurity
- Formula feeding
- Intestinal ischemia
- Bacterial colonization

NEC → ‘Final Common Pathway’

Inflammatory mediator activation → ?
Pathogenesis: Prematurity

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

Why does this patient get NEC?
Early trophic feeding for VLBW Infants: meta-analysis

- Includes 9 trials, 754 VLBW infants
- No evidence that early trophic feeding altered feeding tolerance or growth rates
- No difference in NEC (RR 1.07 CI 0.67-1.70)
- **However**, the data cannot exclude important beneficial or harmful effects and are insufficient to inform clinical practice

Bombell and McGuire, Cochrane Database of Systematic Reviews, March, 2009
Prolonged trophic feedings decreases NEC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Advancing volume (20cc/kg/day)</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>38</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 (8% vs 30%, p < 0.05, Cassady et al, NEJM, 1989)
- Altered autoregulation in preterm/newborn animals
- ? Cocaine, UAC’s, indocin
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
Bacteria
Hypoxia/Ischemia
Enteral feeding

Non-immune factors
Physical barrier
Immune defense

PREMATURITY

MUCOSAL INJURY
HOST DEFENSE

PROINFLAMMATORY ACTIVATION

Receptor activation
Signal transduction
Gene transcription
Chemokine synthesis
Leukocyte activation

SIRS
NEC

TLR’s
PAF cycle

- Phosphatidylcholine precursors
- LysoPAF
- PAF
- PAF-AH

Phospholipase A₂
Arachidonic acid
Acetyltransferase

PAF receptor
PAF and ischemic bowel necrosis

- Intravenous PAF in adult rat causes bowel necrosis
  (Gonzalez-Crussi and Hsueh, 1983)
- LPS, hypoxia, or TNF-induced bowel injury blocked by PAF-receptor antagonists
  (Hsueh 1987, Sun 1988, Caplan 1990)
- PAF-induced intestinal injury involves multiple secondary mediators
  (Hsueh 1987-1995)
- LPS increases intestinal PAF content (Hsueh 1988)
Plasma PAF and PAF-AH levels in VLBW NEC patients and controls

Caplan et al, J Peds, 1990
Effect of Feeding on Human Stool PAF Concentration

Amer et al, Biol Neonate 2004
Serum PAF-AH Activity

Caplan et al, 1990
Formula and asphyxiation increase the incidence of NEC in the neonatal rat model

<table>
<thead>
<tr>
<th>Number of animals</th>
<th>Bacteria</th>
<th>Hypoxia</th>
<th>Formula</th>
<th>Preterm</th>
<th>NEC (%)</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>77</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>13</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>57</td>
<td>57</td>
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<td>8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>75</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>38</td>
<td>75</td>
</tr>
</tbody>
</table>

Caplan et al, Pediatr Path, 1994