Necrotizing Enterocolitis Update

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Incidence

Incidence of neonatal necrotising enterocolitis in high-income countries: a systematic review

Cheryl Battersby,¹ Tharsika Santhalingam,² Kate Costeloe,³ Neena Modi¹

- There is almost fourfolds difference in the rate of NEC in babies < 1500 gm (from 2-7%)
- The difference is almost fivefolds for those babies <1000 g from (5-22%)
- The most commonly applied definition of NEC is Bell’s stage 2 or more

Arch Dis Child Fetal Neonatal Ed 2018
Incidence

- The reasons for these differences:
  - No standardized approach to reporting
  - Study inclusion criteria
  - NEC definition
Incidence

- **In term** infants it occurs in 15% of the cases of NEC
- Onset occurs in the First few days of life.
- Commonly associated with other problems such as asphyxia, CHD, and hypothermia

Neoreviews, March 2006
Incidence

- Incidence of NEC in preterm infants in USA: 6% - 10%
- Death rate from NEC: 20% - 30%
- Surgical NEC: 30% - 40%
- Death rate in Surgical NEC: 50%

Mubina A, Current Opinion in pediatrics. 2018
The IECs barrier (Intestinal Epithelial Cells)
A  Necrotizing enterocolitis (NEC)

Microbial dysbiosis
Contributing factors are:
- Antibiotic exposure
- Acid reducing agents
- Bovine milk-based formula

Immature intestinal barrier
- Decreased mucus
- Low intercellular junctional integrity and increased permeability

Immature immune system
- Exaggerated inflammatory response via innate immune system: Toll-like receptor 4 (TLR-4)
- Decreased IgA

Tissue injury and intestinal necrosis

B  Normal

Commensal bacteria
Mucus
Tight junction
Enterocyte
Blood vessels
Clinical Presentation

- Abdominal distension
  70-98%
- Feeding intolerance and gastric residuals >70%
- Blood per rectum 25-63%
- Diarrhea 4-26%
Clinical Presentation

- Ascites if severe
- Abdominal wall erythema
- Bluish discoloration of the abdomen
- Early systemic signs are non-specific and similar to sepsis
Gross Pathology

- Mucosal edema
- Inflammation
- Hemorrhage
- Coagulation necrosis
- Mucosal ulceration

*Terminal ileum & proximal colon most affected*
## Modified Bell Staging For NEC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Systemic signs</th>
<th>Intestinal signs</th>
<th>Radiological signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Suspected NEC</td>
<td>Temperature instability, apnea, bradycardia</td>
<td>Elevated gastric residuals, mild abdominal distention, occult blood in stool</td>
<td>Normal or mild ileus</td>
</tr>
<tr>
<td>IIA: Mild NEC</td>
<td>Similar to Stage I</td>
<td>Prominent abdominal distention +/- tenderness, absent bowel sounds, grossly bloody stools</td>
<td>Ileus, dilated bowel loops with focal pneumatosis</td>
</tr>
<tr>
<td>IIB: Moderate NEC</td>
<td>Mild acidosis and Thrombocytopenia</td>
<td>Abdominal wall edema and tenderness +/- palpable mass</td>
<td>Extensive pneumatosis, early ascites, +/- PVG</td>
</tr>
<tr>
<td>IIIA: Advanced NEC</td>
<td>As above plus Hypotension Bradycardia Severe apnea</td>
<td>Worsening wall edema and Erythema with induration</td>
<td>Extensive pneumatosis, Early ascites, +/- PVG</td>
</tr>
<tr>
<td>IIIB: Advanced NEC</td>
<td>Vital sign and laboratory evidence of deterioration, shock</td>
<td>Evidence of perforation</td>
<td>Pneumoperitoneum</td>
</tr>
</tbody>
</table>
Imaging

Distension
Imaging

Distension

Bowel wall edema
Imaging

- Distension
- Bowel wall edema
- Pneumatosis intestinalis
Imaging

- Distension
- Bowel wall edema
- Pneumatosis intestinalis
- Perforation
Imaging

- Distension
- Bowel wall edema
- Pneumatosis intestinalis
- Perforation
- PVG & Ascitis
US in NEC

- US can detect free gas
- Its ability to show abdominal fluid, whether this intraluminal or extraluminal
- To assess bowel wall thickness, echogenicity, and peristalsis
- US directly assess arterial perfusion of the bowel wall, as this is not possible with plain abdominal radiography

Monica Epelman, Radiographics March-April / 2007
Francesco Esposito, Quant Imaging Med Surg 2017 ;7(3):336-344
US in NEC

MRI and NEC
Investigation / Non Specific Tests

- Complete blood count
- Coagulation studies
- Serum chemistries
- Sepsis evaluation
Gut –Associated Biomarkers

- Gut-barrier proteins L-FABP, I-FABP, and Trefoil 3 (TFF3) are specific indicators of early enterocyte death

- These biomarkers (L-FABP, I-FABP, and TFF3) and LIT score used for diagnosis of:
  - NEC
  - Differentiate NEC from Septicemia/Control infants
  - Differentiate Surgical NEC from Nonsurgical NEC infants

Jamie R. Robinson, SEMINARS IN PERINATOLOGY (2016)
Eddy Ng, Annals of Surgery Volume 258, Number 6, December 2013
### Diagnostic Values of L-FABP, I-FABP, and TFF3 and LIT Score for Differentiating NEC (n = 20) From Septicemic/Control Cases (n = 80)

<table>
<thead>
<tr>
<th></th>
<th>L-FABP, ng/mL</th>
<th>I-FABP, ng/mL</th>
<th>TFF3, ng/mL</th>
<th>LIT Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median of NEC group</strong></td>
<td>296</td>
<td>7.7</td>
<td>12.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>96</td>
<td>95</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>High cutoff†</td>
<td>650</td>
<td>23.0</td>
<td>16.0</td>
<td>6</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>25</td>
<td>20</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Medium cutoff</td>
<td>235</td>
<td>4.4</td>
<td>9.6</td>
<td>3</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>50</td>
<td>55</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>Low cutoff</td>
<td>70</td>
<td>0.8</td>
<td>4.0</td>
<td>1</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>85</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>60</td>
<td>31</td>
<td>63</td>
<td>50</td>
</tr>
</tbody>
</table>
Investigation / Specific Biomarkers

Gut–Associated Biomarkers

- Panel A: Plasma L-FABP (ng/mL) with a significance level of $P = 0.013$
- Panel B: Plasma L-FABP (ng/mL) with a significance level of $P = 0.006$
- Panel C: Plasma TFF1 (ng/mL) with a significance level of $P = 0.003$
- Panel D: LIT score with a significance level of $P = 0.005$
Fecal Calprotectin

- Antimicrobial protein **Released by granulocytes** and found in stool during intestinal inflammation, levels correlate well with severity of NEC
  - Levels > 350 µg/gm stool seen in infant with GI injury
  - Levels decrease after treatment (evaluate response)
Investigation / Specific Biomarkers

Fecal Calprotectin

**First study prospective**
To create FC reference from 250 samples. 120 Preterms <35 wks gestation with no NEC 1-8 wks of age

**Second study retrospective 2012-2017**
Stool from babies with R/O NEC
After 1 week they concluded if there is NEC or not

Median, lower (10th percentile), and upper (90th percentile)

B. C. MacQueen, J of Perinatol 2018
Prevention / Breast Milk

- Colostrum:
  Has a higher concentration of secretory immunoglobulin A (sIgA), growth factors, lactoferrin, anti-inflammatory cytokines, and secretory immunoglobulin when compared to term colostrum

- Oral colostrum within first day of life is:
  - Safe
  - Improve growth
  - Reduce late onset sepsis & duration of hospital stay
  - May effect inflammation and immunity but no data on the effect of oral colostrum on risk of NEC

Juyoung Lee, Pediatrics Feb. 2015
Rodriguez NA, Adv Neonatal Care 2010
Romano-Keeler, J Perinatol 2017
Breast milk decreases the risk of NEC mainly due to:

- Lower gastric pH
- Enhances intestinal motility
- Promote immunologic maturation (secretary IgA, lactoferrin and oligosaccharides), lower risk and extent of microbial dysbiosis
- Decrease seems dose dependent
- Donor BM decrease NEC stage ≥II by more than 2-3 folds compared to formula
EHM vs Cow’s Milk in extreme preterm infants and NEC

2557 preterm infants studied, over 2 periods (2006-2009 and 2013-2015), GA around 32.5. only 25.6% VLBW infants

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any HM</td>
<td>91.5</td>
<td>96.1</td>
</tr>
<tr>
<td>HM within 48H</td>
<td>75</td>
<td>90.6</td>
</tr>
<tr>
<td>DHM</td>
<td>17.7</td>
<td>71.9</td>
</tr>
<tr>
<td>PF within 3 D of birth</td>
<td>17.7</td>
<td>10.3</td>
</tr>
<tr>
<td>Fed on day of birth</td>
<td>23.9</td>
<td>44.6</td>
</tr>
</tbody>
</table>

The NEC rate declined from 4.1% to 0.4% and from 8.3% to 1.0% for VLBW; (P < 0.001)

All values are percentage. P < 0.001 for all
Prevention / Breast Milk

EHM vs Cow’s Milk in extreme preterm infants and NEC

<table>
<thead>
<tr>
<th></th>
<th>Human Milk</th>
<th>Cow’s Milk</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC</td>
<td>9/167 (5%)</td>
<td>16/93 (17%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Surgical NEC</td>
<td>2/167 (1%)</td>
<td>11/93 (12%)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Mortality</td>
<td>3/167 (2%)</td>
<td>7/93 (8%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

All cause mortality is lower 4.9 vs 6.8% (p=0.009)

NEC related mortality was not statically different 1 vs. 1.7% (p=0.75)

NEC stage ≥II incidence in the VLBW infants was lower in the probiotic group 3.9 vs 6.6% (p=0.0001)

In ELBW infants, the incidence of NEC was not statistically different 8.9 vs 10.6% (p=0.32)
In a subgroup analysis, only the probiotic combination of Bifidobacterium and Lactobacillus, were found to reduce both NEC and all-cause mortality the results from this review still failed to answer the important questions:

- Optimal probiotic strains
- Doses
- Duration of therapy
Bifidobacterium breve BBG-001 in very preterm infants: a randomized controlled phase 3 trial

Kate Costeloe, Pollyanna Hardy, Edmund Juszczak, Mark Wilks, Michael R Millar, on behalf of The Probiotics in Preterm Infants Study Collaborative Group*

- Multicenter, Randomized, Control study
- 1315 preterm infants between 23-30 weeks gestation between 2010-2013
- Given Bifidobacterium breve BBG-001
- Within 48 hours of birth in a daily dose, in 24 hospitals in England
- After randomization, whether or not enteral feeding had begun, and was continued until 36 weeks
- 9% in the probiotic group vs 10% in the control group develop NEC stage II-III
- No adverse effect

Prevention / Lactoferrin

- Promising nutritional supplement
- It is the major whey protein in colostrum, breast milk, tears, and saliva
- Systematic review showed to decrease incidence of NEC and Late onset sepsis when given oral as prophylaxis with or without probiotics. Evidence were low to moderate quality
Many of the bioactive factors contained in maternal breast milk are present in AF.

In Utero they play a role in fetal gastrointestinal development and innate immunity development.

AF contains:
- High concentrations of immuno-modulatory peptides such as IL-10
- Growth factors

AF shown in vitro to reduce the production of pro-inflammatory cytokines (IL-6, IL-12, and TNF)
30 preterm pigs were delivered by CS given supplementation during TPN & PO:

- Colostrum (7), 0% develop NEC
- Control Formula (13), 7/13 developed NEC 54%
- Formula + porcine AF (10), 20% develop NEC

30 preterm pigs, AF supplementation only during PO nutrition: 16 given Formula and 14 given Formula + porcine AF. NEC was 50% in both.

Prevention / Treatment

Amniotic Fluid (AF)

bacterial colonization

Prevention / Treatment

Toll-like receptor 4 (TLR4) Inhibitor (C34)

- TLR4 is a protein from the TLR family. Its activation leads to intracellular signaling & inflammatory cytokine production which is responsible for activation the innate immune system.

- C34 is a potential anti-inflammatory agent.

- Inhibit TLR4 in enterocytes and macrophages and reduced systemic inflammation in mouse models of endotoxemia and NEC.

- C34 inhibit LPS signaling in human ileum that was resected from infants with NEC as well.

Neal MD, PLOS ONE, June 2013
Prevention / Treatment

TLR4 Inhibitor C34

- Mice given
- NEC given:
  - Saline
  - LPS
  - C34
  - LPS + C34

6 hours after LPS, Luciferin (ip) injection was given to evaluate its activity

Neal MD, PLOS ONE, June 2013
Prevention / Treatment

TLR4 Inhibitor C34

- C34 reduces signaling of TLR4 in vivo and in vitro
- Has a therapeutic potential in diseases with exaggerated TLR4 signaling

Neal MD, PLOS ONE, June 2013
Medical Treatment

- NPO and TPN
- Gastric decompression by NGT
- Antibiotics
- Serial abdominal X-Rays (AP and Lateral) and US abdomen
- Supportive care
- Antifungal agents maybe used especially if surgical NEC
Surgical Treatment

(50% of cases)

- Absolute indication
  - Pneumoperitoneum
  - Paracentesis consistent with enteric contents
Surgical Treatment

- **Relative indications:**
  - Deterioration in spite of full medical treatment
  - Abdominal wall edema and discoloration
  - Portal vein gas
  - Extensive pneumatosis or fixed loops
  - Persistent hemodynamic instability or worsening acidosis or thrombocytopenia
They considered 3 or more of these criteria is an indication for surgery

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>Palpable abdominal mass</td>
<td>Fixed persistent mass on serial examinations</td>
</tr>
<tr>
<td>Abdominal erythema</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>MAP &lt; GA OR on any pressor</td>
</tr>
<tr>
<td>Radiographic</td>
<td></td>
</tr>
<tr>
<td>Pneumoperitoneum</td>
<td>Diffuse pneumatosis or focal pneumatosis in all quadrants</td>
</tr>
<tr>
<td>Portal venous gas</td>
<td></td>
</tr>
<tr>
<td>Fixed loop on X-ray</td>
<td></td>
</tr>
<tr>
<td>Severe pneumatosis</td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>Positive blood culture within 96 hours of diagnosis of NEC</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Sodium &lt;130 mEq/L within last 24 hours</td>
</tr>
<tr>
<td>Acidosis</td>
<td>pH &lt;7.25 or receiving bicarb/THAM</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Platelet count &lt;50,000 per mm$^3$</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>Absolute neutrophil count &lt;2,000 per mm$^3$</td>
</tr>
<tr>
<td>Bandemia</td>
<td>Absolute number of immature neutrophils/total number of neutrophils &gt;0.2</td>
</tr>
</tbody>
</table>

MAP, mean arterial pressure; THAM, trishydroxymethyl aminomethane.
## Surgical Treatment

<table>
<thead>
<tr>
<th>Clinical Indicators</th>
<th>Prevalence (%)</th>
<th>Medical Management (%)</th>
<th>Surgical Intervention (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpable abdominal mass</td>
<td>5</td>
<td>30</td>
<td>70</td>
<td>0.74</td>
</tr>
<tr>
<td>Abdominal erythema</td>
<td>34</td>
<td>21</td>
<td>79</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Hypotension</td>
<td>46</td>
<td>28</td>
<td>72</td>
<td>0.01*</td>
</tr>
<tr>
<td>Radiographic indicators</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumoperitoneum</td>
<td>34</td>
<td>4</td>
<td>96</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Portal venous gas</td>
<td>23</td>
<td>26</td>
<td>74</td>
<td>0.06</td>
</tr>
<tr>
<td>Fixed loop on X-ray</td>
<td>23</td>
<td>26</td>
<td>74</td>
<td>0.06</td>
</tr>
<tr>
<td>Severe pneumatosis</td>
<td>39</td>
<td>35</td>
<td>65</td>
<td>0.55</td>
</tr>
<tr>
<td>Laboratory indicators</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>18</td>
<td>26</td>
<td>74</td>
<td>0.13</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>15</td>
<td>28</td>
<td>72</td>
<td>0.22</td>
</tr>
<tr>
<td>Acidosis</td>
<td>55</td>
<td>26</td>
<td>74</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
<td>33</td>
<td>67</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19</td>
<td>26</td>
<td>74</td>
<td>0.1</td>
</tr>
<tr>
<td>Anemia</td>
<td>52</td>
<td>30</td>
<td>70</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

*P* < 0.05 was considered significant.
Surgical Treatment

- Resection then Stoma creation, Primary anastomosis or neither
- No intervention in case of NEC totalis or pan-intestinal necrosis

Barrie S. Pediatrics in Review, Dec. 2017
Surgical Treatment

Primary peritoneal drain (PPD)

- Bed side procedure done for mainly < 1500 gm when general condition does not allow
- 75% of patients with drain require an exploratory laparotomy
Surgical Treatment

PPD Outcome

- Do well after placement PPD Perforation heals
- Develop controlled fistulas at drain sites
- Heal with intestinal obstruction or strictures
- Ongoing uncontrolled sepsis which may require exploratory laparotomy
Surgical Treatment

**PPD Effectiveness**

**NECSTEPS Trial**
North America, 2006 (<1500 gm)
Effective treatment in **33%**

**NET Trial**
European trial, 2008 (<1000 gm)
Effective in **11%**

**Cochrane database 2011**
The combination of the 2 trials revealed no significant benefits or harm of PD vs. Laparotomy could be identified

Mehul V, Neoreviews 2013;14;e393
## Complication of NEC

<table>
<thead>
<tr>
<th>Type</th>
<th>Incidence</th>
<th>Associated factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>8% (3-15%)</td>
<td>More common following enterostomy</td>
</tr>
<tr>
<td>Adhesion ileus</td>
<td>6% (4 –9%)</td>
<td></td>
</tr>
<tr>
<td>Intestinal strictures</td>
<td>24% (17-31%)</td>
<td>more common following intestinal resection and enterostomy</td>
</tr>
<tr>
<td>Intestinal failure</td>
<td>13% (7-19%)</td>
<td></td>
</tr>
<tr>
<td>Biliary stasis</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Short bowel syndrome</td>
<td>9%</td>
<td>Increase with decrease GA</td>
</tr>
<tr>
<td>Neurodevelopment impairment</td>
<td>30-50%</td>
<td>More in surgical NEC</td>
</tr>
<tr>
<td>Growth delay</td>
<td>10%</td>
<td>&lt;50th percentile for Wt. &amp; height. &gt; in SBS</td>
</tr>
</tbody>
</table>

Take home message

- NEC is a devastating frequently encountered condition carries high M&M
- Symptoms & signs confused with those of sepsis, however recent studies showed many new specific biomarkers help in the diagnosis
- US is used widely these days to diagnose NEC and sometimes it is superior to plain X-ray
- Certain indicators may help in guiding surgeons for the timing of surgical intervention in the absence of pneumoperitoneum
- New therapies are shown in animal studies to prevent and treat NEC
- Complications of NEC are many especially neurological