Neonatal Necrotizing Enterocolitis

Steven McElroy MD
Vanderbilt University
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Neonatal Necrotizing Enterocolitis

- Origins of NEC
- Early History
- Definition of NEC
- Current Theories
- Current Treatments
Necrotizing Enterocolitis In The Beginning

- NEC was unknown as a disease before the 1950’s
- First described in 1950’s by Schmid and Quaiser
  - Case reports describing neonates who died from necrotizing lesions of their GI tracts
- NEC became recognized as a clinical entity in 1960’s and 1970’s
  - At this time NEC’s mortality exceeded 70%
  - NEC was initially described as idiopathic gastrointestinal perforations
Necrotizing Enterocolitis In The Beginning

- Management in the 1970’s included
  - Medical Management (10 day course)
    - NPO
    - Nasogastric suction
    - Systemic antibiotics
    - IV fluids
    - Monitoring with clinical signs and X-ray findings
  - Surgical Management
    - Removal of necrotic/nonviable bowel
    - Re-anastomosis at a later time
Necrotizing Enterocolitis Today

• An acute inflammatory disease process of the bowel

• **Effects 1-3% of all NICU admissions**

• Primarily a disease of premature infants
  – 10% of infants under 1500g

• Mortality rate of 20-50%
  – Annual mortality rate in US of approx **2700** infants
Necrotizing Enterocolitis

• Incidence varies inversely with birth weight and gestational age
  – Greatest risk of <1000g and <30 weeks

• Age of onset also varies inversely with gestational age
  – Term infants develop at 2 days of age
  – Infants <30 weeks develop at several weeks of age
The Cost of NEC: Case 1

- Baby Girl NM
- 1081 gm infant born at 27 wks
- APGARS 5/8/8
- Infant with history of feeding intolerance
  - DOL 12 feeds were stopped due to bloody stools
    - No radiologic evidence of NEC
    - Treated with 10 days NPO and antibiotics
- Feeds restarted on DOL 23 and stopped DOL 25
  - Stopped for increased abdominal girth
- Feeds restarted on DOL 35
The Cost of NEC: Case 1

- DOL 44 infant’s abdomen distended by 3 cm and became tense
- Infant developed respiratory failure
- Sent to VCH for surgical evaluation
The Cost of NEC: Case 1

• Upon exploratory laparotomy less than 8cm of bowel was found to be viable

• The infant’s abdomen was closed, the parents were informed, and the infant was withdrawn from care
Necrotizing Enterocolitis

- Presentation includes
  - Abdominal Distention
  - Feeding intolerance
  - Hematochezia
  - Lethargy
  - Apnea
  - Respiratory Failure
  - Circulatory Instability
Necrotizing Enterocolitis

• Presentation includes
  – Leukopenia
  – Thrombocytopenia
  – Hyponatremia
  – Hypokalemia
  – Metabolic acidosis
  – DIC
  – Glucose instability
Necrotizing Enterocolitis

- Predominant lesion is necrosis
  - coagulative or ischemic

Image from the Cornell University Medical College
Necrotizing Enterocolitis

- Lesions can be continuous or discontinuous throughout the bowel
Do You Know NEC?

What is the most common site of NEC?
Do You Know NEC?

What is the most common site of NEC?

A. Stomach

B. Jejunum

C. Ileum

D. Colon

E. Just under your head
Do You Know NEC?

Necrotizing Enterocolitis
Common Site

Terminal ileum/
Proximal Colon
Necrotizing Enterocolitis

- Intestinal Pneumotosis
  - Characteristic radiographic finding

Image from the Cornell University Medical College
Necrotizing Enterocolitis

- Intestinal Pneumotosis
  - Gas created by bacterial fermentation
Intestinal Architecture of NEC

Normal

+1 NEC

+2 NEC

+3 NEC

+4 NEC
Do You Know NEC?

What do we use to determine severity and medical management in NEC?
Do You Know NEC?

What do we use to determine severity and medical management in NEC?

A. Modified Bell Staging

B. Walsh Severity Index

C. Chicken bones and voodoo dice
Do You Know NEC?

What do we use to determine severity and medical management in NEC?

A. Modified Bell Staging Criteria
### Modified Bell's Staging Criteria for Necrotizing Enterocolitis

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## Diagnosing NEC Severity

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*Vanderbilt Children’s Hospital*
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Historical Risk Factors

• Perinatal asphyxia
• Respiratory Distress Syndrome
• Cyanotic Heart Disease
• Vasoconstricting medications (indomethacin)
• Enteral nutrition
• Bacterial Infection
• Prematurity
Risk Factors

- Bacterial Colonization
- Enteral Feeding
- Prematurity
  - Mean gestation 30-32
Do You Know NEC?

True or False: Gastroschisis carries an increased risk of developing NEC…
Do You Know NEC?

Why the Preemie Gut is Different

- Decreased IgA
- Decreased Intestinal T lymphocytes
- Poor Antibody Response
- Higher Membrane Permeability of GI Epithelial Lining
- Lower Gastric Motility
- More Scant and More Permeable Mucin Blanket
Why the Preemie Gut is Different

Luminal Flow
Mucin Layer
Epithelial Cell Layer
Immune System Cells
Why the Preemie Gut is Different

Adult GI Wall

Preemie GI Wall

Luminal Flow
Mucin Layer
Epithelial Cell Layer
Immune System Cells

Luminal Flow
Mucin Layer
Epithelial Cell Layer
Immune System Cells
“I have yet to see a problem, however complicated, that when you look at it the right way does not become more complicated.”

-Paul Aldeston
Intestinal Architecture

- Keep in mind we will be looking at a small slice of an enormous organ that has multiple layers of complexity...
Intestinal Architecture
Intestinal Architecture
Intestinal Architecture
Intestinal Architecture
Intestinal Architecture
Intestinal Defenses

- All that separates us as an organism from the outside environment is a thin layer of cells called epithelial cells.
Intestinal Defenses

- These cells are fastened together by proteins called “tight junctions” which seal the cells together

Intestinal Lumen

Body
Intestinal Defenses

- The epithelial cells secrete a protective layer of glycoproteins known as the glycocalyx.
Intestinal Defenses

- Some of the epithelial cells are specialized cells such as goblet cells or paneth cells which produce antibacterial peptides called cryptins or defensins.

- These peptides have been shown to protect against bacteria such as *Salmonella* and *E. coli* by penetrating and disrupting their cell membranes.
Intestinal Defenses

- Epithelial cells also contribute to host defense by transferring IgA to the gut lumen
And by expressing receptors that sense bacterial and viral compounds such as the Toll-like Receptors (TLRs)

When pathogens attach to these TLRs, the epithelial cells signal cell responses that attract neutrophils, phagocytes, and induce inflammatory responses to deal with the threat
Intestinal Defenses

- So the thin layer of defense is actually a very intricate, coordinated barrier
Proposed mechanism of NEC

Mucin Layer

GI Epithelial Cells
Proposed mechanism of NEC

Enteral feeding induces bacterial proliferation
Electron microscope picture of the Gut’s Lumen

Thaddeus S. Stappenbeck, Washington University School of Medicine
Proposed mechanism of NEC

Hypoxia or mild infection causes mild mucosal damage
Proposed mechanism of NEC

This allows for bacterial adhesion to Toll-like Receptor 4
Proposed mechanism of NEC

This adhesion causes local inflammation and infiltration of PMN and M0 cells.
Proposed mechanism of NEC

These cells release a multitude of inflammatory mediators including TNF and PAF.

TNF is produced in excess by the liver.
Platelet-activating Factor

• Endogenous phospholipid mediator
• Produced by inflammatory cells, endothelial cells, and platelets
• Short ½ life but induces its own production as well as multiple inflammatory mediators including TNF
• Ileum has the highest concentration of PAF receptors in the body
  – Mostly in epithelial cells and eosinophils
Tumor Necrosis Factor

- Potent inflammatory cytokine produced in response to inflammation, infection, and injury
- Involved in inflammation, immunoregulation, proliferation, and cell differentiation
- Causes self induction as well as induction of PAF
- Normally expressed within Paneth cells
  - During NEC, increased in Paneth as well as produced by infiltrating macrophages and eosinophils
- Also recently found to be induced by the liver in NEC models
  - Halpern et al
Proposed mechanism of NEC

TNF and PAF continue the inflammatory response
Proposed mechanism of NEC

- TNF
- PAF

NF-κB

Complement
Leukotriene C4
E-cadherin-P
Norepinephrine
Proposed mechanism of NEC

- TNF
- PAF

- NF-κB
- Complement
- Leukotriene C4
- E-cadherin-P
- Norepinephrine

- Inflammation
- Splanchnic Vasoconstriction
- Increased Membrane Permeability
Proposed mechanism of NEC

PAF

TNF

NF-κB

AP-1
Proposed mechanism of NEC

- TNF
- PAF
- NF-κB
- AP-1
- Inflammation
Proposed mechanism of NEC

- PAF
- TNF
- NF-κB
- Complement
- Leukotriene C4
- E-cadherin-P
- Norepinephrine
- NF-κB
- AP-1
- Inflammation
- Splanchnic Vasoconstriction
- Increased Membrane Permeability

Inflammation
Proposed mechanism of NEC

Increased membrane permeability allows for bacterial invasion
Proposed mechanism of NEC

Increased membrane permeability allows for bacterial invasion
Proposed mechanism of NEC

Increased membrane permeability allows for bacterial invasion
Proposed mechanism of NEC

Splanchnic constriction causes hypoxia with development of O radicals
Prevention of NEC

• **ONLY** known preventative measure is maternal breast milk

  – Lancet article by Lucas and Cole in 1990 showed a decreased number of NEC cases in prospective study of 926 infants
    • Formula fed infants developed *6-10 times more NEC* than breast milk alone
      and *3 times* more than breast milk + formula

  – Several groups have demonstrated a decrease in experimental NEC when feeding rat pups maternal milk instead of formula
Current Treatments of NEC

• Medical Treatment
  – NPO
  – Nasogastric Suction
  – Systemic antibiotics
    • Ampicillin/Vancomycin
    • Gentamycin
    • Flagyl (if perforation)
  – IV fluids
  – Monitoring with clinical signs and X-ray findings

• Surgical Treatment
  – Peritoneal Drain
  – Exploratory Laparotomy
  – Bowel Resection
    • Enterostomy
    • Primary Anastomosis
    • Diverting Jejunostomy
    • Clip and Drop Procedure
Treatment of NEC: Bottom Line

• Despite studying this disease for over half a century,
  
  – we don’t treat babies any differently than we did in the 1970’s
  
  – we haven’t changed outcomes in decades
Do You Know NEC?

What percentage of patients will require a scalpel?
Do You Know NEC?

What percentage of patients will require a scalpel?

A. 1%
B. 20%
C. 45%
D. 80%
Do You Know NEC?

What percentage of patients will require a scalpel?

35-50%
(That would be C. 45%)
Surgical Management

• Little agreement among surgeons
  – Lack of good quality research
  – Most studies look at a small number of babies and are not randomized
• Remember the goal of ANY surgical procedure is to preserve as much viable bowel as possible
Current Treatments of NEC

**Figure 9.** Representation of the small intestine in NEC. NEC begins most often in the terminal ileum, near the ileocecal valve. Often there are areas of completely viable bowel, areas of marginal viability, and irreversibly necrotic and perforated areas. “Leopard skinning” refers to areas with patches of intramural hemorrhage that also may recover viability. NEC may be restricted to small lengths of intestine, or the entire small bowel (pan necrosis). Involvement may extend into the colon; stomach and duodenum are generally spared.

*Critical Care of the Surgical Newborn* Nakayama et al, 1997
Current Treatments of NEC
Indications for Surgery

• Absolute Indications
  – Presence of pneumoperitoneum (perforation)
  – Clinical deterioration despite maximal medical support
  – Persistent intestinal obstruction or sepsis
  – Development of stricture

• Relative (Controversial) Indications
  – Abdominal Wall discoloration
  – Fixed and dilated loops of bowel on X-ray
  – Portal Vein gas
Surgical Choices

- **Peritoneal Drainage**
  - Usually considered in the sickest and smallest preemies
  - Can be done at the bedside
  - If no improvement in 12-24 hours must have a laporotomy anyway

- **Laporotomy**
  - Performed to remove gangrenous bowel and control sepsis
  - Used to determine the extent of disease and further management
    - Resection and enterostomy
    - Resection and primary anastomosis
    - Diverting Jejunostomy (First described by Neblett!)
    - Clip and Drop
Laporotomy vs Drainage

- **Moss trial**
  - 15 centers, 117 infants below 1500g birth weight
  - 5 year study
  - No significant difference in mortality between procedures

- **Rees trial**
  - 31 centers, 69 infants
  - Slight trend towards improved mortality with PD but not found to be significant
    - 65% vs 51%

Adapted from Moss RL et al NEJM 2006
Complications of NEC

- Both surgical and medical treatment
- Metabolic acidosis
- DIC
- Peritonitis
- Abscess formation
- Stricture
- Short-gut (27% of surgical patients)
- Neurodevelopmental Delay (50% of patients)
- Recurrence
Probiotics

• At birth the neonatal intestine is sterile

• Quickly colonized with a variety of bacteria
  – Bacteria outnumber us (10 bacteria to every cell in our body)
  – Most common of the GI flora are *Lactobacilli* and *Bifidobacteria*
  – Preemies colonize initially with *Escherichia, Enterobacter, Klebsiella, Citrobacter*, and *Bacteroides*
  – Preemies do not get a normal flora until around after a month of life
What is a Probiotic?

• The idea that intestinal bacteria can affect our health was first proposed in 1907 by Nobel prize winner Dr. Elie Metchnikoff, a Russian zoologist and microbiologist.

• He proposed that consuming fermented milk was health promoting because it prevented the growth of harmful bacteria.
What is a Probiotic?

- Probiotic is derived from the Latin word “pro” which means “for” and the Greek word biotikos” which means “living”
  - In short “for life”

- This definition was refined in 1989 by Fuller as:
  - Live microbial feed supplements which beneficially affect the host animal by improving its intestinal microbial balance
  - (Fuller R. Journal of Applied Bacteriology1989)
What is a Probiotic?

• Examples include:
  – Bifidobacteria
  – Lactobacilli
  – Saccharomyces boulardii (yeast)

• In general, human derived organisms have done the best.
What makes a good Probiotic?

• Probiotics must be:
  – Non-pathogenic
  – Non-toxic
  – Exert a beneficial effect on the host
  – Capable of surviving through the harsh environments of the stomach (acid) and small intestine (enzymes)
  – Be able to compete with the diverse flora present in the human GI tract
Alternatives to prebiotics include:

- **Prebiotics**: A non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already resident in the colon
  - (Gibson & Roberfriod. *Journal of Nutrition* 1995)

- **Symbiotics**: The combination of Prebiotics and Probiotics together.
How Probiotics Work

• Remember that the GI tract is swarming with 10 bacteria for every cell in your body—an equivalent of up to 15 lbs of bacteria
Proposed Probiotics Mechanisms

- Maintain mucosal barrier integrity
  - Reduce mucosal permeability
  - Increase mucus production
  - Strengthen intestinal tight junctions
  - Inhibit bacterial translocation

- Regulate appropriate bacterial colonization
  - Modulate microflora growth and adherence
  - Produce substances toxic to aerobic bacteria
  - Reduce intraluminal pH
  - Compete against pathogenic bacteria for binding sites
Proposed Probiotics Mechanisms

• Activate general intestinal immune defenses
  – Increase fecal IgA
  – Enhance mucosal IgA response
  – Increase blood leukocyte phagocytosis

• Modulate intestinal inflammation
  – Increase T cell and macrophage production of cytokines
  – Increase production of anti-inflammatory cytokines
  – Decrease pro-inflammatory cytokines
How Prebiotics Work

• Indigestible oligosaccharides (sugars) that occur naturally in fruits and vegetables are the most common prebiotic

• These pass intact through the stomach and small intestine and are able to be digestible nutrition for probiotics (selective)
Probiotics: Necrotizing enterocolitis

- A study looking at *Bifidobacterium infantis* given daily to rat pups resulted in a decreased incidence of NEC (29% vs 70%) and decreased death (33% vs 74%)
Probiotics: Necrotizing enterocolitis

• A recent review by Barclay et al found 18 studies looking at administration of probiotics for necrotizing enterocolitis, only 5 of which qualified for their analysis.
  – Total infants enrolled was 640 study/627 control
  – Heterogeneity of the studies prevented meta-analysis
  – Only 2/5 had significant prevention of NEC
  – But the studies overall had a trend towards a decrease in NEC mortality (15 vs 34)
  – Importantly, the studies found no adverse events such as probiotic sepsis
Probiotics: Necrotizing enterocolitis

- Big 3

Table 4: Randomized Clinical Trials of Probiotic Supplementation for the Prevention of NEC

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>N</th>
<th>Probiotics</th>
<th>Incidence of NEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dani, et al.</td>
<td>&lt;33 weeks’ gestation or, ≤1500 g</td>
<td>585</td>
<td>Lactobacillus GG</td>
<td>Probiotic Group: 4/295 (1.4%)</td>
</tr>
<tr>
<td>Lin, et al.</td>
<td>&lt;1500 g</td>
<td>367</td>
<td>Lactobacillus acidophilus, Bifidobacterium infantis</td>
<td>Control Group: 10/187 (5.3%)</td>
</tr>
<tr>
<td>Bin-Nun, et al.</td>
<td>≤1500 g</td>
<td>145</td>
<td>Bifidobacterium infantis, Bifidobacterium bifidus, Streptococcus thermophilus</td>
<td>Probiotic Group: 3/72 (4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control Group: 12/73 (16.4%)</td>
</tr>
</tbody>
</table>
Probiotics: Necrotizing enterocolitis

- Dani
  - No significant differences in probiotics vs NEC
- Lin
  - Single NICU
  - All infants got breast milk or donor breast milk
    - Control rate of NEC 5.3%
  - Lower rate of sepsis
- Bin-Nun
  - Single NICU
  - Breast milk or premature formula
  - Control rate 16.4%
  - No difference in sepsis
Probiotics: Necrotizing enterocolitis

• Recent Cochrane review (Jan 2008) looking at 9 eligible trials
  – Highly variable with regard to enrollment criteria, baseline risk of NEC, timing dose and formulation of probiotics, and feeding regimens
  – Unable to separate ELBW infants from the rest
  – Enteral probiotic supplementation significantly reduced the incidence of NEC (stage II or more) and mortality
  – Recommended a change in practice for infants >1000g at birth and the need for a large randomized control trial
Probiotics

• The most important thing to remember about probiotics is:
  – We still don’t understand their mechanisms in detail
  – Different strains likely work differently and for different diseases
Not all strains of Probiotics are equal

Both are strains of dog, but have “huge” differences
Not all strains of Probiotics are equal

• Most preparations of probiotics contain more than one species.
Animal Models of NEC

- Original method of creating NEC developed by Barlow in the 1970’s
  - Newborn rat pups were either dropper fed a simulated rat milk formula or dam fed
  - All animals were given an oral inoculation of Kelbsiella at birth
  - Newborn rat pups were sealed in a plastic bag until cyanotic and limp (3-5 min) and then placing them in a cold stress at 7°C for 5 min daily.
- Refined the 1990’s by Caplan and utilized by multiple labs
- But the limitation with rat pups is the inability to utilize genetic manipulation
Animal Models of NEC

0 day old pups

4 day old pup

Pup in a Cup System
Animal Models of NEC
Animal Models of NEC

NEC Protocol
Questions