PEDScore: Necrotizing Enterocolitis

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Objectives

- Epidemiology
- Prevention
- Presentation
- Diagnosis
- Pertinent physiology
- Staging/ grading
- Non-surgical treatment
- Indications & contraindications for procedures
- Pertinent operative anatomy/ histology
- Preoperative preparation
- Steps of operative procedure & technical skills
- Intraoperative decision making
- Complications of operative procedure & their treatment
- Assessment of outcomes
- Long-term follow-up
Epidemiology

- Most common condition leading to emergent surgical intervention in the newborn

- Incidence: 5-10% of newborns (1-3/1,000)
  - Global variance
  - Multifactorial: biologic & environmental
  - VLBW: 10-12%

- Age & Maturity
  - Premature LBW
    - Mean GA: 31 wks
    - Only 13% of NEC occurs in full-term infants
  - Highest risk: <28 weeks, <1000g
Epidemiology

- Feeds
  - 90% of cases after initiation of feeds
  - Increased incidence with advancement >20 kcal/kg/d
    - Randomized trials show no difference:
      - Fast vs slow
      - Early vs delayed
      - Continuous vs intermittent bolus feeds

- Pharmacologic Agents
  - Indomethicin
    - Blocks prostaglandin synthetase $\rightarrow$ vasoconstriction
    - Increased mesenteric vascular resistance $\rightarrow$ decreased blood flow
Pathology

- Single or multiple, discontinuous segments
- Terminal ileum most commonly affected, followed by colon
  - 44% have both small and large intestine involvement
  - NEC totalis = 75% of small and large intestine (19% of NEC cases)
- Markedly dilated bowel, patchy areas of thinning
  - Serosal = red to gray, covered with fibrinous exudate to frank gangrene
  - Subserosal gas collections common
  - Ulcerated mucosal surface
- Coagulation necrosis → edema/ hemorrhage of submucosa → necrosis
- Transmural necrosis – hylaine eosinophilia
- Epithelial regeneration, granulation, fibrosis common
  - Leading to stricture
- Mesenteric thrombosis – usually small vessel
Prevention

- Infection control
  - Limits the incidence and spread

- Augmentation of host defense
  - Oral immunoglobulin preparation
    - Premature gut is IgA deficient
    - Decreases bacterial translocation
  - Maternal glucocorticoid administration
    - Improve gut barrier function
    - Reduce bacterial translocation
    - Down-regulate inflammatory response (with regards to PAF)

- Breast Milk
  - Less lower respiratory tract infections, OM, bacteremeia, etc
  - Contains IgA
Prevention

- Methods to decrease intestinal bacterial colonization & other growth
  - Administration of probiotics
    - Associated with reduced risk of surgical NEC
  - Administration of postbiotics (bacteria metabolites)
    - Butyric – short chained fatty acid
  - Enteral antibiotics

- Methods to deter inflammatory cascade
  - Inflammatory mediators antagonists
    - PAF antagonists
    - PAF-degrading enzyme (PAF acetylhydrolase – in breast milk)
  - Arginine
    - For improved NO synthesis
  - Epidermal growth factor
Presentation

- Lethargy
- Temperature instability
- Recurrent apnea
- Bradycardia
- Hypoglycemia
- Shock
- Edema/ erythema of abdominal wall (2/2 peritonitis)

- Abdominal distention (>70%)
- Bloody stools (>80%)
- Increased gastric residuals (>70%)
- Vomiting (>70%)
- Diarrhea (4-25%)
- Abdominal tenderness
Diagnosis

- **Labs**
  - **Neutropenia**
    - Lower counts = worse prognosis
    - <6000 cell/mm³ = GN septicemia
  - **Thrombocytopenia**
    - Lower nadir = more severe
    - ≤10⁴ is a poor prognostic factor
  - **Metabolic acidosis (40-85%)**
  - **Hypovolemia + sepsis**
  - **FOBT+**
    - Damaged mucosal → carbohydrate malabsorption → fermented/ excreted
    - +Reducing substance
  - **Elevated CRP = early indicator of NEC**
    - Still elevated 10 days later – think abscess, stricture, septicemia
  - **Cultures**
    - **E. coli, Klebsiella**, Proteus, Staphylococcus, Clostridium, Pseudomonas are common
    - Fungus = secondary invaders
Diagnosis

- **2 view abdominal x-ray**
  - Distended loops of bowel
    - Most common finding; may precede clinical symptoms
    - Persistent dilated, fixed loops
      - Indicative of full thickness necrosis
  - Pneumatosis intestinalis
    - Fleeting
    - More frequently noted in fed babies
    - Cystic – granular or foamy appearance; submucosa
    - Linear – small bubbles in the muscularis/subserosa
  - Portal venous gas
    - Fleeting
    - Low incidence (10-30%)
    - Associated with poor prognosis
  - Pneumoperitoneum
    - Up to 30% of NEC
    - “Football sign” → outlines the falciform ligament
    - “Double wall” sign
  - Free fluid
    - Abdomen devoid of gas or central gas filled loops with opacity at flanks, increased haziness, separation of body loops

- **Contrast studies**
  - Useful in patients with equivocal clinical/radiologic signs
  - Water-soluble contrast only
  - Bowel loops separated by edematous walls, irregular mucosa, ulceration, spiculation, pneumatosi
  - Now reserved for evaluating after NEC resolved
  - Risk of rectosigmoid perforation

- **Ultrasound**
  - Can identify necrotic bowel, intraperitoneal fluid, portal venous gas
  - Look for intraperitoneal fluid, reduced bowel wall perfusion, abnormal loops of bowel, bubbles in the portal venous system
  - Useful for patients with a questionable history for NEC

- **MRI**
  - Can identify ischemic bowel
  - Limited utility
Etiology: multifactorial

Impaired Gut Barrier
- Preterm gut
  - Immature cellular & humoral immunity
  - Increased permeability
  - Decreased gastric acid
  - Decreased proteolytic enzymes
  - Decreased motility
  - Decreased barrier function
- Reduced blood flow → hypoxia → injury
  - Exchange transfusion via umbilical vein, umbilical artery catheters, cardiovascular lesions, hyperviscosity
  - Bursts of superoxide radicals → damage cellular/ mitochondrial membranes
- Increase permeability
  - Allows translocation of bacteria/ bacterial toxins
  - Key mediators: PAF, NO, LPS, TNF-alpha

Santuli’s 3 Essentials
1. Injury to intestinal mucosa
2. Presence of bacteria
3. Presence of a metabolic substrate
Infectious Agents

- Breast fed – colonized with bifidobacteria
- Formula fed – colonized with coliforms, enterococci, Bacteroides
- NEC occurs in waves
  - Same infectious agents isolated from affected babies/ caretakers
- Vitamin E administration – interferes with bactericial activity of leukocytes – associated with increased incidence
- NEC like lesions present after administration of LPS
- 80% of NEC babies have GNR bacteremia
- Pneumatosis intestinalis common – extraluminal gas produced by bacterial fermentation

Santuli’s 3 Essentials
1. Injury to intestinal mucosa
2. Presence of bacteria
3. Presence of a metabolic substrate
Growth Factors

Epidermal Growth Factors (EGF)
- Trophic factor for GI tract development \(\rightarrow\) proliferation/ differentiation
- Healing of damaged mucosa & adaptation after injury
- High concentrations in breast milk
- Secreted by salivary & Brunner glands \(\rightarrow\) basolateral membrane of enterocytes
- Levels reduced in babies with NEC

Heparin-binding EGF
- Low levels = increased intestinal permeability, delayed onset of angiogenesis, increased incidence/ severity of NEC in animal studies

Erythropoietin (Epo)
- Produced by kidneys – regulates RBC production
- Found in human breast milk; receptors in fetal/ neonatal small intestines
- Lower incidence of NEC in VLBW babies receiving rEpo
Cytokines

- **PAF**
  - Endogenous phospholipid inflammatory mediator
  - Mesenteric vasoconstriction, capillary leakage, increased mucosal permeability, neutrophil/platelet activation
  - Increased in formula-fed infants

- **LPS**
  - Bacterial product – potent inflammatory mediator
  - Binds pattern recognition receptors on Toll-like receptors and leads to increase cascade function
  - Hypotension, shock, intestinal necrosis

**NO synthesis**

- Produced from arginine by NO synthase
  - NOS-2 inducible – increases with inflammation
    - Sustained release of NO induces cellular injury and failure of mucosal barrier
      - NO + O2- -> ONOO- (cytotoxic)
  - Constitutive NOS – maintain mucosal integrity, regulate permeability, modulate water/electrolyte transport, regulate blood flow and motility

- Exogenous NO decreases severity of NEC (L-arginine)

**TNF-alpha**

- Pro-inflammatory cytokine activates neutrophils, induces leukocyte/endothelial adhesion, PAF
- Causes hypotension, intestinal necrosis
- Pentoxyifylline – TNF-a inhibitor – reduces bowel necrosis in animal models
## Staging & Grading

<table>
<thead>
<tr>
<th>Bell’s Stage</th>
<th>Systemic Signs</th>
<th>Abdominal Signs</th>
<th>Radiographic Signs</th>
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</thead>
<tbody>
<tr>
<td><strong>Stage I</strong></td>
<td>Suspicious for NEC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>Temperature instability, apnea, bradycardia, lethargy</td>
<td>Gastric retention, abdominal distention, emesis, heme +</td>
<td>Normal or intestinal dilation, mild ileus</td>
</tr>
<tr>
<td>IB</td>
<td></td>
<td>Grossly bloody stool</td>
<td></td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td>Definitive NEC</td>
<td></td>
<td></td>
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<tr>
<td>IIA</td>
<td>+ mild metabolic acidosis, thrombocytopenia</td>
<td>+ absent bowel sounds ± tenderness</td>
<td>Intestinal dilation, ileus, pneumatosis intestinalis</td>
</tr>
<tr>
<td>IIB</td>
<td></td>
<td>+ absent bowel sounds, tenderness, ± cellulitis or RLQ mass</td>
<td>+ ascites</td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td>Advanced NEC</td>
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<td></td>
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<tr>
<td>IIIA</td>
<td>+hypotension, severe apnea, combined respiratory/metabolic acidosis, neutropenia</td>
<td>+ peritonitis, tenderness, distention</td>
<td>+ pneumoperitoneum</td>
</tr>
<tr>
<td>IIIB</td>
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</tbody>
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Non-surgical, Alternative, & Adjuvant Treatments

Non-operative intervention: no intestinal necrosis or perforation

- NPO
- Gastrointestinal decompression – sump gastric tube
- IV fluids
- IV antibiotics
  - Penicillin, aminoglycoside, anaerobic coverage
  - High index of suspicious for fungal infections; may need to add antifungal
- Obtain
  - CBC, platelet count, ABG, CRP, BMP q6 hours until stable, then daily
  - Blood & urine cultures
  - KUB q6h
- TPN for nutrition

7 – 14 days
Indications & Contraindications for Procedure

- **Absolute**
  - Pneumoperitoneum – laparotomy vs peritoneal drain placement

- **Relative**
  - Positive paracentesis - $\geq 0.5$ mL brown or yellow brown fluid with bacteria
    - Erythema/edema of abdominal wall, portal venous gas, fixed/dilated loops, abdominal mass, deterioration
  - Portal venous gas
  - Palpable abdominal mass
  - Abdominal wall erythema
  - Fixed loops
  - Clinical deterioration
Operative Management

- Primary Peritoneal Drainage (PD)
  - ELBW infants with perforated NEC → resuscitation, stabilization
  - NECSTEPS (Moss et al NEJM 2006)
    - 117 infants
      - <34 weeks gestation, <1500 g
    - 34.5% mortality in PD vs 35.5% in laparotomy (LAP) at 90d; \( p = 0.92 \)
    - 47.2% of PD TPN dependent vs 40% in LAP; \( p = 0.53 \)
    - Study failed to enroll desired number of patients; power ≤ 77%
    - **Type of operation does not affect 90 day mortality, rate of TPN dependence, or overall length of stay**
    - 69 patients
    - 51.4% survival in PD vs 63.6% in LAP; \( p = 0.3 \)
    - Delayed laparotomy in PD group did not improve survival; RR of mortality 1.4, \( p = 0.4 \)
    - **No difference in 6-month trial between PD and LAP**
    - **Conclusion: PD ineffective as temporizing measure or definitive treatment → high rate of rescue**
  - Meta-analysis (Sola et al)
    - Increased mortality with PD; OR 1.5, \( p = 0.02 \)
      - Higher mortality in 4/5 studies due to premature/ smaller infants
  - Ongoing multicenter trial through NICHD
Operative Management

- Options
  - Resection with enterostomy
  - Resection and anastomosis
  - Proximal enterostomy
  - Clip-and-drop technique
  - Patch, drain, and wait

- Steps
  - Transverse supraumbilical incision
    - Care must be taken with regard to the liver (retractor/ finger dissection injury) leading to spontaneous intraoperative liver hemorrhage
  - Send samples of peritoneal fluid for cultures
  - Run the bowel
  - Resect gangrenous bowel
    - Marginally viable bowel → preserve with proximal diversion or clip-and-drop technique
    - Record the length of viable bowel remaining, presence or absence of ileocecal valve

- Stoma closure
  - No difference in complications at <3 months, 3-5 months, and >5 months
  - No difference in complications <2.5 kg, 2.5-5 kg, or >5 kg
Operative Management

- **Focal**
  - Limited resection
  - Proximal enterostomy with distal mucus fistula
  - Resection and anastomosis
    - Sharply localized
    - Normal remaining bowel
    - Hemodynamically stable

- **Multifocal (>50%)**
  - Multiple resections/ stomas
  - Single high stoma, distal bowel spliced together
  - Resection and anastomosis
  - Patch, drain wait (Moore, 1989)
    - Transverse single layer suture to reapproximate perforation, 2 penrose drains, long term TPN
  - Clip-and-drop-back (Vaughan)
    - Clip ends of resected bowel, re-explore and anastomosis at 48-72 hours

- **NEC totalis**
  - Mortality: 42-`00%
  - Almost all left with short-bowel syndrome
  - High proximal jejunostomy \(\rightarrow\) facilitate healing of distal bowel
Survival

- Progressively improved
  - Earlier diagnosis
  - More effective supportive treatments
    - Improved ventilatory strategies
    - Surfactant
    - TPN
    - Improved ICU care
- Mortality higher in VLBW
- Survival inversely related to number of comorbid conditions
Complications of Operative Procedure & Their Treatment

- Intestinal Strictures
  - Incidence: 9-36%
  - More common after nonoperative treatment
  - Due to fibrotic healing of ischemic injury
  - Most commonly occurs in colon (80%), then terminal ileum (15%)
    - Left colon – splenic flexure
    - Multiple strictures (15%)

- Intestinal Malabsorption and Short Bowel Syndrome
  - Decreased bowel length
  - Decreased absorptive area
  - Enzyme depletion
  - Gut hypermotility
  - Hypersecretion of gastric acid
  - Bacterial overgrowth
  - Decreased intestinal transit time
  - Vitamin B12 and bile acid deficiency
Complications of Operative Procedure & Their Treatment

- Cholestatic Liver Disease
  - Prolonged TPN administration
    - Direct hyperbilirubinemia, hepatomegaly, elevated aminotransferase
  - Prolonged fasting

- Recurrent Necrotizing Enterocolitis
  - 4-6%
  - SVT, percutaneous transluminal angioplasty, allergic enterocolitis associated

- Anastomotic Ulceration
  - Rare complication
Long-term Follow-up

- Neurodevelopmental Complications
  - Developmental screening every 4 months x 1 year, then every 6 months x 1 year
  - 50% of infants with NEC have neurodevelopmental complications
  - May not only be due to prematurity and comorbidities
Review Questions
Questions

A former 26 week 1200gm, now 5-week-old infant in the NICU develops increasing abdominal distention, gastric residuals and elevated WBC. What is your approach to developing a differential diagnosis? When do you consider operation? What diagnostic interventions can help with the decision to operate?
A former VLBW (1100 gm) newborn develops pneumoperitoneum at 4 weeks of life. What is your management approach?
A former ELBW (800 gm) newborn is found to have pneumoperitoneum that is believed to be secondary to NEC. The infant is being maintained on the jet ventilator and is requiring vasoactive medication to maintain adequate blood pressure. What is your management approach? What would your approach be if the ability to ventilate became acutely compromised?
A former 1100 gm newborn is taken to the OR for laparotomy secondary to perforated NEC. How do you explore the abdomen in a premature newborn? How would you manage the findings of numerous non-contiguous areas of gangrenous intestine? How would you manage the situation where almost all of the bowel is ischemic or necrotic?
A former VLBW infant is 4 weeks post operation for perforated NEC and has an ileostomy and a long Hartman’s pouch having approximately 60 cm of small bowel removed. The infant is being fed, yet is not gaining weight effectively. What are the possible contributing factors, and how would you manage the inability to gain weight? What would the refeeding options be if a mucous fistula had been performed? When would you consider closing the stoma, and what would be the considerations in terms of timing of ostomy closure? Would timing of ostomy closure be affected by whether a Hartmann’s pouch had been formed versus a mucous fistula?