Necrotizing Enterocolitis

R2 Peerawit Songsiri
History

1820s • France report “gangrenous necrosis” of intestine

1944 • Disease process in Switzerland

1960s • Disease process in New York

1970-2015 • Research and publications increased from 1-2 to 400 per year
Epidemiology

- Overall incidence 1 per 1000 live birth
- Mostly in premature (< GA 36 weeks) and LBW
  - 5-10% of newborn
  - 10-12% of VLBW (< 1500g)
  - 7-13% of full term (0.5 per 1000 live birth)
- Higher rate in urban area
- Typically present in first 2 weeks of life after onset of bacterial colonization
Epidemiology

**Mortality**

- Over all mortality 30%
- Lower age and younger GA $\rightarrow$ higher risk of death
- Babies that *need surgery* have higher rate of neuro development and intestinal failure
PATHOPHYSIOLOGY
Risk factor

- Prematurity
- Hypoxia
- Bacterial infection
- Congenital heart disease (ischemia) -> most significant
- Initiation of enteral nutrition
Pathophysiology

Immaturity of bowel
- Poor microcirculation
- Impaired integrity of the epithelial barrier
- Various immune deficiencies

Insult trigger
- Microbial dysbiosis
- Disturbed nutrient metabolism
- Genetic predisposition

Increased intestinal permeability
- Translocation of bacteria
- Necrosis and inflammatory state
Histologic findings

- Gross
  - Bowel distended with patchy or diffuse area of gray to dark discoloration
  - Hemorrhagic and friable surface on mucosa
Histologic findings

- **Histology**
  - Inflammatory changes
    - Bowel wall edema, submucosal gas, neutrophilic and lymphocytic infiltrati
  - Bacterial overgrowth
  - Coagulation necrosis

Figure 65.2 Dense lymphocytic infiltrate in the intestinal wall in NEC.
Intestinal barrier

1. Gastric acid

- Low pH is first defensive to pathogen
- Mature at 24 weeks of gestation
2. Intestinal motility and digestion

- Develops during 3rd trimester fully mature at 8th month gestation
- Immature motility -> expose noxious substance + poor clearance of bacteria -> ↓ nutrition digestion and absorption -> direct epithelial injury
- ↓ gastric and pancreatic exocrine function
- ↓ level of ileal bile acid binding protein -> ↑ ileal bile acid (cytotoxic) -> mucosal injury
  - Formula feeding -> more secretion of bile acid
Intestinal barrier

3. Mucous layer

- Goblet cell -> mucin
  - Lubrication
  - Mechanical barrier of bacterial approach and gastric acid
  - Assist fixation of pathogen
- Mature mucin
  - Higher viscosity, better pH buffering, resistance to bacterial breakdown

Deficiencies in production or composition of mucin -> NEC
Intestinal barrier

4. Tight junction

- Link mucosal poles of epithelial cell form “semipermeable” membrane
- Maturation during GA 26th wks and term
- Immaturity -> increased permeability -> pathogenesis of NEC

**Components**

- Occludins, Claudin proteins
- Junctional adhesion molecules
Immunologic defense of the gastrointestinal tract

1. Passive immunity
2. Innate and adaptive immunity
Immunologic defense of the gastrointestinal tract

Passive immunity

- IgG antibodies transfer via placenta is neonate’s first passive defense
- Antibody transfer start at 13 wks, majority at last 4 wks of gestation
  - Neonate born 22 wks have < 10% of maternal level
  - Term have 130%
- ** clinical trial to replace IGG and IGG orally have not altered risk of NEC
Immunologic defense of the gastrointestinal tract

- **Bioactive protein**
  - lactoferrin and lysozyme
- **Anti-inflammatory cytokines**
  - IL-10, TGF-beta
  - intestinal homeostasis, prevent enterocolitis, induce production of gut IgA
- **Growth factor**
  - EGF, IGF-1, IGF-2
  - Reduces apoptosis of epithelial cell and promote proliferation
  - Reduce NEC in animal model
Innate and adaptive immunity

**Innate immunity**
- Intraepithelial lymphocyte at bowel epithelial cell
- T-cell with alpha-gramma receptor
- Secrete epithelial growth factor and signaling molecule

**Natural Killer cell**
- Support intestinal barrier and suppress inflammation

**Neutrophil**
- Involved in both protective and harmful in NEC
- Phagocytosis and proinflammatory processes such as produce reactive oxygen species
- Release IL-22 -> proliferation of epithelial cell, regrowth of damaged intestinal tissue
Innate and adaptive immunity

Intestinal macrophage
- Present in bowel wall
- Tolerance of bacteria related to hyporesponsiveness to exotoxins including lipopolysaccharide (LPS)

Blood macrophage
- Response to injury and differentiate into activated M1 macrophages
- Elaborate variety of proinflammatory cytokines, and epithelial apoptosis

Dendritic cell
- Antigen presenting cell at gut wall
- In premature neonate contribute to pathologic inflammation
Molecular mechanism of inflammation and injury

1. Lipopolysaccharide
   - Endotoxin portion of gram neg bacterial cell wall
   - Most abundant proinflammatory stimuli
   - Impair intestinal barrier function
     - Inhibit repair
     - Promote signaling molecule and proinflammatory cytokines (NO, IFN-gamma, COX-2, Rho-A) -> intestinal injury
Molecular mechanism of inflammation and injury

2. Nitric oxide

<table>
<thead>
<tr>
<th>Level of NO</th>
<th>Function</th>
</tr>
</thead>
</table>
| Low level   | • Regulate vascular muscle tone  
              • Maintenance of mucosal capillaries  
              • Scavenging free radicle |
| High level  | • Enterocyte apoptosis  
              • Inhibit enterocyte proliferation and migration  
              • Impaired mitochondrial function  
              • ↓ leukocyte recruitment |
Molecular mechanism of inflammation and injury

3. Platelet-Activating factor

- Phospholipid inflammatory mediator produced by most of cell and tissue

Initiate of inflammatory cascade

- Produce oxygen-derived free radicals
- Leukocyte migration and activation
- Capillary leakage

Apoptosis in affected enterocyte
Molecular mechanism of inflammation and injury

3. Platelet-Activating factor

- PAF-degrading enzyme PAF acetyl hydrolase (PAF-AH) shown to be deficient in sick infants with NEC
- Administration of PAF-AH or PAF receptor antagonist reduces degree of intestinal injury
- PAF-AH present in maternal breast milk
| 4. Epidermal growth factor | Peptide secrete into intestinal lumen
|  | Key role in both development and maturation of gut tissue, intestinal repair and adaptation -> gut barrier healthy, prevent bacterial translocation
|  | Heparin binding EGF
|  | amniotic fluid and breast milk protective against development of NEC
|  | Improve microvascular blood flow
|  | In some studies, has been related to tumor |
Neonatal vasculature and the pathogenesis of NEC

- Newborn intestinal circulation is a low resting vascular resistance
- Controlled by
  - Extrinsically by autonomic nervous system
  - Intrinsic via local signaling pathway
    - Mediated by Endothelin (ET)-1: vasoconstrictor produced by endothelium
    - NO vasodilator produced by eNOS and iNOS
- Endothelial dysfunction -> ET-1 mediated vasoconstriction -> compromise blood flow -> intestinal ischemia and injury
Microbiome and NEC

• Secondary inflammation occur as a result of host-microbe interaction is a heart of NEC pathophysiology

• Microbiota of VLBW infants concluded relative
  • Higher level of Gram-negative facultative bacilli (Gammaproteobacteria)
  • Lower levels of strict anaerobic bacteria (Negativicutes)

• Assoc with exposure to antibiotic, H2 blocker
Clinical Diagnosis
Presentation

• Specific symptom present in 70%

1. Feeding intolerance
   • High gastric residual
   • Frank vomiting
   • Abdominal distension *** most common finding

2. Non specific sign: lethargy, temp instability, recurrent apnea, bradycardia, hypoglycemia, shock, gross or occult blood in stool

3. History of sudden increase ventilator requirement
Physical examination

- Abdominal distension
- Abdominal wall discoloration or erythema (suggest peritonitis)
- Bowel loops project through skin
- Palpable loops of bowel
- Peritonitis
- Fixed abdominal mass and erythema of abdominal wall *** strongly predict NEC (10%)
Plain abdominal radiograph

- **Pneumatosis intestinalis*** hallmark radiographic finding
- Early stage (Bell I)
  - Dilated loops of bowel
  - Paucity of bowel gas
- **Portal venous gas** → poor prognostic sign
- “**Fixed loop**” of bowel or dilated loops of intestine in same place from multiple plain film → nonfunctional segment necrosis should be concern
Plain flim

- **Pneumatosis intestinalis**
  - intramural gas
  - Air within bowel wall related to gas produced by enteric bacteria with failure or breakdown of mucosa barrier
• **Portal venous gas**
  - Air escapes into mesenteric veins or lymphatic
  - Appear on plain films as branching bands of air projecting over the liver
  - Assoc with pan-involvement and unfavorable outcome
Plain flim

- **Pneumoperitoneum**
  - Perforation with complete disruption of the intestinal wall with leakage of intraluminal gas
Ultrasonography

- Observation of
  - Bowel peristalsis
  - Wall thickening
  - Vascularity
  - Free fluid
  - Pneumoperitoneum
- More sensitive than plain film for diagnosis
Ultrasonography

• Useful in
  1. concern NEC without pneumatosis on plain film
  2. questionable plain film + well infant
  3. making decision to operate upon an infant with clear well-demonstrated pneumatosis, medical NEC with poor clinical course, equivocal set of lab
Other modalities

- **CT and contrast fluoroscopy**
  - No clear role in evaluating infant with acute NEC

- **Near-infrared spectroscopy (NIRS)**
  - Improve assessment of bowel perfusion neonate
  - Measure tissue hemoglobin oxygen saturation
  - NIRS + I-FABP in piglet -> identify NEC earlier than conventional test
Staging: Bell’s criteria

- Confirmation combines **signs and symptoms** + **radiologic finding**

### Table 33.1 Modified Bell Classification for NEC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Findings</th>
<th>Radiographic Findings</th>
<th>Gastrointestinal Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Apnea, bradycardia, and temperature instability</td>
<td>Normal gas pattern or mild ileus</td>
<td>Mild abdominal distention, stool occult blood, gastric residuals</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>Apnea, bradycardia, and temperature instability</td>
<td>Ileus with dilated bowel loops and focal pneumatosis</td>
<td>Moderate abdominal distention, hematochezia, absent bowel sounds</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>Metabolic acidosis and thrombocytopenia</td>
<td>Widespread pneumatosis, portal venous gas, ascites</td>
<td>Abdominal tenderness and edema</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>Mixed acidosis, coagulopathy, hypotension, oliguria</td>
<td>Moderate to severely dilated bowel loops, ascites, no free air</td>
<td>Abdominal wall edema, erythema, and induration</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>Shock, worsening vital signs and laboratory values</td>
<td>Pneumoperitoneum</td>
<td>Bowel perforation</td>
</tr>
</tbody>
</table>
Bell's classification

• Bell I
  • Sign and symptom are non specific
  • May reflect any septic illness in preterm, particularly VLBW infant
  • Many studies do not include Bell I as NEC
  • Bell I is essentially “NEC watch”

• Severity is highly variable

• Can effect both large bowel and small bowel or isolated

• Spectrum range from SIP to entire intestine (“NEC totalis”)
<table>
<thead>
<tr>
<th>Stage Classification</th>
<th>Systemic Signs</th>
<th>Abdominal Signs</th>
<th>Radiographic Signs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA suspected</td>
<td>Apnea</td>
<td>Mild abdominal distension</td>
<td>Normal</td>
<td>Bowel rest (NPO, OGT)</td>
</tr>
<tr>
<td></td>
<td>Bradycardia</td>
<td>Emesis or high gastric residuals</td>
<td>Nonspecific mild intestinal dilatation</td>
<td>Antibiotics × 3-5 days unless symptoms progress</td>
</tr>
<tr>
<td></td>
<td>Temperature instability</td>
<td>Fecal occult blood</td>
<td>Mild ileus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IB suspected</td>
<td>Same as IA</td>
<td>Same as IA + gross fecal blood</td>
<td>Same as IA + intestinal dilatation</td>
<td>Same as IA</td>
</tr>
<tr>
<td>IIA Definite</td>
<td>Same as IA</td>
<td>Same as IB + Absent bowel sounds +/- Abdominal tenderness</td>
<td>Same as IB + pneumatosis intestinalis</td>
<td>Bowel rest</td>
</tr>
<tr>
<td>Mildly III</td>
<td>Same as IA</td>
<td></td>
<td></td>
<td>Antibiotics × 7-10 days</td>
</tr>
<tr>
<td>IIB Definite</td>
<td>Same as IA + Mild metabolic acidosis</td>
<td>Same as IIA + Definite abdominal tenderness +/- Abdominal cellulitis or RLQ mass</td>
<td>Same as IIA + Portal venous gas +/- Ascites</td>
<td>Bowel rest</td>
</tr>
<tr>
<td>Moderately III</td>
<td>Mild thrombocytopenia</td>
<td></td>
<td></td>
<td>Antibiotics × 14 days</td>
</tr>
<tr>
<td>Stage Classification</td>
<td>Systemic Signs</td>
<td>Abdominal Signs</td>
<td>Radiographic Signs</td>
<td>Treatment</td>
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<td>--------------------------</td>
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<td>--------------------------------------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>IIIA Advanced</td>
<td>Same as IIB +</td>
<td>Same as IIB +</td>
<td>Same as IIB + Definite ascites</td>
<td>Bowel rest</td>
</tr>
<tr>
<td>Severe III Bowel intact</td>
<td>Severe apnea</td>
<td>Peritonitis</td>
<td></td>
<td>Antibiotics × 14 days</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>Marked abdominal tenderness and distension</td>
<td></td>
<td>Fluid resuscitation</td>
</tr>
<tr>
<td></td>
<td>Shock</td>
<td></td>
<td></td>
<td>Inotropic support</td>
</tr>
<tr>
<td></td>
<td>Respiratory acidosis</td>
<td></td>
<td></td>
<td>Ventilator support</td>
</tr>
<tr>
<td></td>
<td>Metabolic acidosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DIC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB Advanced</td>
<td>Same as IIIA</td>
<td>Same as IIIA</td>
<td>Same as IIIA + Pneumoperitoneum</td>
<td>Same as IIIA + Surgery</td>
</tr>
<tr>
<td>Severe III Bowel perforated</td>
<td>Same as IIIB</td>
<td>Same as IIIA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NPO, nil per os; OGT, orogastric tube; RLQ, right lower quadrant; DIC, disseminated intravascular coagulopathy.
Laboratory studies

- Not use to prove NEC
- CBC
  - leukocytosis with bandemia or leukopenia,
  - thrombocytopenia -> poor prognosis
- E’lyte, Blood gas: metabolic acidosis, hypercapnea
- Increase C-reactive protein, IL-6, IL-10
- Fecal calprotectin
  - Marker of intestinal inflammation
  - Assoc with system illness (Bell III), and perforation (sensitivity 76%, specificity 92%)
Laboratory studies

• I-FABP
  • Located in enterocyte in small bowel villi
  • Cell lysis -> protein is release into blood -> cleared in the urine

• One study found panel of 7 urinary protein that can identify patient who later developed surgical NEC
Differential diagnosis
Other modalities

- Septic ileus
  - Clinical + film are common except pneumatosis intestinalis
- Bacterial or viral enterocolitis
- Other causes of bowel obstruction
  - Hirschsprung disease
  - Ileal atresia
  - Volvulus
  - Meconium ileus
  - Intussusception
Spontaneous intestinal perforation

- Either variant of NEC or distinct clinical entity present in premature neonate as pneumoperitoneum
- Defined by small “punched out” hole in the intestinal wall without surrounding necrosis (usually at distal ileum)
- No bowel injury beyond focal area of perforation
- Presentation
  - VLBW, and early postnatal steroid (< 26 weeks gestation)
  - Present in 1st week of life
  - Assoc with indomethacin, and steroid
Spontaneous intestinal perforation

- **Diagnosis**
  - Finding of pneumoperitoneum
  - Not associated with bowel injury beyond focal perforated area

- **Management**
  - Some surgeon treat with peritoneal drain over laparotomy
Management
Medical management

• Primary management of medical NEC is supportive
  • Bowel rest
  • Gastric decompression
  • IV fluid resuscitation
  • TPN
  • Broad-spectrum ATB covered anaerobic and gram-negative
  • Cardiopulmonary support if necessary
  • Blood transfusion in thrombocytopenia or coagulopathy
Surgical management

- Clinical factors alone couldn’t predict which infant need surgical therapy
- 50% of patient develop NEC end up with surgical intervention

**Absolute indication**
- “pneumoperitoneum” on abdominal radiograph
- Paracentesis with positive for enteric content

**Relative indication**
- Failure to respond to optimal medical therapy
- “fixed loop” of bowel on serial radiograph
- Portal venous gas
# Surgical management

## Table 46-2: Indications for Surgery

<table>
<thead>
<tr>
<th>Type</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute</td>
<td>Intestinal perforation (pneumoperitoneum)</td>
</tr>
<tr>
<td>Relative</td>
<td>Fixed intestinal loop on serial plain abdominal radiographs</td>
</tr>
<tr>
<td></td>
<td>Abdominal wall erythema</td>
</tr>
<tr>
<td></td>
<td>Portal venous gas on plain abdominal radiograph</td>
</tr>
<tr>
<td></td>
<td>Palpable abdominal mass</td>
</tr>
<tr>
<td></td>
<td>Positive paracentesis*</td>
</tr>
<tr>
<td></td>
<td>Failure of maximal medical therapy</td>
</tr>
<tr>
<td></td>
<td>- Increasing respiratory support</td>
</tr>
<tr>
<td></td>
<td>- Increasing third-space fluid losses</td>
</tr>
<tr>
<td></td>
<td>- Persistent acidosis and thrombocytopenia</td>
</tr>
</tbody>
</table>

*Positive paracentesis: at least 0.5 cc of free-flowing fluid that is brown or yellow-brown in color and/or has bacteria seen on Gram stain. Negative paracentesis: clear ascitic fluid and no organisms on Gram stain.
Surgical management

• Some studies evaluated markers for intestinal necrosis
  • Severe thrombocytopenia

Currently practice is highly personal based on overall assessment by surgeon
Surgical management

- **Tepas and colleagues** identified 7 clinical and laboratory findings:
  - Positive blood culture
  - pH < 7.25
  - Bandemia with I/T > 0.2
  - Sodium < 130
  - Platelets < 50,000
  - MAP < gestational age or on vasopressor
  - ANC < 2000

3 out of 7 is a relative surgical indication.
Surgical management

Surgical intervention algorithm

Indication for surgical intervention

Weight <1500 g
- Unstable
  - Peritoneal drainage
  - Resuscitation
- Stable

Weight >1500 g
- Stable
  - Laparotomy

Resuscitation

Laparotomy
Operative approach

2 principle
1. Remove gangrenous or perforated bowel
2. Preserve bowel length to minimizing short bowel

• Exploratory laparotomy with choice
  • Laparotomy with resection of necrotic bowel and creation of stomas
  • Proximal enterostomy
  • “patch, drain, and wait” (PD&W)
  • “clip and drop back”
  • Resection with primary anastomosis
Primary peritoneal drainage

- Introduced by Ein et al in 1977
- Placing intraperitoneal drain
- Developed as a temporizing measure in premature neonates intended as a bridge to laparotomy
- PPD only for VLBW infants with hemodynamically unstable to tolerate laparotomy
Peritoneal drainage technique

- Local anesthesia is injected
- Small incision made at left lower quadrant away from liver
- Open peritoneum sharply
- Half-inches penrose is placed along anterior abdominal wall from left to epigastrium
- Drain is sutured to the skin
Classification extent of disease

1. Focal
2. Multifocal (>50% viable)
3. Pan-intestinal/NEC totalis (<25% viable)
1. Focal disease

Single segment is gangrenous or perforated

Limited resection of this required

- Mesenteric vessel are sequentially ligated on mesenteric side
- Rapid resection can be performed, ileocecal valve should be preserved
Focal disease

- Creation of proximal enterostomy with or without distal mucous fistula
- Short segment of terminal ileum remain (<2cm)
  - Ligated and left in abdominal cavity as “Hartmann pouch”
- Decompress bowel before create stoma
Focal disease
Multifocal disease (>50% viable)

- Diffuse or patchy intestinal involvement
  - Large resection $\rightarrow$ short bowel syndrome
  - Failure to resect $\rightarrow$ worsen illness or recurrent perforation
Multifocal disease (>50% viable)

Historically, multiple resection with multiple stoma → High morbidity and mortality rate

Single proximal enterostomy, distal bowel resected and reconnect with multiple primary anastomosis →
- Significant fluid and electrolyte loss
- Skin complication
Multifocal disease (>50% viable)

- **Penrose drain and wait (Moore 1989)** “resect no gut and do no enterostomies”
  1. Irrigate abdominal cavity
  2. Transverse single-layer suture approximations of perforations (patch)
  3. Insert 2 penrose drain placed from diaphragmatic edge to lower abdomen with loop in pelvis exit in the lower quadrant (drain)
  4. Gastrostomy
  5. Long term parenteral nutrition (wait 2 weeks - 2 months for second operation)
Penrose drain and wait

- Allow evacuation of fecal soilage and function as enterostomies

- Necrotic bowel is not resected → does not control sepsis
- *** May be alternative approach but future studies are needed
Multifocal disease (>50% viable)

- Clip and drop-back (Vaughan)
  - Area of obviously necrotic intestine are resected
  - Cut ends are closed with either titanium clips or stapled
  - No enterostomy or primary repairs are performed
  - Re-exploration in 48-72 hrs later
  - Remove clips and reanastomose bowel without stoma creation
Clip and drop-back
FIGURE 46-4 The algorithm outlining available surgical techniques for the treatment of NEC depending on the extent of disease.
Panintestinal disease/NEC totalis (< 25% viable)

Resect all necrotic intestine and place multiple stoma or single proximal stoma

Not recommend at initial exploration

Initial PD or silo placement -> re-exploration after resuscitation

Proximal diversion without resection of intestine -> second-look laparotomy
Panintestinal disease/NEC totalis (< 25% viable)

- Almost all of the few survivors with NEC totalis are left with short bowel syndrome
- Mortality rate 100%
- Surgeon may decide with family that treatment is futile
- Natural death allowed with family bedside
• 2001, RCT 117 infant GA < 34 wks, BW <1,500 g c perforated NEC
• 55 PPD vs 62 laparotomy
• Mortality 90 days after operation was not significantly different between 2 group
• No significant differences in the rates of dependence on parenteral nutrition 90 days after surgery or in the mean duration of hospital stay
Primary peritoneal drainage

• In nonrandomized arm in the same study
  • Mortality rate was 15% in laparotomy vs 41% in PD

Experienced clinical judgement and careful selection can achieve better outcome
• 2006, A prospective, cohort study in 16 clinical centers
• 156 NEC from 2987 ELBW patient (96 preop diagnosis, 60 presumed)
• 76 laparotomy vs 80 PPD
• Overall outcome was poor
  • 50% of patient died, 72% died or neurological impair at 18-22 months
  • Survival to discharge was higher in the laparotomy vs PD (57% vs 46%)
  • Survival without NDI at 18-22 month was higher in laparotomy (62% vs 37%)
  • Unadjusted odds ratios (ORs) for adverse outcomes in laparotomy group to PD were all less than 0.1
Important advantage of laparotomy over PPF
Still need RCT to evaluate relative effectiveness
Peritoneal Drainage or Laparotomy for Neonatal Bowel Perforation?

A Randomized Controlled Trial

Clare M. Rees, MB, ChB, MRCS,* Simon Eaton, PhD,*
Edward M. Kiely, FRCSI, FRCS, FRCPCH(Hon),* Angie M. Wade, PhD, CStat,†
Kieran McHugh, FRCR,‡ and Agostino Pierro, MD, FRCS(Engl), FRCS(Edin), FAAP(Hon)*

- 2008, RCT
- 69 patient with BW < 1000 + pneumoperitoneum
- 35 PPD vs 34 laparotomy
- 26/35 (74%) of PPD require laparotomy
- No significances differences in mortality or secondary outcome

PPD is not a safe alternative to laparotomy
<table>
<thead>
<tr>
<th></th>
<th>NET Trial (Europe)</th>
<th>NECSTEPS (North America)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>69</td>
<td>117</td>
</tr>
<tr>
<td>Centers represented</td>
<td>18 centers in 8 countries</td>
<td>15 centers in USA and Canada</td>
</tr>
<tr>
<td>Birth weight criteria</td>
<td>&lt;1000 g</td>
<td>&lt;1500 g</td>
</tr>
<tr>
<td>Gestational age criteria</td>
<td>None</td>
<td>&lt;34 weeks</td>
</tr>
<tr>
<td>Confirmation of intestinal perforation</td>
<td>Radiologic evidence of pneumoperitoneum required</td>
<td>Radiologic evidence of pneumoperitoneum, paracentesis results, or clinical decision accepted</td>
</tr>
<tr>
<td>Randomization</td>
<td>Assigned by weighted minimization techniques accounting for weight at enrollment, gestational age, platelet count, mechanical ventilation, inotropic support, facilities for onsite laparotomy, and geographic location</td>
<td>Permuted blocks of four and stratified by birth weight (&lt;1000 g vs 1000–1500 g)</td>
</tr>
<tr>
<td>Primary peritoneal drainage instruction</td>
<td>One-fourth inch soft drain inserted in the right or left lower quadrant and irrigations via the drain were not recommended</td>
<td>One-fourth inch, right lower quadrant incision with manual expression of stool and pus and irrigation until clear followed by Penrose drain placement. Additional drain placement as per operating surgeon</td>
</tr>
<tr>
<td>Postoperative care</td>
<td>Per operating surgeon and treating neonatologists Mortality at 1 and 6 months Total hospital length of stay, ventilator dependence, dependence on parenteral nutrition and time to full enteral feeding</td>
<td>Uniform care pathway Mortality at 90 days Parenteral nutrition dependence at 90 days and length of stay for patients surviving 90 days postoperatively</td>
</tr>
</tbody>
</table>

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### PPD VS laparotomy

<table>
<thead>
<tr>
<th>NET</th>
<th>NECSTEPS</th>
</tr>
</thead>
</table>
| - Better survival in the laparotomy group (65%) compared with PPD (51%)  
- Non significant relative risk mortality 0.5  
- No evidence to support use of PPD in ELBW infants with intestinal perforation | - No different in mortality at 90 days  
- Length of stay was similar between group  
- The choice of surgical intervention does not affect mortality |

No evidence from trial to support the use of PPD in ELBW infants with intestinal perforation
PPD vs laparotomy

• In United States
  • > 2/3 of VLBW with surgical NEC undergo laparotomy first
  • Nearly half of patient who underwent PPD first → laparotomy
Postoperative management
Resuscitation

- Initially aimed at maintaining hemodynamic status and support respiratory function

- Significant third space loss
- Coagulopathy
- Thrombocytopenia and anemia

- Aggressive fluid resuscitation and judicious use of dopamine
- Blood product
- OGT with low suction
• Consensus guidelines state that infant should continue to receive parenteral antibiotics for at least 7 to 10 days
• Longer duration if blood culture positive
Feeding

- Total parenteral nutrition (TPN)
  - Should started postoperatively

- Enteral feeding
  - Held until return of bowel function
  - Start at trophic rate and slowly increased to the desired goal
Ostomy management and restoration of intestinal continuity

- Delay bag placement up to 72 hrs to avoid rough handling of the wound
- Jejunal and more proximal ileal ostomies present with high output -> dehydration and electrolyte imbalance

**Timing of closure**
- 1-4 month after stoma creation
- Most suggest wait 6-8 weeks or until weight > 2000g
- Performed contrast before take down
Outcomes
Recurrence

- Varies but may be high as 10%
- Second episode more likely in lower birth weight infants, persistent cardiac issues, other congenital anomalies
- > 80% of recurrence require operation
- Mortality and stricture rate similar to single episode
Mortality

- Range of 30%
- Risk factor is prematurity, congenital heart disease, degree of bowel involvement
- Mortality is inversely proportional to BW and GA
- Medical NEC 20%, surgical NEC 35–50%
Intestinal failure

Definition

- Inadequate functional bowel to satisfy nutrient and fluid homeostasis via digestion and absorption
- Requirement of PN for > 90 days

- > 1/3 of intestinal failure are NEC
- Majority of infants have short bowel syndrome
- 42% of surgical and 2% of medical NEC -> IF
Intestinal failure

**Risk factor**

- Parenteral antibiotics on the of diagnosis
- Birth weight < 750 g
- Mechanical ventilation
- Exposure to enteral feed prior to diagnosis
- Remaining length
Intestinal failure

**Risk factor**

**length**
- 50% with length > 35 cm of bowel will wean from PN
- Still < 10 cm of bowel -> can survive with long-term PN or intestinal transplant

**Location of resected bowel**
- Mortality in small bowel resection is higher than colonic NEC
- Jejunal resection appear better than ileal resection

NEC are more likely to wean PN earlier than other IF causes
Stoma complication

- Most serious complication include prolapse, stricture, retraction
- Proximal jejunostomy
  - Electrolyte and water losses -> fluid imbalance, weight gain, skin breakdown
Intestinal stricture

- Occur in 12-35%
- Primary anastomosis does not increase stricture rate
- Most common site is colon esp. descending colon
- Management
  - Laparotomy with resection and re-anastomosis
  - Balloon dilatation in selected cases
  - Spontaneous resolution also reported
Intestinal stricture

• For surgical patient, should undergo routine imaging for distal intestine before closure
• However, medical or PPD can developed stricture
• Presentation
  • Asymptomatic -> partial or intermittent bowel obstruction

Some surgeon prefer contrast studies in all NEC prior to feeding
Neurodevelopmental outcomes

- ELBW neonates with NEC is an independent risk factor for NDI
- Surgical NEC survivors were high risk of NDI

Risk of surgical treatment was twice than medical
Neurodevelopmental outcomes

- Underlying reason for high rate NDI in surgical NEC still unclear

- Systemic illness + hemodynamic instability
- Release cytokines (TNF-α, IL-6, PAF)
- Assoc with white matter injury
Neurodevelopmental outcomes

• Mode of surgery PPD VS laparotomy
• A multicenter prospective cohort studies 2006
  • Infant undergoing laparotomy may have lower risk of NDI at 18 months than PPD
Prevention
Probiotic

- Supplement or medication contain live organism aimed to improving health by change or control the composition of intestinal microbiome.
- Most commonly delivered species:
  - Lactobacillus
  - Bifidobacterium
  - Streptococcus
  - Escherichia
  - Enterococcus
  - Bacillus
  - Saccharomyces
Probiotic

• Healthy breast-fed infants have intestinal flora that different from neonatal ICU (exposed to ATB)

- Prolong absence enteral feeding
- Hospital environment
- Gastric acid blockade

- Increase gram-negative Proteobacteria and gram positive Firmicutes

- Sepsis
Probiotic

- Many studies report that probiotic reduce NEC and mortality
- Probiotic organism also shown in placebo or control group -> protective effect are greater than they appear in quoted trial
- Bifidobacteria and lactobacilli -> produce bactriocins and secrete anti-inflammatory factor -> inhibit growth of harmful bacteria
- Current product: Florababy, Infloran, NatrenLife Start powder, Biogaia Protectis
Human milk

- Provides a variety factor that support passive immunity (IgA) and help to mature infant’s adaptive immunity

**Mechanism**
- Lowering gastric pH → prevent colonization of pathologic bacteria
- Decreasing intestinal permeability
- Providing beneficial intestinal flora and oligosaccharides
- Better tolerated than formula in premature neonate

**Protective effect is dose dependent**
- Threshold of 50% of total calories to provide optimal protection
- 2–4 wks of life is critical time period that most helpful
Human milk

• Donor human milk (DHM)
  • Is pasteurized -> destruction IgA, growth factor, protective bacteria, lactoferrin, lipase
  • Decrease lipase -> less stimulation of bile salt -> decrease fat absorption
  • Assoc with neonatal growth
  • DHM and formula milk no different in rate of sepsis/NEC
Feeding strategies

• **Timing of initiation and trophic feed**
  • Optimal volume and postnatal age to start enteral feed in premature remain controversial
  • Early feeding does not seem to increase incidence of NEC
  • If use maternal milk, appear to be protective
Feeding strategies

• Cohort study compared VLBW fed within 48 hrs and after 72 hrs

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<tr>
<th>Feed within 48 hrs</th>
<th>Feed after 72 hrs</th>
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<tr>
<td>- Start feed 1-2 ml/kg q 4-6 hr advanced 1-2 ml/kg/day</td>
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<td>- Decreased duration of PN, time to weight gain and shorter LOS</td>
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• One study show that trophic feeding VS fasting less likely to acquired bacterial sepsis
• Insufficient evidence support trophic feeding over fasting to prevent NEC
Feeding strategies

- Feeding Advancement

One RCT
- Higher incidence of NEC in group that feed rapidly advance

Cochrane review
- Slow (15-20 ml/kg/day) VS Fast (30-35 ml/kg/day)
- No significant in risk NEC or death
Amino acid supplement

- Cochrance review: both arginine and glutamine demonstrated no significant benefit
Antibiotic prophylaxis

- Significant NEC risk reduction,
- Considered with safety of widespread use of antibiotic and the risk of bacterial resistance
Lactoferrin

- Glycoprotein found in high concentrations in colostrum
- Broad-spectrum antimicrobial activity via sequestration of iron and/or microbial cell membrane lysis
- Effect greatest if start in first 3 days of life with optimal duration 28-45 days
- RCT found that
  - Lactoferrin reduced risk of NEC with RR 0.3