Neonatal bowel injury: Diverting energy to avoid a nutritional crisis
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Types of Bowel Injury
- Gastroesophageal reflux disease (GERD)
- Gastritis
- Gastroenteritis
- Spontaneous intestinal perforation
- Necrotizing enterocolitis
- Allergic Colitis

The Developing Gut
- Cytodifferentiation
- Morphogenesis
- Digestion
- Absorption
- Swallowing
- Viability Line

Preterm Risk Factors for Bowel Injury
- Ischemia
- Immature gut and systemic immune system
- Dysmotility
- Underdeveloped physical mucosal barrier (tight junctions, mucus)
- Poor acid production
- Abnormal bacterial colonization

Pathogenesis of NEC
- Immaturity
- Ischemia
- Enteral Feeding
- Infectious organism
- Mucosal disruption
- Mucosal damage
- Bacterial translocation
- Macromolecular absorption
- Necrotizing enterocolitis
Onset of NEC is inversely correlated with gestational age

Statistics of NEC
- 1–3 per 1000 live births
- 2–5% of neonatal intensive care unit (NICU) admissions
- Occurs in 7% of infants born under 1500 g
- Occurs in 10% of infants born under 1000 g

Surgery
- 30-50% require surgery
- Case fatality rate with surgical intervention as high as 50%

Complications of NEC
- Ischemic stricture formation (25-35%)
- Short bowel syndrome (cholestasis, sepsis)
- Wound infection, dehiscence, abscess formation, enterocutaneous fistula, enterocysts
- Stoma-retraction, prolapse, peristomal hernia
- Occasional recurrence of the disease due to ischemia
- Mortality has been reported to range from 9% to 28% that has not appreciably changed
- Independent risk factor for long-term neurodevelopmental impairment

Economic costs of NEC
- Costs to health care system
  - $5 billion annually (assume 10% incidence of NEC and 30% mortality)
  - Constitutes 19% of the total costs for initial care for all newborns in the US
  - Increased length of stay, hospital costs
- Medical NEC (22 days)- US $73,700 (1992-94)
- Surgical NEC (2 months)- US $186,200
- US $ 7.2 million/year on unit and US $238,333 per survivor (not including doctor’s fee + TPN + antibiotics)

Clinical Features
- Systemic signs
  - Non specific signs similar to sepsis e.g lethargy, temp. instability
  - Apnea and Brady’s

- Gastrointestinal Signs
  - Abdominal distension 70 to 98%
  - Feeding intolerance>70%
  - Emesis >70%
  - Gross blood per rectum 25 to 63%
  - Occl G I bleeding 22 to 59%
  - Occasional diarrhea 4% to 26%

Clinical Features
- Variable
- Common findings- abdominal distension, feed intolerance, blood in stool, shock/ sepsis, DIC
- Bells staging
  - Stage I suspect NEC
  - Stage II, definite NEC, (pneumatosis)
  - Stage III, advanced NEC ± perforation
### Modified Bell's Staging for NEC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Systemic signs</th>
<th>Abdominal signs</th>
<th>Radiographic signs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Suspected</td>
<td>Temperature instability, apnea, bradycardia, lethargy</td>
<td>Gastric retention, abdominal distention, emesis, heme-positive stool</td>
<td>NPO, antibiotics x 3 days</td>
</tr>
<tr>
<td>IB</td>
<td>Same as IA</td>
<td>Same as IA</td>
<td>Same as IA</td>
<td>Same as IA</td>
</tr>
<tr>
<td>IIA</td>
<td>Definite, mildly ill</td>
<td>Same as IA</td>
<td>Same as IA, plus absent bowel sounds</td>
<td>NPO, antibiotics x 7-10 days</td>
</tr>
<tr>
<td>IIB</td>
<td>Definite, moderately ill</td>
<td>Same as IIA</td>
<td>Same as IIA, plus mild metabolic acidosis and thrombocytopenia</td>
<td>NPO, antibiotics x 14 days</td>
</tr>
<tr>
<td>IIIA</td>
<td>Advanced, severely ill, intact bowel</td>
<td>Same as IIIA</td>
<td>Same as IIIA, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, DIC, and neutropenia</td>
<td>NPO, antibiotics x 14 days, fluid resuscitation, inotropic support, ventilator therapy, paracentesis</td>
</tr>
<tr>
<td>IIIB</td>
<td>Advanced, severely ill, perforated bowel</td>
<td>Same as IIIA</td>
<td>Same as IIIA, plus pneumoperitoneum</td>
<td>NPO, antibiotics x 14 days, surgery</td>
</tr>
</tbody>
</table>

### Necrotizing enterocolitis versus spontaneous intestinal perforation (SIP)

<table>
<thead>
<tr>
<th>NEC</th>
<th>SIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Prematurity</td>
<td>- Extreme prematurity</td>
</tr>
<tr>
<td>- Ischemia</td>
<td>- Ischemia</td>
</tr>
<tr>
<td>- Inflammation</td>
<td>- No inflammation</td>
</tr>
<tr>
<td>- Feeding</td>
<td>- No feeding relationship</td>
</tr>
<tr>
<td>- Bowel dysmotility</td>
<td>- Bowel dysmotility</td>
</tr>
<tr>
<td>- Antenatal corticosteroids are protective</td>
<td>- Corticosteroids</td>
</tr>
<tr>
<td>- PDA (??)</td>
<td>- PDA</td>
</tr>
<tr>
<td>- COX inhibitors (??)</td>
<td>- COX inhibitors</td>
</tr>
</tbody>
</table>

### Risk Factors for SIP
- Extreme prematurity (<1000 grams)
- Early hydrocortisone use day 0-3
- PDA
- Early indomethacin use
- More surfactant use ??
- Outborn birth status (risk of transport)
- Less antenatal steroid use
- More pressor use

### What is Short Bowel Syndrome?
- Leading cause of prolonged parenteral nutrition administration in children
- Leading cause of intestinal failure

### Intestinal Failure
- Reduced absorption of nutrients from the gastrointestinal tract resulting in the need for parenteral nutrition for survival

### How do we define Short Bowel Syndrome?
- **Malabsorption** resulting from anatomical or functional loss of a significant length of the small intestine
  - Anatomic
    - a residual jejunoileal segment of <75 cm secondary to a surgical resection or congenital malformation
  - residual bowel that is 25% of predicted length for gestational age
  - Functional
    - PN dependency
    - >6 weeks (42 days)

### Costs of bowel injury in neonates
- One case of NEC is estimated to cost $70,000 for medical NEC and $200,000 for surgical NEC
- One case of Short Bowel Syndrome (SBS) is estimated to cost $125,040

*Costs calculated from Health Records Resource Intensity Weight (RIW)
**These are conservative estimates

**Short Bowel Syndrome**

**Etiology**

**Newborn**
- Necrotizing enterocolitis
- Gastrochisis
- Intestinal atresia
- Volvulus
- Congenital short bowel

**Adult**
- Crohn’s disease
- Neoplasia
- Trauma
- Radiation enteritis
- Mesenteric infarction

**Who gets intestinal failure?**

- Short bowel syndrome (n = 48)
- Disorders of motility (n = 16)
- Structural enterocyte defects (n = 14)
- Multiple food intolerance (n = 10)
- Autoimmune enteropathy (n = 7)
- Others or unknown (n = 14)

**Intestinal failure**

Reduced absorption of nutrients from the gastrointestinal tract resulting in the need for parenteral nutrition for survival.


**Intestinal failure results in a heavy morbidity and mortality burden**

**Anatomic Risk Factors**

- **DUODENUM**
  - iron and folate absorption
  - limited absorptive capacity
  - high output intestinal losses
- **JEJUNUM**
  - bile acid, B12 deficiency, ileal brake
- **ILEUM**
  - magnesium absorption
  - water reabsorption
  - GLP2 production

**Common anatomy**

- with colon, TPN dependency likely if <50cm small bowel left
- absorbers vs. secretors
- in jejunostomy
- >200cm…fine
- 100-200…oral supplements
- 0-100cm…parenteral needs

**Intestinal length**

- mean length of bowel 240cm at birth
- adult intestinal length varies from 300 – 850cm
- doubling of intestinal length from 27 weeks to term
- greatest period of gut growth during third trimester
- Does gut grow post resection?
Adaptation

- within 24-48 hrs, remaining small bowel undergoes epithelial hyperplasia
- villi lengthening, increases surface area, increased digestive and absorptive function
- gross dilatation, lengthening, thickening of bowel
- mucosal hyperplasia does not occur in the absence of enteral nutrition
- limit of intestinal adaptation ~36-48 mo

<table>
<thead>
<tr>
<th>_FUNCTIONS</th>
<th>JEJUNUM</th>
<th>ILEUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrient absorption capacity</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Fluid and electrolyte absorption</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Cell-to-cell junction/paracellular water and solute movement</td>
<td>leaky</td>
<td>tight</td>
</tr>
<tr>
<td>Adaptive potential</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Specialized function</td>
<td>B12, active bile salt uptake, ileal brake</td>
<td></td>
</tr>
</tbody>
</table>

The Leaking Gut

- **JEJUNUM**
  - Lumen: Na, H2O
  - Paracellular water and solute movement

- **ILEUM**
  - Lumen: Na, H2O
  - Tight junctions restrict water and solute loss

Optimal nutritional management is the cornerstone of intestinal rehabilitation

What stimulates the gut to adapt?

- enteral nutrients
  - long chain fatty acids
  - free fatty acids
  - disaccharides
  - complex proteins (polypeptides)
  - "enteral load"
- pancreaticobiliary secretions
- growth factors (GH, GLP2, IGF1, KGF, EGF)
- prostaglandins
- polyamines (spermine, spermidine, putrescine)

SBS: Management

- Water and mineral losses
  - Supplementation
  - Octreotide
  - Acid blockade
- Small bowel bacterial overgrowth
  - Selective bacterial decontamination
  - Pre/probiotics
- Line complications
  - Antibiotic/heparin impregnated catheters
- TPN associated cholestasis
  - Cycling TPN
  - Ursodiol
  - Cholecystokinin
  - Cholangial irrigation
  - Reduction of Mn, Cu
  - Modified intravenous lipids
  - Reduced methionine
  - Corticosteroids
  - S-adenosymethionine
“The process of intestinal rehabilitation is almost exclusively luminal nutrient-dependent, and the use of enteral substrate is required to stimulate its completion.”

Proteins
• polypeptides > amino acids for stimulating gut adaptation
• usually well absorbed in SBS
• predominant absorption is that of di- and tri-peptides

Carbohydrates
• Complex carbohydrates reduce the osmotic load and potentially exert a positive effect on the adaptation process
• Proximal jejunum usually not resected and retains lactose digestive abilities
• Concentrated sugars, such as fruit juices, should be avoided as they increase osmotic load and watery output

Fat
• most calorie dense
• overall, least contributor to osmotic load in colon
• LCT and free fatty acids best stimulants for gut adaptation
• LCT absorption compromised in face of reduced biliary excretion

Role of the colon
1. Resorption of water
2. Resorption of minerals (Mg)
3. Nutrient uptake
   1. Amino acids?
   2. Glucose
   3. Prebiotics
   4. Fatty acids
4. Bacterial fermentation
   1. Postbiotics
   2. Energy contribution
   3. Immune tolerance

Fat
• MCT oil do not require pancreatic enzymes for their absorption
• a diet enriched in MCT resulted in improved overall energy and fat absorption in the patients with a colon
• in those without a colon, there was no improvement in overall energy absorption because of concurrent decrease in carbohydrate and protein
Colonic energy salvage

The colon accounts for 20-30% of the total energy intake. Bacterial fermentation results in the generation of new substrates that positively act on the bowel.

Growth factors

GH (growth hormone)
- has been shown to improve fluid and electrolyte, nutrient transport in the human GI tract
- increased
  - energy absorption
  - micronutrient absorption
  - weight
  - lean body mass
  - D-xylose absorption
- plasma citrulline (enterocyte biomarker) NOT increased
- enhanced functional adaptation at the enterocyte level
- BUT effects seen are transient and disappear once drug is removed

Growth factors

- GLP2 (glucagon like peptide 2) [teduglutide-GLP2 analogue]
- open label trial suggests a benefit to patients with SBS
- increase in overall energy absorption
- decrease in fecal wet weight
- slowing of gastric emptying
- nonsignificant increase in villus height and depth

Octreotide

- somatostatin analogue
- reduces a variety of gastrointestinal secretions (anti-secretogogue)
- not been shown to lead to the removal of PN
- increased risk of cholelithiasis
- expensive
- animal models suggest it may inhibit bowel adaptation
- reserved for patients with large volume stool losses in whom fluid and electrolyte management is problematic

SBBO (small bowel bacterial overgrowth)

- No controlled studies
- Use of antisecretory and antimotility drugs
- Carbohydrate restriction
- Intermittent flushing with PEG
- Use of prokinetic agents
- Pre/probiotic agents
- Bowel tapering / enteroplasty

Complications of SBS

- TPN associated cholestasis
- Sepsis
- Thrombosis
TPN associated cholestasis

- Cholestasis: impairment of bile formation and flow
- Serum BR > 34 umol/L
- Active transport of solute across the canalicular membrane is the rate limiting step in bile formation

Pathogenic factors

- Lack of GI stimuli for biliary secretion
- Lack of GI stimuli for gallbladder motility
- Abnormalities in bile acid metabolism (particularly deoxycholate and lithocholate)
- Concomitant sepsis (release of cholestatic endotoxins)
- Toxicity of individual components in TPN formula

Pathogenesis of TPNAC

Fish based oil (omega-3 FA)

- Omega-3 fatty acid emulsions
- High in omega-3 fatty acids
  - eicosapentaenoic and docosahexaenoic acids
  - Contain sufficient amount of essential fatty acids.
- May have a protective effect on the liver
- Thought to inhibit de novo lipogenesis, and reduction of inflammatory mediators.

I.V. LIPID PREPARATIONS

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Comparison of Parenteral Fat Emulsions (10 g Fat/100 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product</td>
<td>Arimistad (Baxter HealthCare/Wyeth)</td>
</tr>
<tr>
<td>Oil source, g</td>
<td></td>
</tr>
<tr>
<td>Soybean</td>
<td>10</td>
</tr>
<tr>
<td>Sunflower</td>
<td>0</td>
</tr>
<tr>
<td>Fish</td>
<td>0</td>
</tr>
<tr>
<td>Fat composition, %</td>
<td></td>
</tr>
<tr>
<td>Linoleic</td>
<td>50</td>
</tr>
<tr>
<td>arachidonic</td>
<td>9</td>
</tr>
<tr>
<td>EPA</td>
<td>0</td>
</tr>
<tr>
<td>DHA</td>
<td>0</td>
</tr>
<tr>
<td>Oleic</td>
<td>26</td>
</tr>
<tr>
<td>Palmitic</td>
<td>10</td>
</tr>
<tr>
<td>Stearic</td>
<td>3.5</td>
</tr>
</tbody>
</table>

EPA indicates eicosapentaenoic acid, DHA, docosahexaenoic acid.

1 g kg/day versus 2 g kg/day

Treating Cholestasis with Fat

Summary of Omegaven®

- Omegaven® has the ability to restore liver function in SBS patients with advanced liver disease
- Has the potential to fundamentally change the management of children with SBS liver disease as it should provide time for ongoing gut adaptation allowing for increased rates of successful enteral adaptation, and in patients with no adaptive potential permit survival until an intestinal transplant is possible
Omegaven drug accessibility

BUT...
- NOT FDA approved
- Requires IND application for compassionate use of drug
- May not see light of day in US

Enteral Fish Oil (FO)

- Rationale
  - Anti-inflammatory effects of FO
  - Better balance of Omega-3:Omega-6 ratio

French Experience

Reduction of lipids to reduce PNALD
- 10 children on long-term PN
- 24 'episodes of cholestasis'
- 17 of 24 resolved with decreasing or discontinuing lipid

Bowel nomenclature

- Jejunum (J)
- Ileum (IL)
- Ileocecal valve (ICV)
- Colon (COL)
- Stoma (@)
- Closed end of bowel (#)

Effluent vs Formula

- **Proximal effluent**
  - Digestive enzymes
  - Partially digested substrates
  - Fermentable

- **Formula**
  - No digestive enzymes
  - Highly refined macronutrients
  - Fermentable
Testing the stoma out

Define the anatomy by contrast study
UGI, contrast enema, ostomy-gram, fistulogram
Detail dilated loops of bowel
Dilated loops = poor motility or obstruction
may be beneficial to use bowel US

Deciphering the stoma

Types of stomas

PROXIMAL STOMA
 DISTAL MUCUS FISTULA

UPPER GI TRACT FROM STOMACH
JEJUNOSTOMY
ILEOSTOMY
COLOSTOMY

DISTAL GI TRACT TO ANUS

Benefits of refeeding the distal fistula

• Energy salvage
• Accommodation of distal segment for better reanastomosis at time of surgery
• Improved gut adaptation (e.g. GLP2)
• Protection against infection?

Considerations for refeeding the mucus fistula

• Collect effluent from proximal stoma in bag and load in syringe
• Refeed continuously over 6 hours based on past 6 hour shift ostomy losses
• Use 5Fr feeding catheter, placing at least 5 cm internally through distal fistula
• Tape catheter through hole through ostomy bag
• If not enough effluent, can supplement with amino-acid based formula, prefer to mix with some effluent to capture digestive juices and partially digested substrate

Role of real-time bowel ultrasound (RTBUS)
bowel wall thickening
bowel dilatation
bowel peristalsis
bowel perfusion (yes or no)

Sonographic Progression of NEC

Epelman et al., 2007 Radiographics
Bowel injury remains common in the NICU
An understanding of the pathophysiology of bowel injury is essential to good management of patients with bowel injury
The best bowel is a fed bowel
The colon is an active part of the gut and essential to the best health of the host

Happy Refeeding!!!