The Role of the Gut in Critical Illness & Injury

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Objectives
• Review pathways of GI mediated immunocompetence
• Recognize clinical presentations of disruption in gut immune function
• Explore strategies for protecting and restoring gut immunocapacity

GI Mediated Immunocompetence
• Gut microbiome
• Peristalsis
• Cellular barrier
• Mucosal immunity
• Gut-liver axis

Gut Microbiome
• Reservoir of bacteria
  - $10^{12}$ total bacteria
  - $10^9$ potentially pathologic Gram Negative
• Enough endotoxin to kill host many times over
• Roles
  - Keep bacteria & toxins within lumen
  - Process & absorb nutrients

Gastric Acid Suppression
• PPI alter GI bacterial population in 50% of patients
  - Small intestine bacterial overgrowth (SIBO) more common
  - Diarrhea more common, especially in elderly
  - More common in long term users
• Omeprazole associated with higher rates of SIBO

Disclosures
No disclosures related to this presentation
Antibiotic Effect on Microbiome
- Promotes resistant bacterial strains
- Alters microbial co-dependence
- Changes production of metabolites
  - Regulate water and electrolyte absorption
  - Maintain intestinal barrier
  - Modulate cell proliferation
  - Apoptosis

Impact of Critical Illness
- SIRS patients have decreased anaerobic bacterial counts within 6 hours of insult
- Change in fecal pH of 1
  - 3x increase in bacteremia
  - 2x increase in mortality

Peristalsis

Cellular Barrier
- Tight intracellular junctions (TJ) allowing movement between intestinal lumen and the bloodstream
- Intracellular space 10-15μA
- Dynamic structures with rapid and coordinated responses
- Responsive to countless extracellular signals

GALT
- Contains 70% of total antibody immunity
- Differentiates bacteria
- Responsible for "oral tolerance"
- Composed of
  - Lymphocytes
  - Peyer's patches
  - Lymphoid follicles
  - Intraepithelial lymphocytes
GALT - MALT Pathway

- Secreted by sensitized B cells
- Establish antiviral and antibacterial defenses
- Create ability to respond to new infections

B cell

TH1

TGF-B

IL-10

Plasmacytes

SIgA

Mucosal Surfaces

Cytokines

Defensins

NK-KB

APOPTOSIS

Bacterial Antigen

King BK, Kudsk KA. Arch Surg. 1997;132:1303-1309

Lack of Feeding

- Decreased antiviral, antibacterial, and antibody formation in nasal passages
- Decreased in number of GALT cells
- Impaired ability to respond to new infectious challenges

Gut Liver Access

- Bile Salts
  - Excretion of lipids
  - Intestinal fat absorption
  - Detoxification of endotoxin
- Biliary tract mucosal tissue initiates adaptive and innate immunity

Kupffer Cells

- Macrophages that clear bacteria from circulation when intestinal defenses overwhelmed
- Resistant to endotoxin
- Signal downstream cytotoxin and neutrophil

Hepatic Case Example

- 26 year old GSW
- Branch of left hepatic artery clamped in OR
  - Labs:
    - WBC 76,000 (normal 4-10 x 10^9/L)
    - ALT 10,256 u/L (normal 0-40 u/L)
    - AST 22,105 u/L (normal 0-30 u/L)
    - LDH 14,322 u/L (normal 100-200 u/L)
    - INR 1.7
    - Hct 24 mg%
Hepatic Infarction

- Caused by overall shock, or focal interruption of hepatic blood supply
- Evidence of liver injury delayed
- Leukocytosis & Transaminitis, normalizes in 7-10 days
  - AST
  - Aik Phos
  - Serum Bili
- Synthetic function normal or mildly impaired
- Mortality increased with need for vasopressor and coagulation factor replacement

When the Gut is Insulted

- MSOF
- Sepsis
- Repeated infections
  - Poor wound healing
  - Prolonged mechanical ventilation
  - Delayed recovery

Gut Hypothesis for MOF

SHOCK, HYPOPERFUSION
↓
PREFERENTIAL SHUNTING
↓
O2 DELIVERY TO SPLEEN, INTESTINAL MUCOSA
↓
ISCHEMIA
↓
APOPTOSIS OF VILLI CELLS, TRANSMURAL NECROSIS
↓
BREAKDOWN OF GUT BARRIER

A Tale of Gut Ischemia

- 22 year old male “found down”
- Stabbed in femoral artery
- Admit pH 6.91, Base Deficit 26
- Day 3 ....
  - INR 6.0
  - Hct 20
  - Encephalopathic
  - Anuric
  - Hypotensive on multiple pressors

Effect of Alcohol

- All components of the intestinal barrier
  - μ mucin production at 25-60 days
  - Chronic ETOH results in decreased mucin production
  - Mucin content and activity impaired
  - TJs disrupted in ETOH & trauma and burns
- ↑ bacterial translocation and infection in hospitalized trauma patients
- ETOH & burns lead to higher degrees of inflammation & neutrophil infiltration

“Poking the Bear”

- Patients immunosuppressed
- Broad spectrum Abx allow colonization
- Antacids & H2 blockers allow colonization in stomach & upper airways
- Ileus allows intestinal stasis & overgrowth
- Hypoosmolar enteral feeding & TPN disrupt ecology of normal gut flora
- Hypotension & vasopressors result in splanchnic ischemia
Protecting the Gut

- Restoring perfusion
- Enteral nutrition
- Maintaining ecologic balance
  - antibiotic stewardship
  - probiotics
- Restoring microbiome

Enteral Nutrition is Essential

- Lack of mucosal contact with nutrients
  - Lymphoid tissue atrophy
  - Decline in immune function
  - Increase in bacterial translocation

Enteral Feeding

- ↓ Infection rates
- ↓ Hospital LOS
- ↓ Mortality
- Improved wound stability and healing
- More rapid liberation from ventilator

- Start within 24-48 hours after admission
- Advance to goal over next 48-72 hrs
- Parenteral nutrition only when EN not feasible for first 7 days

Probiotics

- "Live microorganisms in which, when administered in adequate amounts, confer a health benefit on the host"
- Human Origin
- Viable & hardy in human GI tract
- Acid & bile stable
- Adhesion to mucosa
- Clinically demonstrated benefit
- Safe

- L. casei
- L. acidophilus
- L. salivarius
- B. bifidum
- S. boulardii

Probiotics

- Inhibit growth of pathogenic enteric bacteria
- Improve epithelial & mucosal barrier function
- Block epithelial attachment or invasion by pathogens
- Eliminate pathogenic toxins
- Alter host immune response

- Monostrain vs. multi-strain?
- Pre, pro, or synbiotic?
- Quantity and quality for desired effect?
- How to assess the activity & viability?
- Probiotic safety?
- When are probiotics contraindicated?
Clostridium Difficile

- Gram Negative, spore-forming
- Spread by fecal-oral route
- Survive gastric acidity
- Outgrow normal intestinal flora
- Recurrent
  - 1x: 20-25%
  - 2x or more: 50-60%

Pathogenesis

- Toxin A
  - Intestinal permeability
  - Fluid secretion
- Toxin B
  - Cytotoxin
  - Colonic inflammation

Symptoms

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Diffuse pain, profuse diarrhea, leukocytosis, hypoaalbuminemia</td>
</tr>
<tr>
<td>Severe</td>
<td>Hypotension, fever, leukocytosis, elevated lactate, evidence of end organ failure</td>
</tr>
<tr>
<td>Fulminant colitis</td>
<td>Toxic megacolon, colonic perforation, death</td>
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</tbody>
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Treatment with Antibiotics

<table>
<thead>
<tr>
<th>Severity</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Metronidazole 500 mg po tid x 10 days  OR Vancomycin 125 mg po qid x 10 days</td>
</tr>
<tr>
<td>Severe</td>
<td>Vancomycin 125 qid x 10 days AND Metronidazole 500 mg IV tid AND Surgery Consult</td>
</tr>
<tr>
<td>Recurrent</td>
<td>Repeat either Vanco or Metronidazole up to 3 times</td>
</tr>
</tbody>
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Treatment with Fecal Microbiota Transplant

- FDA classified fecal matter as an investigative new drug and biologic in 2013
- Approved for administration by qualified physicians to treat recurrent C. diff.

The Transplant

- 200-300 g healthy donor stool
- Mixed with water or saline
- Filtered to remove particulate matter
- Instilled into GI tract
  - Retention enema (81-100%)
  - Nasogastric or nasoduodenal tube (73-83%)
  - Colonoscopy (86-100%)
  - Capsules
Concluding Thoughts

- The Gut is resilient yet fragile
- Lion's share of immunocompetence
- "It takes a village"
- Multiple pathways for harm
- Emerging strategies to repair and protect

References