The Role of the Gut in Critical Illness & Injury

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Disclosures

• No disclosures related to this presentation
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
Factors affecting the Microbiome

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
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
Effect of Alcohol

• All components of the intestinal barrier
  - mucin production at 25-60 days
    - Chronic ETOH results in decreased mucin production
    - Mucin content and activity impaired
    - TJ's disrupted in ETOH & trauma and burns
  - bacterial translocation and infection in hospitalized trauma patients with detectable ETOH levels
• ETOH & burns lead to higher degrees of inflammation & neutrophil infiltration in mice
Impact of Critical Illness

- Intestinal hypoperfusion leads to gut ischemia and mucosal injury
- 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
Gut Hypothesis for MOF

1. Shock, Hypoperfusion
2. Preferential Shunting
3. ↓O₂ Delivery to Spleen, Intestinal Mucosa
4. Ischemia
5. Apoptosis of Villi Cells, Transmural Necrosis
6. Breakdown of Gut Barrier
Peristalsis
Cellular Barrier

- Tight intracellular junctions (TJ) allowing movement between intestinal lumen and the bloodstream
- Intracellular space 10-15°A
- Dynamic structures with rapid and coordinated responses
- Responsive to countless extracellular signaling
Zonulin system

- Physiologic modulation of intestinal epithelial paracellular pathway
- Movement of bacteria, fluid, macromolecules and leukocytes
- Protection against microorganism colonization of the proximal intestine (innate immunity)
  - Celiac disease
  - Asthma
  - Type 1 Diabetes
  - Autism
Mucosal Barrier

• Mucosal tissue provide efficient protection
  - 50% of total body immunity
  - 70% of total antibody protection in the form of Secretory IgA (SIgA).
• Excrete metabolic products
• Communicate between
  - Enteric Nervous System (ENS)
  - Gut Associated Lymphoid Tissue (GALT)
  - Microbiome
GALT

• Contains 70% of total immune system cells
• Responsible for “oral tolerance”
• Differentiates bacteria
• Composed of
  - Lymphocytes
  - Peyer’s patches
  - Lymphoid follicles
  - Intraepithelial lymphocytes
Secretory IgA

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

Bacterial Antigen

B cell → TH1

TGF-B

IL-10

Plasmacytes

Cytokines

Defensins

NK-KB

Mucosal Surfaces

APOPTOSIS

SIgA

SIgA
Lack of Feeding

- Decreased antiviral, antibacteria, 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 ligated
- Labs:
  - WBC 76,000
  - ALT 10,256 u/L (normal 4-36 u/L)
  - AST 22,105 u/L (normal 0-35 u/L)
  - LDH 14,322 u/L (normal 100-190 u/L)
  - INR 1.7
  - Hct 24mg%
Hepatic Case Example 2

- 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
When the Gut is Insulted

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

- Restoring perfusion
- Maintaining ecologic balance (antibiotic stewardship)
- Enteral nutrition
- Probiotics
- Restoring microbiome
Enteral Nutrition

- 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

Ventilator associated pneumonia
Pancreatitis
VRE
Clostridium difficile
Infectious diarrhea
Probiotics

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

- Loss of intestinal barrier

- Leakage of fluid into intestine

- Migration of granulocytes into lumen
## Symptoms

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

<table>
<thead>
<tr>
<th>Severity</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Metrodidaole 500 mg po tid x 10 days OR Vancomycin 125 mg po quid x 10 days</td>
</tr>
<tr>
<td>Severe</td>
<td>Vancomycin 125 quid 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>
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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.
- Cure rates:
  - Primary 91%
  - Secondary 91-98%
The Transplant

- 200-300 g health 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
• Does the Lion’s share of immunocompetence
• “It takes a village”
• Multiple pathways for harm
• Emerging strategies to repair and protect
References

Thank You!
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