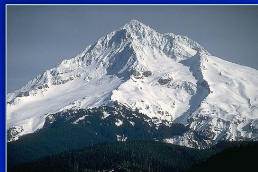


## The Role of the Gut in Critical Illness & Injury



Christine Schulman, RN, MS, CNS, CCRN  
 Critical Care & Trauma CNS  
 Legacy Health  
 Portland, Oregon



## 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

## 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

## 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

## Mucosal Barrier

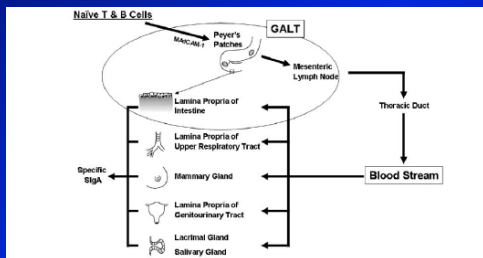
## Cellular Barrier

- Tight intracellular junctions (TJ) allowing movement between intestinal lumen and the bloodstream
- Intracellular space 10-15 $\text{\AA}$
- Dynamic structures with rapid and coordinated responses
- Responsive to countless extracellular signals

## GALT

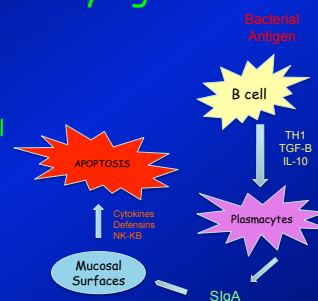
- Contains 70% of total antibody immunity
- Differentiates bacteria
- Responsible for "oral tolerance"
- Composed of
  - Lymphocytes
  - Peyer's patches
  - Lymphoid follicles
  - Intraepithelial lymphocytes

## GALT -MALT Pathway



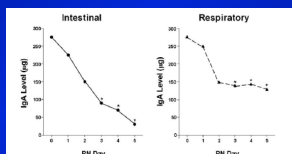
## Secretory IgA

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



## 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



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

## 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
  - 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%

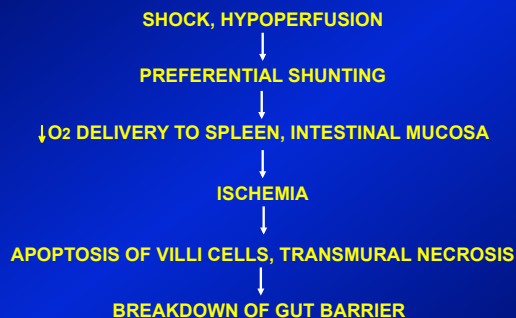
## Hepatic Infarction

- Caused by overall shock, or focal interruption of hepatic blood supply
- Evidence of liver injury delayed
- Leukocytosis & Transaminitis, normalizes in 7-10 days
  - AST
  - Alk 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



## 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
  - ↑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

Ventilator associated pneumonia  
Pancreatitis  
VRE  
Clostridium difficile  
Infectious diarrhea

### Probiotics

Inhibit growth of pathogenic enteric bacteria

Improve epithelial & mucosal barrier function

Block epithelial attachment or invasion by pathogens

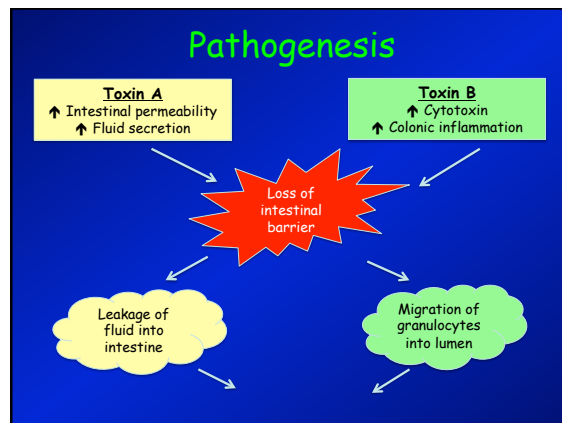
Alter host immune response

Eliminate pathogenic toxins

- 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%



## Symptoms

Type	Symptoms
Mild	Difuse pain, profuse diarrhea, leukocytosis, hypoalbumemia
Severe	Hypotension, fever, leukocytosis, elevated lactate, evidence of end organ failure
Fulminant colitis	Toxic megacolon, colon perforation, death

## Treatment with Antibiotics

Severity	Treatment
Mild	Metrodizole 500 mg po tid x 10 days <i>OR</i> Vancomycin 125 mg po quid x 10 days
Severe	Vancomycin 125 qid x 10 days <i>AND</i> Metronidazole 500 mg IV tid <i>AND</i> Surgery Consult
Recurrent	Repeat either Vanco or Metronidazole up to 3 times

## 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

## Thank You!



[cschulma@lhs.org](mailto:cschulma@lhs.org)  
[csschulman@comcast.net](mailto:csschulman@comcast.net)

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