Can Critical Illness and the Microbiome Play Nice Together?

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Disclosures

• Project Director on a collaboration grant between Geisinger Health System and AstraZeneca pharmaceuticals in the area of cardiovascular science.

Objectives

• Understand the relationship between critical illness and the human microbiome.
• Identify patients whose microbiome is likely to be affected by critical illness.
• Apply evidence to maintain the microbiome in the setting of critical illness.

The Microbiome Defined

• All the bacteria, viruses, fungi, etc. living on or in the human body
• Approximately 40 trillion cells
• 2-20 million microbial genes
• 1.5 kg organ

The Microbiome as a Functioning Organ

Microbiome
- Host defense
- Maintain mucosal barrier homeostasis
- Degrade plant polysaccharides and protein
- Drug metabolism

The Gut Microbiota


Dysbiosis in Critical Illness

Loss of Diversity in Gut Microbiota


p < 0.0001
Changes in Gut Microbiota Throughout ICU Stay

Serial Changes in Bacteroidetes to Firmicutes Ratio

Dysbiosis Across Body Sites

Dysbiosis Across Body Sites
Loss of a Diverse Microbiome in the Critically Ill


Microbiota Disruption in PICU Patients

Gut
Skin
Tongue


Exposure Versus Illness


Alteration of the Microbiome in Critical Illness

Antimicrobials
Acid Suppressants
Nutrition
Invasive Procedures
Decontamination
Opioids and Catecholamines

Effect of Antibiotics on the GUT Microbiota of Healthy Subjects

Influence of Nutrition on the Gut Microbiota
- Dietary intake influences major taxonomic phyla
- Enteral formula composition associated with dysbiosis
- Withholding enteral nutrition leads to decline in epithelial barrier function and increased bacterial translocation
- Parenteral nutrition changes intestinal microbiota and impairs intestinal barrier function and innate immunity; enteral supplementation reverses these effects

Alteration of the Gut Epithelium
- Mucosal inflammation
- Increased nitrate concentration
- Altered mucosal oxygen gradient
- Decreased butyrate production
- Degradation of colonic epithelial cells
- Altered immune function
- Damaged mucus layer
- Decreased protection from microorganisms and digestive enzymes


Alteration of the Respiratory Tract

- **Increased Immigration**
  - Accelerated with depressed consciousness and intubation
  - Change from oropharynx to gastrointestinal source

- **Decreased Elimination**
  - Decreased cough reflex
  - Impaired mucociliary transport
  - Inactivation of alveolar surfactant

- **Favorable Growth**
  - Nutrient-rich alveoli
  - Establishment of oxygen and temperature gradient pockets
  - Host signaling selects pathogen growth


Microbiota of the Respiratory Tract in Intubated Patients

- **Upper Respiratory Tract**
- **Lower Respiratory Tract**

Gut-Organ Axes

- Lung
- Gut Microbiota
- Brain
- Kidney
Alteration of the Lung Microbiota with Gut Bacteria in ARDS

Maintaining the Microbiome

Selective Digestive Decontamination

Effect of SDD on MODS

Minimize Pathogenic Enteral Bacteria

Components

Extensively Studied

Positive Outcomes

Effect of SDD on MODS


Spectrum of Probiotic Research in the ICU

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Research Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic-Associated Diarrhea</td>
<td>Meta-analyses estimate 40%-50% reduction</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Meta-analyses estimate approximately 60% reduction</td>
</tr>
<tr>
<td>Hepatic Encephalopathy</td>
<td>Meta-analyses show limited benefit in reducing progression</td>
</tr>
<tr>
<td>Necrotizing Enterocolitis</td>
<td>Meta-analyses find reduce severity and mortality</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Meta-analyses demonstrate approximately 40% reduction in ICU infections</td>
</tr>
<tr>
<td>Postoperative Infections</td>
<td>Limited primary data, found to increase mortality in a randomized trial</td>
</tr>
<tr>
<td>Septic and MODS</td>
<td>Limited primary data; found approximately 25%-40% reduction in ICU infections</td>
</tr>
<tr>
<td>UTIs</td>
<td>Limited primary data; no meaningful benefits demonstrated</td>
</tr>
<tr>
<td>VAP</td>
<td>Meta-analyses suggest 50%-70% reduction</td>
</tr>
</tbody>
</table>

Effect of Probiotics on ICU Mortality


Probiotics for Prevention of VAP

PER-PROTOCOL ANALYSIS

INTENT TO TREAT ANALYSIS

Effect of Probiotics on Overall ICU Infection

Effect of Probiotics on VAP

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Probiotics</th>
<th>Control</th>
<th>Total Events</th>
<th>Total Participants</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virginia 2005</td>
<td>22</td>
<td>15</td>
<td>75</td>
<td>44</td>
<td>1.47</td>
<td>0.54-6.27</td>
<td>0.53</td>
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<tr>
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<td>37</td>
<td>42</td>
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<td>0.44-2.56</td>
<td>0.92</td>
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<tr>
<td>Arizona 2007</td>
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<td>15</td>
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<td>50</td>
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<td>0.37-2.68</td>
<td>0.89</td>
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<tr>
<td>California 2008</td>
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<td>13</td>
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<td>46</td>
<td>0.97</td>
<td>0.36-2.96</td>
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<td>12</td>
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<td>48</td>
<td>1.12</td>
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<tr>
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<td>42</td>
<td>1.00</td>
<td>0.24-4.28</td>
<td>0.94</td>
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<tr>
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<td>10</td>
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<td>20</td>
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<td>Oregon 2011</td>
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<tr>
<td>Georgia 2012</td>
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<td>16</td>
<td>24</td>
<td>1.00</td>
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<td>0.99</td>
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<td>Florida 2013</td>
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<td>21</td>
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<td>0.23-4.28</td>
<td>0.99</td>
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<tr>
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<td>1105</td>
<td>1105</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
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Probiotics for Prevention of Antibiotic Associated Diarrhea

- Systematic review and meta-analysis by Susanne Hempel and colleagues
- 86 Randomized controlled trials included in analysis, 63 in the pooled random effects model (8188 participants)
- Probiotics associated with a reduction in antibiotic associated diarrhea: RR 0.58; 95% CI, 0.50 to 0.68; P = 0.001; I² = 54%
- Significant heterogeneity in pool results
- Not conducted in ICU patients

Probiotics for Prevention of Clostridium difficile-Associated Diarrhea

- Limited evidence of DOE outcomes in critically ill
- Heterogeneity among trials
- Various products and combination therapies studied

Limitations of Literature Support for Probiotic Use in the ICU
**Effects of Prebiotics on Survival**

<table>
<thead>
<tr>
<th>NO ANTIBIOTIC TREATMENT</th>
<th>WITH ANTIBIOTIC TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Graph 1" /></td>
<td><img src="image2.png" alt="Graph 2" /></td>
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**Effect of Prebiotics on Microbiota Diversity**

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<th>WITH ANTIBIOTIC TREATMENT</th>
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<tbody>
<tr>
<td><img src="image3.png" alt="Graph 3" /></td>
<td><img src="image4.png" alt="Graph 4" /></td>
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**Fecal Microbiota Transplantation or Therapy**

- Homogenized and filtered feces from healthy donors administered enterally
- Besides microbiota also contains other common gastrointestinal biologic products (e.g. bile salts, proteins, bacteriophages, etc.)
- Primarily studied for the treatment of refractory recurrent *C. difficile* infection
- Trials with this therapy are lacking in critically ill patients

**WHAT CAN BROWN DO FOR YOU?**

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- Besides microbiota also contains other common gastrointestinal biologic products (e.g. bile salts, proteins, bacteriophages, etc.)
- Primarily studied for the treatment of refractory recurrent *C. difficile* infection
- Trials with this therapy are lacking in critically ill patients
Fecal Microbiota Transplant for Life-Threatening C. difficile Infection

- Retrospective review of 6 patient cases
- All developed life-threatening septic shock from C. difficile during their ICU admission
- All were ordered emergent FMT as rescue therapy; one patient expired during FMT preparation
- Successful in all patients who received treatment
  - Stool consistency and odor changed within 12 hours
  - Significant vasopressor reduction at 48 hours
  - 3 patients survived to 30 days; survival data unknown for 2 patients


Future Microbiome Interventions in the ICU

- Targeted Probiotics or Fecal Microbiota Transplant
- Autologous Fecal Microbiota Transplants
- Utilization of Microbiota-derived Components and Metabolites
- The Microbiome as a Prognostic Tool

In Summary

- The microbiome plays an important role in host response to critical illness, functioning as an essential "organ"
- Alterations in the microbiome (dysbiosis) can adversely affect outcomes of the critically ill
- Many factors in the critically ill contribute to alterations in the microbiome
- Probiotics, prebiotics and fecal microbiota therapy are promising treatments to preserve or restore the microbiome in the critically ill, but more research is needed