GHAPP
Gastroenterology & Hepatology
Advanced Practice Providers

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Gut Microbiome: Role in GI and Hepatology

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Dr. Susan T. Wolgamott

Speakers Bureau: AbbVie, Clinical Area- IBD, EPI, (previously Allergan) - IBS-D, IBS-C, CIC

Speakers Bureau: Salix, Clinical Area- IBS-D IBS-C, CIC, HE

Speakers Bureau: Ironwood, Clinical Area- IBS-D

Sub-Investigator: Clinical Research Institute of Michigan, Clinical Area – IBD, IBS-D, IBS-C, CIC, Chronic Pancreatitis, Gastroparesis, GERD, EoE, Colonoscopy Prep, NASH, Cirrhosis, HE, Celiac Disease, Smoking Cessation
Overview

- What is the Gut Microbiome?
- Hot topic/Media attention
  - Dysbiosis
  - ‘Leaky Gut’
- Gastroenterology
  - FMT Registry
  - Probiotics/Prebiotics/Synbiotics
  - Antibiotics/Xenobiotics
  - FODMAP/Polyphenols
  - IBS
- Hepatology
  - HE
  - NAFLD/NASH
- Pipeline
• >1000 species but only a few phyla
  – Bacteroidetes and Firmicutes
  – Diverse in the gut compared to other body sites
  – Species stable over decades
  – Commonalities, adult family members
  – Gut community types, metadata
    • Breastfeeding, gender, education

Several large scale endeavors

- NIH Human Microbiome Project (HMP)
  - Community types, location, stability
- European Metagenomics of the Human Intestinal Tract (MetaHIT)
  - Gene sequencing
- Pharmaceutical Research

Gut Microbiome in Gastroenterology
Dysbiosis

- Disruption to the eustasis
- Variety of symptoms
  - Pain, cramping, bloating, diarrhea
- Identified by origin/symptom prevalence
  - Traveler’s diarrhea
  - SIBO
  - IBS
  - Food poisoning
  - Antibiotic-induced diarrhea
  - Acute gastroenteritis
  - *Clostridium difficile*

Intestinal permeability and intestinal barrier function

Compromised physical structures in the intestinal lining (tight junctures) resulting in abnormal or increased gut permeability

Reliably associated with several diseases
- GI diseases: IBD, IBS, celiac disease
- Systemic diseases: Type I Diabetes, graft vs host, HIV, MS, Rheumatic Disease

Leaky Gut Syndrome associated with large variety of symptoms and diseases
- Chronic fatigue syndrome, fibromyalgia, allergies, depression, and skin disorders

Barrier restoration ≠ Disease Cure

Barrier dysfunction should target the underlying disease

## Role of Microbiota in Disease: Examining the Evidence

### Extensive supporting data

<table>
<thead>
<tr>
<th>Disease</th>
<th>Human data regarding intestinal permeability</th>
<th>Association supported by animal model(s)?</th>
<th>Prognostic implications of increased permeability</th>
<th>Role of microbiota</th>
<th>Treatment improves disease-associated permeability defects?</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD</td>
<td>Positive correlation with disease activity; present in some healthy first degree relatives (CD)</td>
<td>Yes [16, 47, 51, 56]</td>
<td>Increased risk of relapse in some studies of CD patients [56, 60]</td>
<td><em>Trichuris suis</em> (whipworm) infection and fecal microbial transplantation clinical trial data are encouraging [53, 54]</td>
<td>Yes (in patients and experimental models)</td>
</tr>
<tr>
<td>Graft vs. Host Disease</td>
<td>Positive correlation of pre-conditioning GI toxicity (presumed to indicate degree of transient barrier loss) with disease activity [67]</td>
<td>Yes [58]</td>
<td>Unknown</td>
<td>Antibiotics reduce disease incidence in patients and experimental animals [59, 60]</td>
<td>Yes (in experimental models) [68]</td>
</tr>
<tr>
<td>Type I diabetes</td>
<td>Increased in pre-diabetic and diabetic patients [61]</td>
<td>Yes [65]</td>
<td>Unknown</td>
<td>Changes in microbiome modify incidence of experimental disease [63, 64]</td>
<td>Unknown</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>Increased in HIV enteropathy [65], positive correlation with disease stage [68]</td>
<td>Yes [67]</td>
<td>Unknown</td>
<td>Serum LPS is elevated in patients. Bacterial translocation has been postulated to cause immune activation [67]</td>
<td>Yes (in patients) [68]</td>
</tr>
<tr>
<td>Multiple organ dysfunction syndrome</td>
<td>Correlates with increased disease severity [69]</td>
<td>Yes [70, 71]</td>
<td>Unknown</td>
<td>Controversial</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

## Role of Microbiota in Disease: Examining the Evidence

### Some supporting data

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<tr>
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</thead>
<tbody>
<tr>
<td>Irritable bowel syndrome</td>
<td>Increased in diarrhea predominant, post-infectious, and non-post-infectious IBS(^{72, 73})</td>
<td>No</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>Positive correlation with disease activity(^{74}); increased in patients and healthy relatives(^{75})</td>
<td>Yes(^{76, 77})</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Yes(^{74})</td>
</tr>
</tbody>
</table>
### Role of Microbiota in Disease: Examining the Evidence

Limited or no supporting data

<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>Autism</td>
<td>Increased in patients and relatives; correlates with food intolerance[78]</td>
<td>No</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Eczema</td>
<td>Increased in subset of patients; possible correlation with disease activity[75, 80]</td>
<td>No</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Inconclusive</td>
<td>No</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>Positive correlation with disease activity[81]</td>
<td>Yes[82, 83]</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Yes (in experimental models)[82, 84]</td>
</tr>
<tr>
<td>Parkinson's disease</td>
<td>Increased in subset of patients[85, 86]</td>
<td>No</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Increased in subset of patients; correlation with disease activity not studied[82]</td>
<td>No</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Depression</td>
<td>Unknown</td>
<td>No</td>
<td>Unknown</td>
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<td>Unknown</td>
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</table>

## Role of Microbiota in Disease: Examining the Evidence

### Limited or no supporting data

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<tbody>
<tr>
<td>Chronic Fatigue Syndrome</td>
<td>Unknown</td>
<td>No</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Asthma</td>
<td>Increased in asthmatic patients; no correlation with disease activity[^93]</td>
<td>No</td>
<td>Unknown</td>
<td>Hypothesized to provide possible protective role[^99]</td>
<td>No</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Increased in subset of patients; normal in remission[^91]</td>
<td>No</td>
<td>Unknown</td>
<td>Reduced experimental disease in germ free mice[^92]</td>
<td>Unknown</td>
</tr>
<tr>
<td>Rheumatic diseases (RA, AS)</td>
<td>Increased in patients[^93]; NSAID treatment is confounding factor[^94]</td>
<td>No</td>
<td>Unknown</td>
<td>Symptoms correlate with germ-free status in rat model[^99]; Gut flora worsens disease in mouse models[^96]</td>
<td>Unknown</td>
</tr>
<tr>
<td>NAFLD</td>
<td>Positive correlation with disease activity[^97, 98]</td>
<td>No</td>
<td>Unknown</td>
<td>Correlation in humans.[^97]; Strong association in mice.[^96, 100]</td>
<td>Unknown</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>Increased in subset of patients; correlation with disease activity not studied[^101]</td>
<td>No</td>
<td>Unknown</td>
<td>Postulated to be the source of LPS that leads to liver damage and inflammation.[^102]</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Established September 2017
Estimated completion 2026
Used to study the Microbiome
Develop full safety profile for FMT
90% cure rate in CDI in 98% with first transfer
Stool banks
Delivery
- Capsules
- NG/OG/EGD
- Colonoscope
- Enema

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 In patients with <em>C difficile</em> infection, we recommend the use of probiotics only in the context of a clinical trial.</td>
<td>No recommendation</td>
<td>Knowledge gap</td>
</tr>
<tr>
<td>2 In adults and children on antibiotic treatment, we suggest the use of <em>S boulardii</em>; or the 2-strain combination of <em>L acidophilus</em> CL1285 and <em>L casei</em> LBC80R; or the 3-strain combination of <em>L acidophilus</em>, <em>L delbrueckii</em> subsp <em>Bulgari</em>icus and <em>B bifidum</em>; or the 4-strain combination of <em>L acidophilus</em>, <em>L delbrueckii</em> subsp <em>bulgaricus</em>, <em>B bifidum</em>, and <em>S salivarius</em> subsp <em>thermophilus</em> over no or other probiotics for prevention of <em>C difficile</em> infection.</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td>3 In adults and children with Crohn's disease and ulcerative colitis, we recommend the use of probiotics only in the context of a clinical trial.</td>
<td>No recommendation</td>
<td>Knowledge gap</td>
</tr>
</tbody>
</table>

### AGA Summary of Recommendations on Probiotic Use

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4</strong> In adults and children with pouchitis, we suggest the 8-strain combination of ( L \text{paracasei} ) subsp ( \text{paracasei} ), ( L \text{plantarum} ), ( L \text{acidophilus} ), ( L \text{delbrueckii} ) subsp ( \text{bulgaricus} ), ( B \text{longum} ) subsp ( \text{longum} ), ( B \text{breve} ), ( B \text{longum} ) subsp ( \text{infantis} ), and ( S \text{salivarius} ) subsp ( \text{thermophilus} ) over no or other probiotics.</td>
<td>Conditional</td>
<td>Very low</td>
</tr>
<tr>
<td><strong>5</strong> In symptomatic children and adults with irritable bowel syndrome, we recommend the use of probiotics only in the context of a clinical trial.</td>
<td>No recommendations</td>
<td>Knowledge gap</td>
</tr>
<tr>
<td><strong>6</strong> In children with acute infectious gastroenteritis, we suggest <strong>against</strong> the use of probiotics.</td>
<td>Conditional</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
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<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>In preterm (less than 37 weeks gestational age), low-birth-weight infants, we suggest using a combination of <em>Lactobacillus</em> spp and <em>Bifidobacterium</em> spp (<em>L. rhamnosus</em> ATCC 53103 and <em>B. longum</em> subsp <em>infantis</em>; or <em>L. casei</em> and <em>B. breve</em>; or <em>L. rhamnosus, L. acidophilus, L. casei, B. longum</em> subsp <em>infantis</em>, <em>B. bifidum</em>, and <em>B. longum</em> subsp <em>longum</em>; or <em>L. acidophilus</em> and <em>B. longum</em> subsp <em>infantis</em>; or <em>L. acidophilus</em> and <em>B. bifidum</em>; or <em>L. rhamnosus</em> ATCC 53103 and <em>B. longum</em> Reuter ATCC BAA-999; or <em>L. acidophilus, B. bifidum, B. animalis</em> subsp <em>lactis</em>, and <em>B. longum</em> subsp <em>longum</em>), or <em>B. animalis</em> subsp <em>lactis</em> (including DSM 15954), or <em>L. reuteri</em> (DSM 17938 or ATCC 55730), or <em>L. rhamnosus</em> (ATCC 53103 or ATC A07FA or LCR 35) for prevention of NEC over no and other probiotics.</td>
<td>Conditional</td>
<td>Moderate/high</td>
</tr>
</tbody>
</table>

Prebiotics/Synbiotics

- Food for bacteria
- Certain roots, fruits, vegetables
- Apple cider vinegar
- Kombucha
- Fermented foods, Kimchi
- Synergistic combinations of probiotics and prebiotics

Antibiotics/Xenobiotics

• Overuse/over prescribing
  – Most common source of injury to eustasis
  – Killing both pathogenic and commensal
  – Reshaping ecology with functional consequences
  – Effects on diseases
    • Malnutrition, obesity, diabetes, *C difficile*

• Non-absorbable antibiotics
  – Rifaximin/rifamycin
  – Neomycin

• Primarily pharmaceuticals
• Microbiome plays integral role in metabolism
  – Xenobiotic metabolizing enzymes
  – Bacterial genera harboring
  – Critical link to pharmacokinetic variations among individuals

Irritable Bowel Syndrome

- Rome IV Criteria
- Affects 1 in 4
- High disease burden
- Multiple possible causes
  - Dysbiosis
  - Brain-gut axis
  - Gut-liver axis
  - Environmental
  - Psychological/Stress
  - Diet
  - Genetic/Epigenetic
  - Chronic infections
  - Immune dysregulation
  - Food allergy/intolerance
  - Any combination

Symptoms of IBS:
- Abdominal pain
- Cramping
- Bloating
- Excess Gas
- Diarrhea or constipation
- Mucus in the stool

FODMAP/Polyphenols

Foods suitable on a low-fodmap diet

- **Fruit**: banana, blueberry, boysenberry, cantaloupe, cranberry, durian, grape, grapefruit, hawthorn, jujube, kiwi, lime, lime, mandarin, orange, passionfruit, papaya, raspberry, rhubarb, rockmelon, star anise, strawberry, tangerine, nectarine, plum, pear, plum, apricot, kiwi, kumquat.

- **Vegetables**: aloe, bamboo shoots, beet, celery, chives, choy sum, endive, grape, green beans, lettuce, onions, parsnip, potato, pumpkin, radish, kale, leek, okra, turnip, yam, zucchini, horseradish, chili, carrot, ginger, lemon grass, marjoram, mint, oregano, parsley, rosemary, thyme.

- **Grain foods**: gluten-free bread, rice, oat, polenta, other: arrowroot, millet, psyllium, quinoa, sorghum, tapioca.

- **Milk products**: lactose-free milk, oat milk, rice milk, soy milk, whey for baby foods.

- **Other**: tofu, sweeteners (sugar, sucrose, glucose, artificial sweeteners not ending in ‘-ol’), honey substitutes (golden syrup, maple syrup), thickeners, trace elements.

- **Butter substitutes**: olive oil.

Eliminate foods containing fodmaps

- **Excess fructose**: fruit (apple, mango, nashi, pear, tinned fruit in natural juice, watermelon, sweeteners), fructose, high fructose corn syrup.

- **Lactose**: milk (milk from cows, goats, sheep, custard, ice cream, yogurt, cheeses).

- **Fructans**: vegetables (artichokes, asparagus, beetroot, broccoli, brussels sprouts, cabbage, eggplant, fennel, garlic, leek, okra, onion (all), shallots, spring onion, corn, lettuce, kidney beans, lentils, soy beans).

- **Galactans**: legumes (baked beans, chickpeas, kidney beans, lentils, soy beans).

- **Polys**: fruit (apricots, apricot, avocado, blackberry, cherry, longan, yam, nashi, medlar, peach, pear, prune, prunes, watermelon, vegetables (cauliflower, green capsicum, bell pepper), mushroom, sweet corn, sweeteners (sorbitol, fructose, maltitol, erythritol, xylitol)).

Gut Microbiome in Hepatology
Hepatic Encephalopathy

- Function of ammonia levels and alterations in microbiota
- High ratio of healthy to pathogenic bacteria
- Microbiota secrete biologically active compounds
  - Inhibit pathogens
  - Metabolism of toxic compounds (e.g., ammonia)
- Fecal microbiota evolve with increasing Child-Pugh and MELD scores
  - Stool microbiota, same
  - Mucosal microbiota, differ
  - Translocation, mucosal interface, immune response
- Multiple mechanisms in cirrhosis contribute to decreased GI motility thus increasing fermentation and dysbiosis

Hepatic Encephalopathy

- Gut-Liver Axis
  - 70% of Portal circulation from the gut
  - Absorption/metabolism of nutrition/drugs
  - Lack of bile acid homeostasis results in diarrhea and bacterial overgrowth
  - Cirrhosis decrease GI motility increasing infection risk (e.g., SBP)

- Lactulose – No change in fecal microbiota w/ treatment or withdrawal
- Rifaximin – Modest changes in fecal and mucosal microbiota
- Combined positive symptom response
  - Increased microbial metabolic function
  - Improved dysbiosis

- Affects >83 Million Americans
- Will surpass all causes for transplant by 2030
- Predictors include
  - **Obesity (highest)**, Diabetes/insulin resistance, HLD, metabolic syndrome
- Pathophysiology multifactorial
  - Gut Microbiota changes in obesity and T2D result in decreased Microbial Gene Richness (MGR)
  - Prevalence of low MGR increases in severity with increase in obesity
  - Low MGR associated with pro-inflammatory status and worse adiposity and metabolic alterations
  - Distinct microbial signatures in mild, compensated disease vs advanced fibrosis or decompensated cirrhosis
  - Patients with low MGR display ↑ bacteria that are able to synthesize LPR resulting in worsening insulin-resistance and a worse lipidemic profile

NAFLD

**Low to mild fibrosis**
- Frequently associated with ↑ Proteobacteria (phylum level)
- *Rikenellaceae* and *Rumminococcaceae* are ↓ (family level)
- *Escherichia* and *Dorea* are ↑↑ while *Anaerosporobacter, Coprococcus, Eubacterium, Faecalibacterium* and *Prevotella* are ↓ (genera level)

**Advanced fibrosis**
- Associated with ↑ gram-neg microbes, ↓ *Firmicutes* and ↑ Proteobacteria (phylum level)
- *Escherichia coli* and *Bacteroides vulgatus* ↑, while *Eubacterium rectale* was ↓ (species level)
- *Enterobacteriaceae* and *Streptococcus* were ↑ (genera level)

- Probiotics and next generation probiotics
  - Most studied in murine and human trials
  - Modifying dysbiosis, reduces endotoxemia, improved intestinal barrier function and minor reduction of BMI
- Polyphenols
  - Modify GM resulting in modulation of the Gut-Liver Axis
- Prebiotics
  - Improve mouse metabolic health by reducing weight, insulin resistance, endotoxemia, improving gut barrier function.
  - Human studies are still controversial regarding their effects on metabolic health

NAFLD

• FMT
  – Increased MGR for a short period with no improvement in the NAFLD, decrease in weight/BMI
• Synbiotics
  – Studies are scarce. Showing a reduction in steatosis and fibrosis
• Exercise (combined endurance and strength training)
  – Reduces markers of systemic inflammation, steatosis, fibrosis and LFTs
• Diet
  – Modulate the Gut-Liver Axis, with or without weight loss
  – Low carbohydrate diet more efficient at reducing intrahepatic triglycerides

• Control group
• High fat diet (HFD) induced-obesity
• Effects of moderate calorie restriction (CR) after FMT

• Fecal transplant – Autologous and Heterologous
  – Decreased glucose levels, triglycerides, insulin levels and insulin resistance
  – Induces lipolysis of adipose tissue
  – Increases fatty acid oxidation in the liver
  – Increases bacterial diversity/richness

FMT-TRIM Human Trial
Can Altering the Gut Microbiota Impact Systemic Metabolism?

- 12 week, double-blinded, placebo controlled trial
- Oral FMT capsules from healthy lean donors
- Subjects were obese and had mild to moderate insulin resistance
- Primary parameter was change in insulin sensitivity
- Secondary metabolic outcomes
  - HgbA1c, body weight, body composition, metabolic rate, engraftment of donor bacterial components
- Conclusion
  - Engraftment achieved to 12 weeks
  - No other measurable changes

Pipeline

- Asthma
- Maternal Gut & Vaginal Flora
- Diabetes
- Neurotransmitters
  - Behavior/Mood
    - ‘Gut Feeling’
  - Multiple Sclerosis, Myasthenia Gravis, Cerebral Palsy, Autism


