MAINTAINING A HEALTHY MICROBIOME

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DISCLOSURES

Kimberly Kearns, APRN has the following disclosures:

• Speakers Bureau
  • Medtronic
  • Salix Pharmaceuticals
  • Takeda Pharmaceuticals
OBJECTIVES

• Discuss the microbiome

• Evaluate etiologies that are linked to alterations in the microbiome

• Review microbiome directed therapies

• Analyze special considerations when choosing microbiome directed therapies
THE GUT MICROBIOME

• One of the most promising areas of science today

• How do we manipulate the gut microbiome to treat disease and restore health?
WHAT IS THE GUT MICROBIOME?

• Trillions of bacteria, viruses, fungi, archaea and eukaryotic make up what is collectively called the gut microbiome

• Gut microbiota influence:
  • Metabolism/Obesity
  • Nutrient Synthesis
    • B vitamins, Vitamin K, Folate and short chain fatty acids
  • Immune system
  • Enteric Nervous System

WHAT IS CONSIDERED A HEALTHY MICROBIOIME?

• No standard definition
• Characteristics include:
  • High levels of diversity
  • Stability
  • Resistance to stress-related change
  • High level of redundancy of metabolic pathways

FACTORS THAT CAN INFLUENCE THE MICROBIOME

• Early life events
  • Birth
  • Breast feeding
  • ABX exposure
• Environment
• Diet
• Pathogens/Infection

• Health behaviors
  • Smoking
  • ETOH use
• Stress
• Medications
  • ABX
  • PPI
  • Metformin
DYSBIOSIS

Imbalance of gut microbiota
• Altered GI motility
• Increase in GI permeability
• Immune activation
• Increase in lymphocytes
  • Seen in post-infectious IBS
• Mast cells
• Proinflammatory cytokines

CONDITIONS ASSOCIATED WITH ALTERATION IN THE MICROBIOME

• Diarrhea
  • C-diff
• Irritable Bowel Syndrome
• SIBO
• Inflammatory Bowel Disease
• Liver disease

• Non-GI related conditions:
  • Allergic conditions
  • Diabetes
  • Metabolic Syndrome
  • Obesity

Question remains…are the changes in the microbiome the cause or effect of the disease?
Irritable bowel syndrome (IBS) is a chronic gastrointestinal condition that may be characterized by abdominal pain, bloating, distention, flatulence, and bowel disturbances.
ROME IV CRITERIA FOR IBS

Recurrent abdominal pain at least 1 day/week in the last 3 months, associated with 2 or more of the following criteria:

- Related to defecation
- Associated with change in stool frequency
- Associated with an change in the stool form/appearance

Criteria fulfilled for the last 3 months, with onset of symptoms 6 months before diagnosis

25% of BM is the threshold for classification.
GUT BRAIN AXIS

Influence on:
- Weight Gain
- Bowel Movements
- Nutrient Delivery
- Microbial Balance

Influence on:
- Neurotransmitters
- Stress/Anxiety
- Mood
- Behaviour
SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

Definition:
- Small bowel is colonized by excessive aerobic and anaerobic microbes that are normally present in the colon.

Clinical manifestations:
- Post-prandial bloating
- Abdominal pain
- Diarrhea, Constipation or both
- Flatulence

SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

• Diagnosis
  • Clinical evaluation on symptoms
  • Breath Test
    • Measures H₂ and CH₄ gas produced by the bacteria
    • Helpful in determining appropriate treatment (H₂ vs CH₄)
ETIOLOGY OF SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

- Long term PPI use
- Anatomic Abnormality
  - Billroth surgery
- Small bowel motility disorder
  - Diabetes
  - Scleroderma
- Long term probiotic/prebiotic use
- NASH/Cirrhosis
- Narcotic use
- Pancreatic insufficiency
- Immunocompromised

INFLAMMATORY BOWEL DISEASE (IBD)

- **Ulcerative colitis**
  - Inflammatory disease of the colon
  - Inflammation/ ulceration of mucosal layer
- **Crohn’s disease**
  - Inflammatory disease that can effect entire GI tract
  - Transmural inflammation

- **Pouchitis**
PHARMACOLOGICAL APPROACH TO RESTORING THE MICROBIOME
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dosing</th>
<th>Target Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotic:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fidaxomicin (Dificid)</td>
<td>200 mg orally twice daily for 10 days</td>
<td>C-diff</td>
</tr>
<tr>
<td><strong>Antibiotic:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500 mg orally three times daily for 10 days</td>
<td>C-diff</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pouchitis</td>
</tr>
<tr>
<td><strong>Antibiotic:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>125 mg orally four times daily for 10 days</td>
<td>C-diff (now first line)</td>
</tr>
<tr>
<td><strong>Fecal Transplant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsules: up to 40</td>
<td></td>
<td>C-diff</td>
</tr>
<tr>
<td>Colonoscopy: 200-300g of followed by retention enema in 24 hours</td>
<td>Two or more recurrences of CDI and for whom traditional antibiotic treatment has been ineffective</td>
<td></td>
</tr>
<tr>
<td>Retention enema: 200-300g for 5 days</td>
<td>? IBD</td>
<td></td>
</tr>
<tr>
<td>NJ tube: 25-30 gm x 1</td>
<td></td>
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</tr>
</tbody>
</table>

Clin Infect Dis 2018; 66(7):987-994
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Dosing</th>
<th>Target Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic: Rifaxamin (Xifaxan)</td>
<td>550 mg TID for 14 days May repeat up to 2x</td>
<td>IBS SIBO-hydrogen predominant (off label)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic: Neomycin</td>
<td>500mg po BID for 14 days with Xifaxan x 14 day</td>
<td>SIBO-methane predominant (off label)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloride Channel Activator/laxative: Lubiprostone (Amitiza)</td>
<td>8mcg po BID</td>
<td>IBS-C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>Low FODMAP, no Gluten</td>
<td>IBS, SIBO, Diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prebiotic: Psyllium</td>
<td>Up to 30g/d in divided doses</td>
<td>IBS, Constipation, Diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum-derived bovine immunoglobulin/protein isolate (SBI) Enterogam</td>
<td>5gms=1 packet 1-4 packets daily depending on stool frequency</td>
<td>Diarrhea, IBS, SIBO</td>
</tr>
<tr>
<td>Drug</td>
<td>MOA</td>
<td>Time to peak plasma level</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>Macrolide</td>
<td>Unknown</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Antibacterial, Antiprotozoal</td>
<td>1.2 hrs</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Glycopeptide</td>
<td>Unknown</td>
</tr>
<tr>
<td>Rifaxamin</td>
<td>Non-aminoglycoside, derived from Rifamycin</td>
<td>1 hour</td>
</tr>
<tr>
<td>Neomycin</td>
<td>Aminoglycoside</td>
<td>1-4 hours</td>
</tr>
<tr>
<td>Lubiprostone</td>
<td>Chloride Channel Activator</td>
<td>1.1 hours</td>
</tr>
<tr>
<td>Enterogam</td>
<td>Immunoglobulin/protein isolate</td>
<td>30-120 min Dose dep.</td>
</tr>
<tr>
<td>Drug</td>
<td>Considerations Common Side Effects</td>
<td>Pregnancy/Lactation</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>S/E: Nausea, vomiting, abdominal pain, GI bleed, anemia, neutropenia</td>
<td>Cat B-use only if needed/ok w/breastfeeding</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>No ETOH</td>
<td>Contraindicated in 1st trimester/Caution with breast feeding.</td>
</tr>
<tr>
<td></td>
<td>S/E: N/V, metallic taste, diarrhea, candidiasis, furry tongue</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>S/E: Vomiting, flatulence, nausea (PO)</td>
<td>Ok for tx of C-diff/ ok w/ breastfeeding</td>
</tr>
<tr>
<td>Rifaxamin</td>
<td>Not systemically absorbed</td>
<td>Avoid in pregnancy/exercise caution</td>
</tr>
<tr>
<td></td>
<td>No known antibiotic resistance with re-treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S/E Nausea, increase in AST/ALT</td>
<td></td>
</tr>
<tr>
<td>Neomycin</td>
<td>BLACK BOX: neuro/oto/nephro toxicity</td>
<td>Class D/Do not use while breast feeding</td>
</tr>
<tr>
<td></td>
<td>S/E: Nausea, emesis, diarrhea</td>
<td></td>
</tr>
<tr>
<td>Lubiprostone</td>
<td>S/E of Nausea, give with food.</td>
<td>Avoid in pregnancy/Avoid when breastfeeding</td>
</tr>
<tr>
<td></td>
<td>Diarrhea, abdominal pain, bloating, dyspnea-1st hour of dose</td>
<td></td>
</tr>
<tr>
<td>Enterogam</td>
<td>2-4 weeks before improvement of symptoms then decrease dose. Made of beef protein</td>
<td>No data-use caution</td>
</tr>
<tr>
<td></td>
<td>S/E: Nausea, metallic taste, constipation and diarrhea</td>
<td></td>
</tr>
</tbody>
</table>
RIFAXAMIN (XIFAXAN) FOR TREATMENT OF IBS

TARGET I and TARGET II

• 1258 patients

• Evaluate relief of IBS symptoms after a 2-week course of rifaximin

• Target I
  • 41% (Rifaxamin) vs 31% Placebo

• Target II
  • 41% (Rifaxamin) vs 31% Placebo

Both studies resulted in statistical significance.

RIFAXAMIN (XIFAXAN) FOR TREATMENT OF SIBO

• Meta-analysis, Gatta 2017
• 32 studies, over 1300 patients
• Overall eradication rate 70.8

Improvement in symptoms 67.7% in patients with eradicated SIBO

US RCT: Primary and Key Secondary Endpoints

83 IBS-D patients randomized to LFD or mNICE diet x 4 weeks

% Adequate Relief

- m-NICE: 41% (N = 38)
- Low FODMAP: 52% (N = 45)

p = 0.30

Average Daily Abdominal Pain Scores (0-10)

Baseline Week 1 Week 2 Week 3 Week 4
m-NICE Low FODMAP m-NICE Low FODMAP

Average Daily Abdominal Bloating Score (0-10)

Baseline Week 1 Week 2 Week 3 Week 4
m-NICE Low FODMAP m-NICE Low FODMAP

P values refer to the change WITHIN group comparing to baseline score

* = p ≤ .05
○ = p ≤ .01
# = p ≤ .001
$ = p ≤ .0001

Eswaran et al. Am J Gastro 2016;111:1824-1832
US RCT: Effects on Quality of Life

Proportion with Improvement from Baseline ≥ 14 in IBS-QoL Scores

- m-NICE: 21%
- Low FODMAP: 52%

p = .0105

Eswaran, Chey et al. DDW 2016
Probiotics
Mechanism of action
<table>
<thead>
<tr>
<th>Therapy: Probiotic</th>
<th>Dosing</th>
<th>Target Condition</th>
<th>Target Symptoms</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bifidobacterium infanti (Align)</td>
<td>1 capsule daily x 4 weeks</td>
<td>IBS</td>
<td>Abdominal pain, bloating, straining, irregular bowel habits</td>
<td>Gas, Bloating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abx associated diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saccharomyces boulardii lyo (Florastor)</td>
<td>2 capsules 1-2 x per day</td>
<td>IBS</td>
<td>Abd pain, bloating irregular bowel habits</td>
<td>Constipation Thirst Bloating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abx associated diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bifidobacterium breve, B. longum, B. infantis, Lactobacillus acidophilus, L. plantarum, L. paracasei, L. bulgaricus, Streptococcus thermophilus (VSL 3 or Visbiome)</td>
<td>900 billion CFU per packet-RX needed f</td>
<td>IBS-D: 1/4-1/2 PPD</td>
<td>IBS-D: Bloating and Flatulence</td>
<td>Bloating 3-4 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UC: maintenance: 1/2-1 PPD</td>
<td>UC: hematochezia, abdominal pain</td>
<td>Do not take with ABX</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pouchitis: 1-2 PPD/BID 9-12 mo</td>
<td>Pouchitis: abdominal pain, hematochezia, urgency, increase in stool frequency.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Did not confirm mucosal healing</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Due to fecal stasis</em></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapy: Probiotic</th>
<th>Dosing</th>
<th>Target Condition</th>
<th>Target Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. Casei (DanActive)</td>
<td>65 ml per week x 4 weeks</td>
<td>Constipation or Diarrhea</td>
<td>Improvement in stool consistency and frequency at week 2</td>
</tr>
<tr>
<td>Lactobacillus Rhamnosus GG (Culturelle)</td>
<td>10 billion CFU 1 cap daily or 1 cap BID</td>
<td>Diarrhea</td>
<td>ABX associated Diarrhea</td>
</tr>
<tr>
<td></td>
<td>BID for tx and 7 days after completion of tx</td>
<td>PPX for diarrhea related to H-pylori tx</td>
<td>Infectious Diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Shen, et al Gastroenterology, 2017; 152 (8) 1889-1990</td>
</tr>
</tbody>
</table>
PROBIOTIC SPECIAL CONSIDERATIONS

Saccharomyces boulardii lyo (Florastor):
• Yeast found naturally on the skin of lychees and mangosteens
• Vegetarian, gluten free and appropriate for lactose intolerance
• Case reports of bacteremia and endocarditis and fungemia
• Do not use in acute care setting with central lines, open arterial/venous access
• Caution in immunocompromised population

• VSL 3/Visbiome:
  • Live bacteria: use caution in immunocompromised population
  • Contains milk

PROBIOTICS AND IBS

• Multiple studies on Probiotics in patients with IBS
  • Results remain mixed
  • Different Probiotics are like “different drugs”
    • Different Strains
    • Unique dosing
  • No standardization
• IBS unique condition with multiple symptoms
• More research needed

PROBIOTICS AND SIBO

• 2017 meta-analysis, 18 studies

• No significant difference in the incidence of SIBO in patients on probiotics as compared with the control group

• Patients with SIBO who were treated with probiotics:
  • Higher rates of gut decontamination
  • Decrease in breath hydrogen concentration
  • Reduction in abdominal pain
  • No significant improvement in diarrhea

ALTERATION IN MICROBIOME DUE TO PROTON PUMP INHIBITOR

- PPI use has been associated with an increased risk of *C. difficile* infection, even in the absence of antibiotic use
  - PPI influences composition of the normal intestinal flora
  - Hypothesis: vegetative forms that would normally be destroyed by gastric acid might survive in the less-acidic environment
ALTERATION IN MICROBIOME DUE TO PROTON PUMP INHIBITORS

PPI use has been associated with increase in risk of community-acquired pneumonia

- Hypothesis: PPI use may have “upstream” effect on the oropharyngeal microbiome which increases risk for pneumonia
- Gastric acid reduction may lead to growth of aerobic bacteria in the stomach
MECHANISM OF ACTION OF PPI

• PPI inhibit the H-K-ATPase, the final step in gastric acid secretion by parietal cells

• PPI are benzimidazole derivatives
  • Acts on secretory area of parietal cell
  • Interacts with external surface of the H-K-ATPase
  • Impairment of gastric acid secretion
## PHARMACOKINETICS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing mg</th>
<th>Time to peak plasma level</th>
<th>Half-life</th>
<th>Primary Excretion</th>
<th>Liver metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexlansoprazole</td>
<td>30, 60</td>
<td>1-2 hr and 4-5 hr</td>
<td>1-2 hr</td>
<td>Hepatic</td>
<td>CYP2C19, CYP3A4</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>20, 40</td>
<td>1.6 hr</td>
<td>1-2.5 hr</td>
<td>Hepatic</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>15, 30</td>
<td>1.5-3 hr</td>
<td>0.9-1.5 hr</td>
<td>Hepatic</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>10, 20, 40</td>
<td>0.5-3.5 hr</td>
<td>0.5-3 hr</td>
<td>Hepatic</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Omeprazole/sodium bicarbonate</td>
<td>20/1100 &amp; 40/1100</td>
<td>0.5-3.5</td>
<td>0.5-3 hr</td>
<td>Hepatic</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>20, 40</td>
<td>2-2.5 hr</td>
<td>1 hr 3.5-10 in CYP2C19 poor metabolizers</td>
<td>Hepatic</td>
<td>CYP2C19, CYP3A4</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>20</td>
<td>2-5 hr</td>
<td>1-2 hr</td>
<td>Hepatic</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Drug</td>
<td>Common Side Effects</td>
<td>Pregnancy/Lactation</td>
<td></td>
<td></td>
<td></td>
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<td>-------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexlansoprazole</td>
<td>Diarrhea, headache, abdominal pain, nausea, URI, flatulence</td>
<td>Caution advised/choose alternate tx</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Esomeprazole                 | Headache, flatulence, diarrhea, abdominal pain, nausea, constipation  
*Rare: Pancreatitis | Caution advised/may use when breastfeeding |
| Lansoprazole                  | Headache, diarrhea, constipation  
*Rare: Pancreatitis | Caution advised/choose alternate tx      |
| Omeprazole                    | Headache, abdominal pain, nausea, diarrhea, vomiting flatulence  
*Rare: Pancreatitis | Caution advised/choose alternate tx      |
| Omeprazole/sodium bicarbonate| Headache, Diarrhea, abdominal pain  
*Rare: Pancreatitis | AVOID/choose alternate tx               |
| Pantoprazole                  | Headache, diarrhea, abdominal pain, nausea/emesis, ALT/AST elevation  
*Rare: Pancreatitis | Caution advised/may use when breastfeeding |
| Rabeprazole                   | Headache, diarrhea, nausea/emesis, abdominal pain, flatulence                      | Caution advised/choose alternate tx      |
PPI SUMMARY

• The absolute risk for serious side effects are so low that the fear of these risks SHOULD NOT drive your decision to prescribe PPI therapy

• When PPIs are prescribed appropriately their benefits exceed any real or potential risk

• D/C PPIs that are not prescribed appropriately
  • Always use the lowest dose for the shortest duration of time
HOT TOPICS IN THE MICROBIOME

• Fecal Microbiota Transplant (FMT)
• Colon Cancer
  • Environmental and dietary factors influencing colon cancer risk by modifying microbiome.
• Pancreatic Cancer and Pancreatic Diseases
• Liver disease: NAFLD, Fibrosis, Hepatocellular cancer
• IBD
• Mood disorders
• Opiate effect on Microbiome
• Mental health in adolescents
• Chronic illness
• Lack of oral nutrition contributing to toxicity of microbiome
• Athletes unique microbiome
CASE STUDY

• 33 y/o female presents to office with abdominal bloating and diarrhea
• Symptoms began 3 months ago
• Having diarrhea 2-3x per week with associated abdominal pain
• No nocturnal diarrhea, no blood in stool
• No recent travel or use of antibiotics
• No fever/chills or weight loss
  • Any thing else we should ask?
  • Recalls episode of gastroenteritis
• Has tried diet modification, probiotics and Loperamide prior to this consultation.
CASE STUDY

• PMHX: Denies
• Allergies: NKA
• Medications: OTC Multivitamin
• Social: No Smoking, Social ETOH (1-2 drinks per week)
• Family Hx: Mother with hypothyroidism, Father with DM.

• What else should we ask our patient?
CASE STUDY

• Physical Exam:
  • Vital signs are normal
  • Abdominal exam: + BS, soft, NTND, no mass, no organomegaly
  • Rectal exam: normal rectal tone, no heme noted during exam

• Labs:
  • CBC, Celiac profile, Fecal calprotectin, Stool studies all normal

• Any other tests for our patient?
  • Breath test?
CASE STUDY

• Can we make a diagnosis of IBS on our patient?

• What therapy would you recommend?

• Xifaxan 550mg po TID for 14 days

• Any other suggestions?
MAINTAINING A HEALTHY MICROBIOME

• DIET is the number one influence on the microbiome

• Avoid unnecessary therapies
  • ABX
  • PPI
  • Probiotics?

• Recognize patient population at high risk for alteration of the microbiome

• We can harness the power of the microbiome to prevent disease and restore health…and so much more to come

Eamonn, M Clinical Gastroenterology and Hepatology 2019;17:333–344
THANK YOU

Any questions?