



# **MAINTAINING A HEALTHY MICROBIOME**

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# DISCLOSURES

Kimberly Kearns, APRN has the following disclosures:

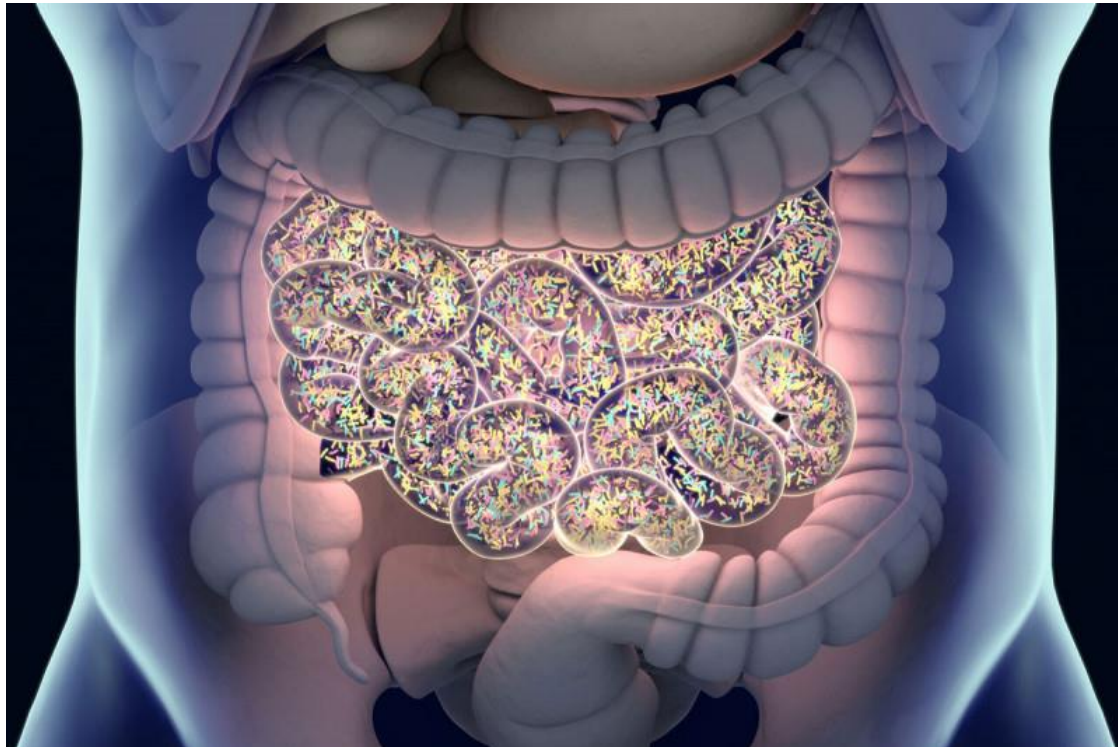
- Speakers Bureau
  - Medtronic
  - Salix Pharmaceuticals
  - Takeda Pharmaceuticals

# 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?

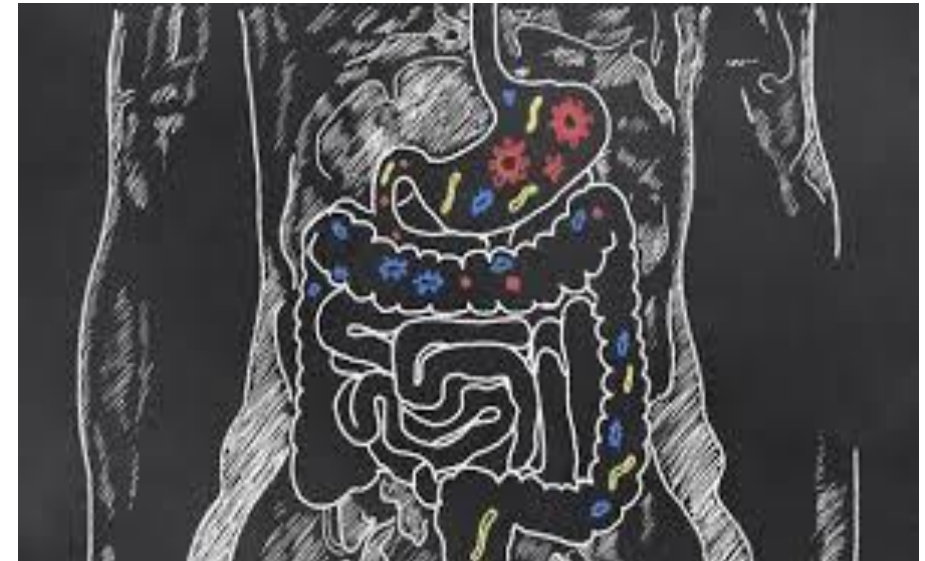
# WHAT IS THE GUT MICROBIOME?

- 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 MICROBIOME?

- 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

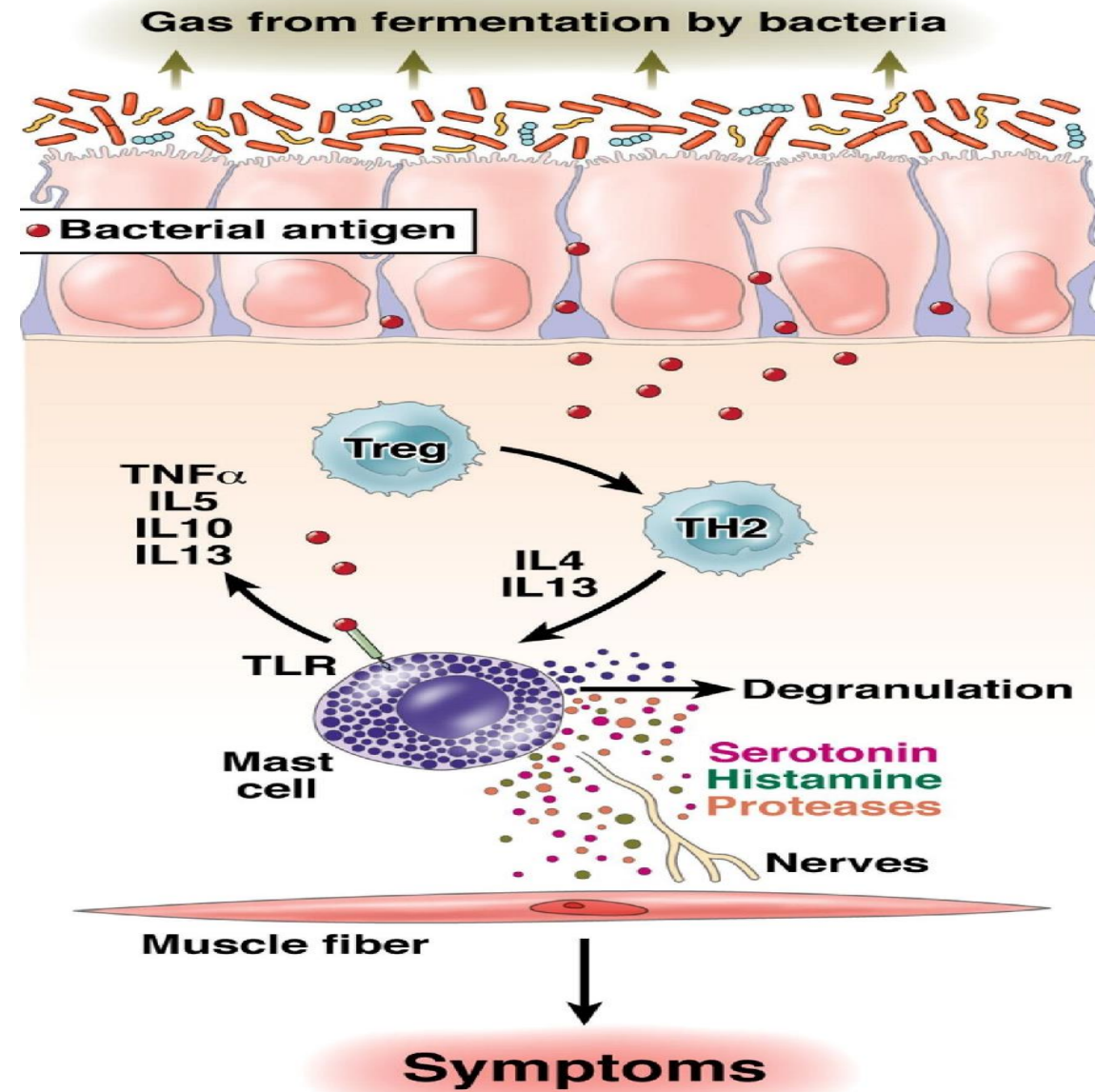
- Early life events
  - Birth
  - Breast feeding
  - ABX exposure
- Environment
- Diet
- Pathogens/Infection
- Health behaviors
  - Smoking
  - ETOH use
- Stress
- Medications
  - ABX
  - PPI
  - Metformin



# 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

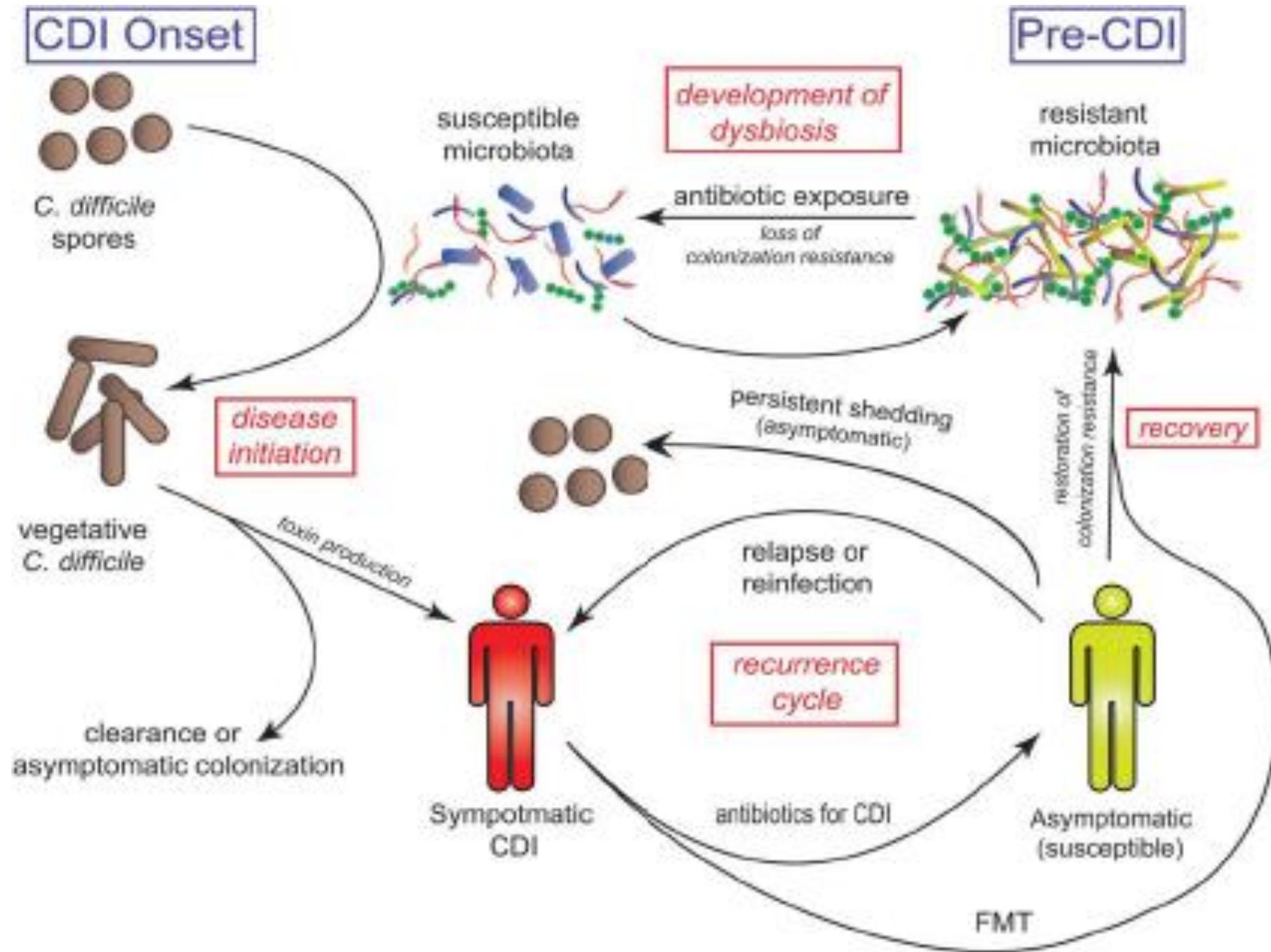




# CONDITIONS ASSOCIATED WITH ALTERATION IN THE MICROBIOME

- 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



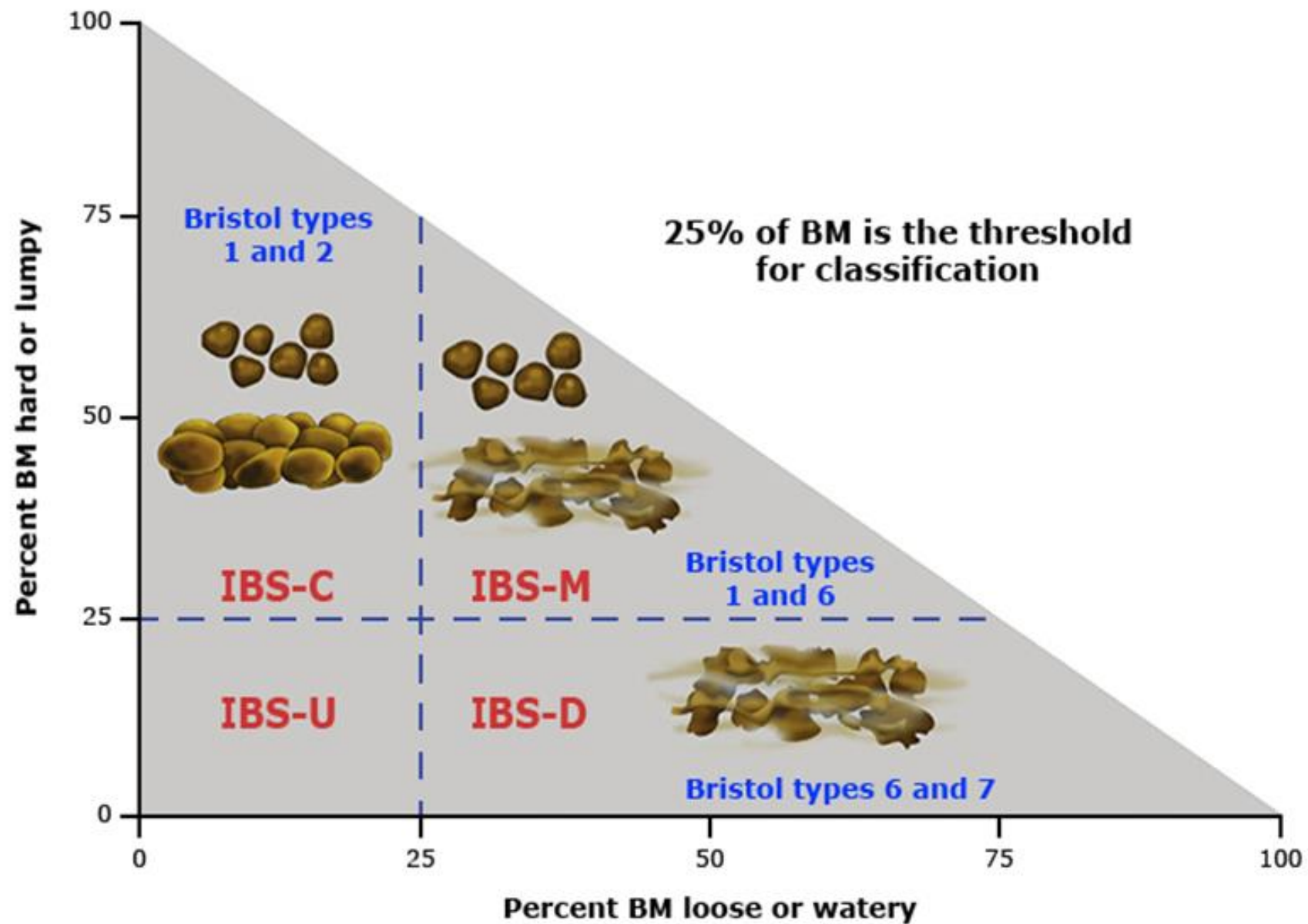
Associated with  
change in stool  
frequency



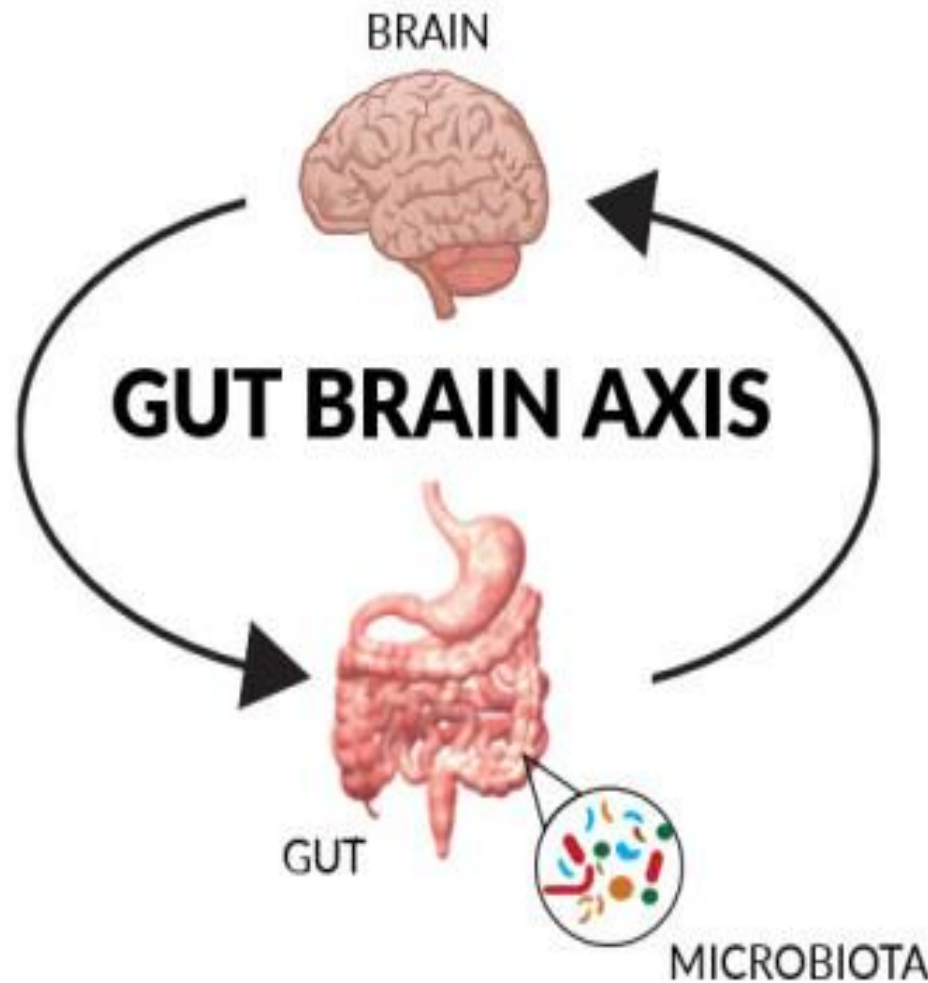
Associated with an  
change in the stool  
form/appearance

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





**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  $H_2$  and  $CH_4$  gas produced by the bacteria
  - Helpful in determining appropriate treatment ( $H_2$  vs  $CH_4$ )



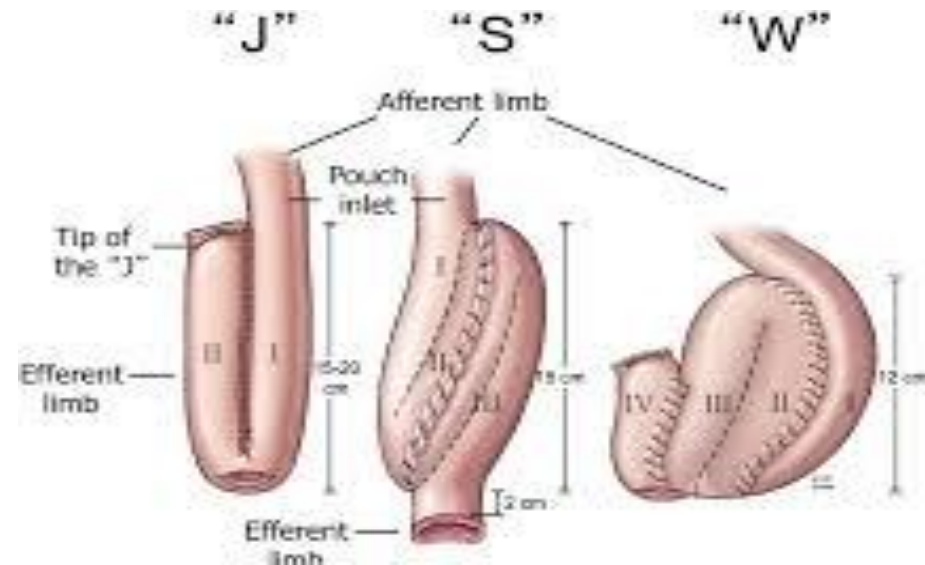
# ETIOLOGY OF SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

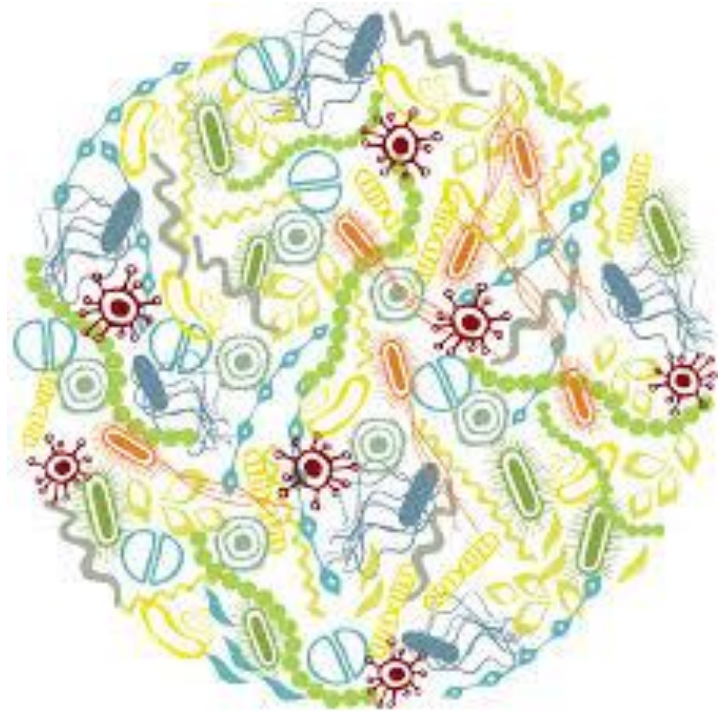
- Long term PPI use
- Anatomic Abnormality
  - Billroth surgery
- Small bowel motility disorder
  - Diabetes
  - Scleroderma
- Long term probiotic/prebiotic use
- NASH/Cirrhosis
- Narcotic use
- Pancreatic insufficiency
- Immunocompromised

# 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**

Therapy	Dosing	Target Condition
Antibiotic: Fidaxomicin (Dificid)	200 mg orally twice daily for 10 days	C-diff
Antibiotic: Metronidazole	500 mg orally three times daily for 10 days	C-diff Pouchitits
Antibiotic: Vancomycin	125 mg orally four times daily for 10 days	C-diff (now first line)
Fecal Transplant	Capsules: up to 40 Colonoscopy: 200-300g of followed by retention enema in 24 hours Retention enema: 200-300g for 5 days NJ tube: 25-30 gm x 1	C-diff Two or more recurrences of CDI and for whom traditional antibiotic treatment has been ineffective  ? IBD



Therapy	Dosing	Target Condition
Antibiotic: Rifaxamin (Xifaxan)	550 mg TID for 14 days  May repeat up to 2x	IBS SIBO-hydrogen predominant (off label)
Antibiotic: Neomycin	500mg po BID for 14 days with Xifaxan x 14 day	SIBO-methane predominant (off label)
Chloride Channel Activator/laxative: Lubiprostone (Amitiza)	8mcg po BID	IBS-C
Diet	Low FODMAP, no Gluten	IBS, SIBO, Diarrhea
Prebiotic: Psyllium	Up to 30g/d in divided doses	IBS, Constipation, Diarrhea
Serum-derived bovine immunoglobulin/protein isolate (SBI) Enterogam	5gms=1 packet 1-4 packets daily depending on stool frequency	Diarrhea, IBS, SIBO

# PHARMACOKINETICS

Drug	MOA	Time to peak plasma level	Half-life	Primary Excretion	Dose Considerations
Fidaxomicin	Macrolide	Unknown	11.7 hr	Primary Fecal Less than 1 % urine	No dose adjustments
Metronidazole	Antibacterial, Antiprotozal	1.2 hrs	7-8 hrs	Urine 60-80% Fecal 6-15%	Adjust for renal and hepatic impairment
Vancomycin	Glycopeptide	Unknown	4-6 hrs	Primarily fecal	Adjust for renal impairment
Rifaxamin	Non-aminoglycoside, derived from Rifamycin	1 hour	5.6 hours	Primary Fecal Less than 1% urine	Caution with severe hepatic impairment
Neomycin	Aminoglycoside	1-4 hours	2-3 hours	Primary Fecal – minimal Urine	Adjust for renal impairment
Lubiprostone	Chloride Channel Activator	1.1 hours	0.9-1.4 hours-??	Urine 60% Fecal 40%	Severe hepatic impairment
Enterogam	Immunoglobulin/ protein isolate	30-120 min Dose dep.	6 or more hours	Fecal	No adjustment needed

Drug	Considerations Common Side Effects	Pregnancy/Lactation
Fidaxomicin	S/E: Nausea, vomiting, abdominal pain, GI bleed, anemia, neutropenia	Cat B-use only if needed/ok w/breastfeeding
Metronidazole	No ETOH S/E: N/V, metallic taste, diarrhea, candidiasis, furry tongue	Contraindicated in 1 <sup>st</sup> trimester/Caution with breast feeding.
Vancomycin	S/E: Vomiting, flatulence, nausea (PO)	Ok for tx of C-diff/ ok w/ breastfeeding
Rifaxamin	Not systemically absorbed No known antibiotic resistance with re-treatment S/E Nausea, increase in AST/ALT	Avoid in pregnancy/ exercise caution
Neomycin	BLACK BOX: neuro/oto/nephro toxicity S/E: Nausea, emesis, diarrhea	Class D/Do not use while breast feeding
Lubiprostone	S/E of Nausea, give with food. Diarrhea, abdominal pain, bloating, dyspnea-1 <sup>st</sup> hour of dose	Avoid in pregnancy/Avoid when breastfeeding
Enterogam	2-4 weeks before improvement of symptoms then decrease dose. Made of beef protein S/E: Nausea, metallic taste, constipation and diarrhea	No data-use caution

# 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

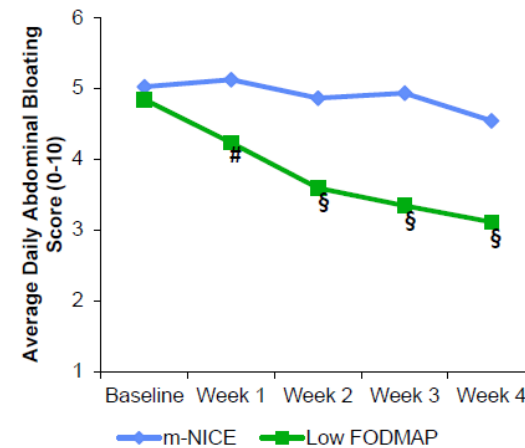
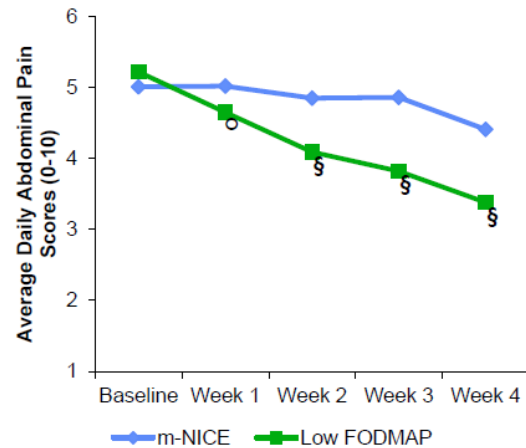
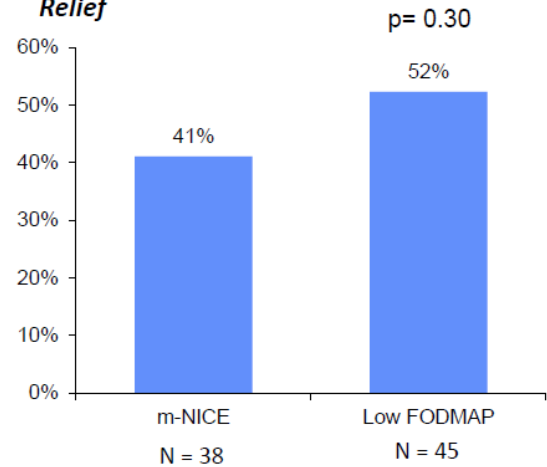
**Improvement in symptoms 67.7% in  
patients with eradicated SIBO**



# US RCT: Primary and Key Secondary Endpoints

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

% Adequate Relief



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

\* =  $p \leq .05$

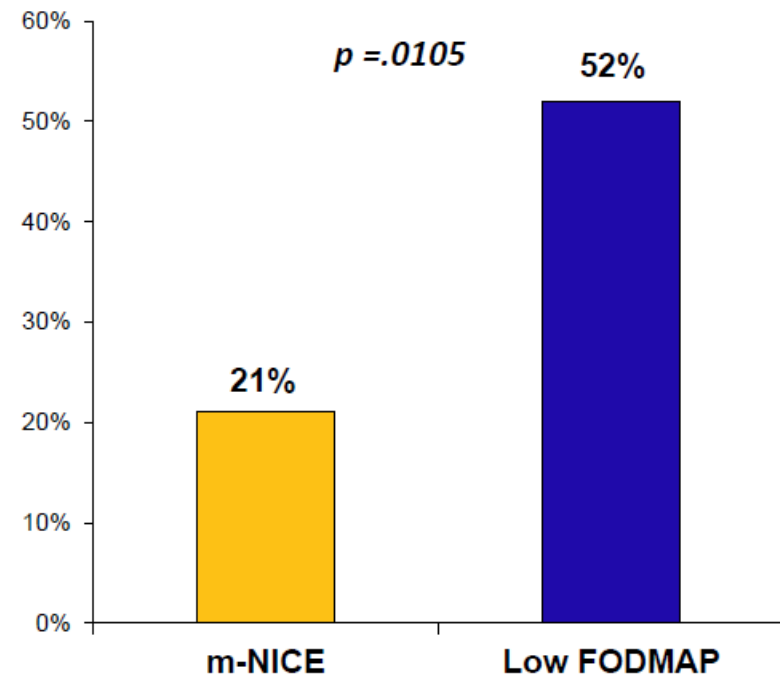
° =  $p \leq .01$

# =  $p \leq .001$

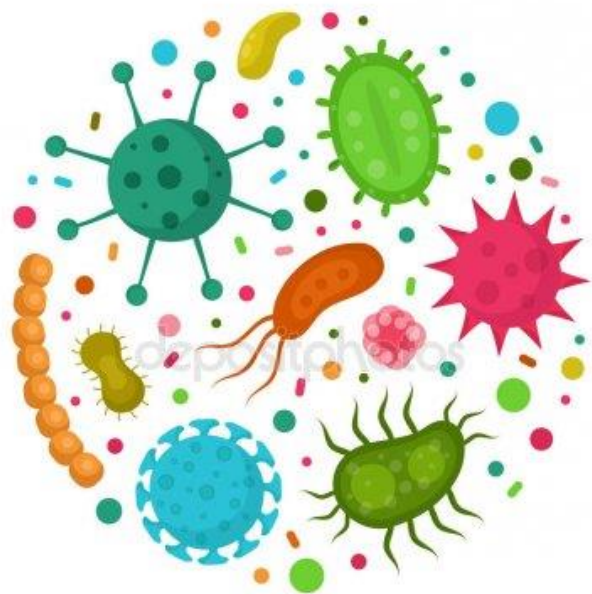
§ =  $p \leq .0001$

## US RCT: Effects on Quality of Life

*Proportion with Improvement  
from Baseline  $\geq 14$  in IBS-QoL Scores*

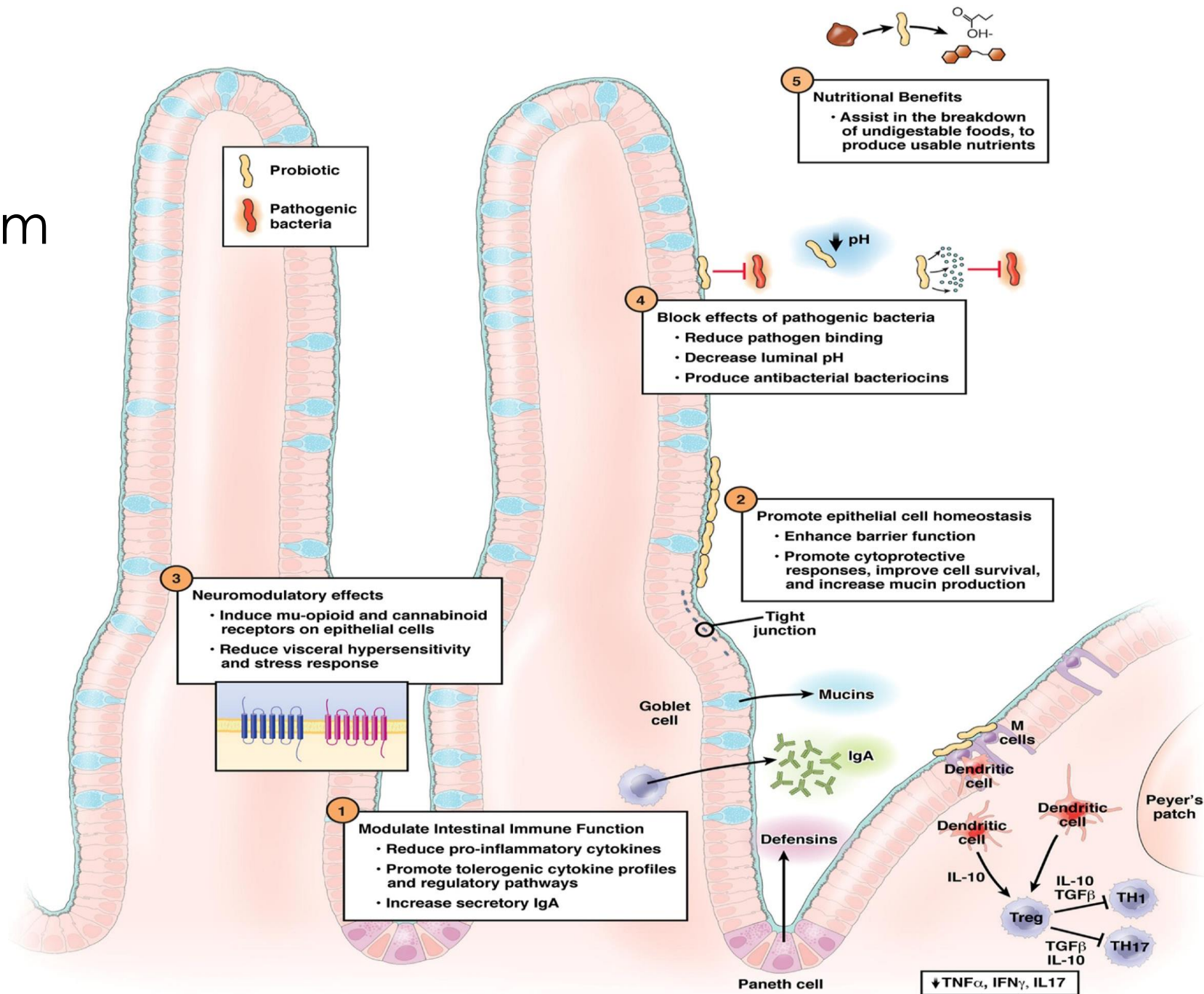


*Eswaran, Chey et al. DDW 2016*



# PROBIOTICS

# Probiotics Mechanism of action





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



Therapy: Probiotic	Dosing	Target Condition	Target Symptoms
L. Casei <b>(DanActive)</b>	65 ml per week x 4 weeks	Constipation or Diarrhea	Improvement in stool consistency and frequency at week 2 <small>Koebnick, et al, 2003 Can J gastro 2003; 17, (11) 655-659</small>
Lactobacillus Rhamnosus GG <b>(Culturelle)</b>	10 billion CFU 1 cap daily or 1 cap BID  BID for tx and 7 days after completion of tx	Diarrhea  PPX for diarrhea related to H-pylori tx	ABX associated Diarrhea  Infectious Diarrhea  <small>Shen, et al Gastroenterology, 2017; 152 (8) 1889-1990</small>

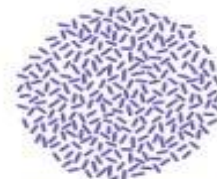
# PROBIOTICS



LACTOBACILLUS



LACTOCOCCUS



PROPIONIBACTERIUM



STREPTOCOCCUS THERMOPHILUS



BIFIDOBACTERIUM



BULGARICUS

# 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



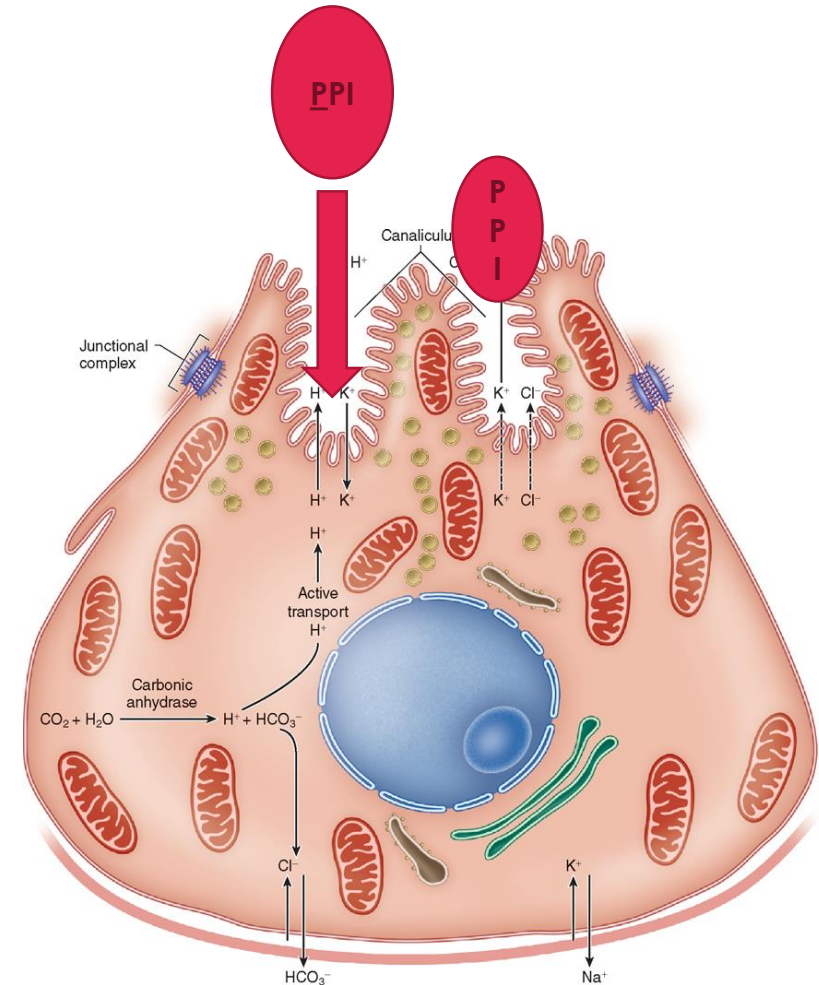
# ALTERATION IN MICROBIOME DUE TO PROTON PUMP INHIBITORS

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

Drug	Dosing mg	Time to peak plasma level	Half-life	Primary Excretion	Liver metabolism
Dexlansoprazole	30, 60	1-2 hr and 4-5 hr	1-2 hr	Hepatic	CYP2C19, CYP3A4
Esomeprazole	20, 40	1.6 hr	1-2.5 hr	Hepatic	CYP2C19
Lansoprazole	15, 30	1.5-3 hr	0.9-1.5 hr	Hepatic	CYP2C19
Omeprazole	10, 20, 40	0.5-3.5 hr	0.5-3 hr	Hepatic	CYP2C19
Omeprazole/sodium bicarbonate	20/1100 & 40/1100	0.5-3.5	0.5-3 hr	Hepatic	CYP2C19
Pantoprazole	20, 40	2-2.5 hr	1 hr 3.5-10 in CYP2C19 poor metabolizers	Hepatic	CYP2C19, CYP3A4
Rabeprazole	20	2-5 hr	1-2 hr	Hepatic	CYP2C19

Drug	Common Side Effects	Pregnancy/Lactation
Dexlansoprazole	Diarrhea, headache, abdominal pain, nausea, URI, flatulence	Caution advised/ choose alternate tx
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

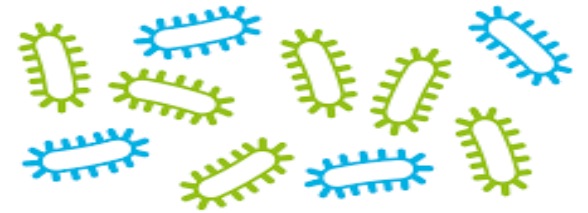
# PPI SUMMARY

- 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





# GUT MICROBIOTA FOR HEALTH

World Summit 2019

- 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

***THANK YOU***

Any questions?

