Promoting Gut Barrier Function for Better Health: Addressing Leaky Gut Through Diet

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TODAY'S AGENDA:

- Introduction & Housekeeping
- Speaker Introduction
- Presentation
- Q&A
- Closing

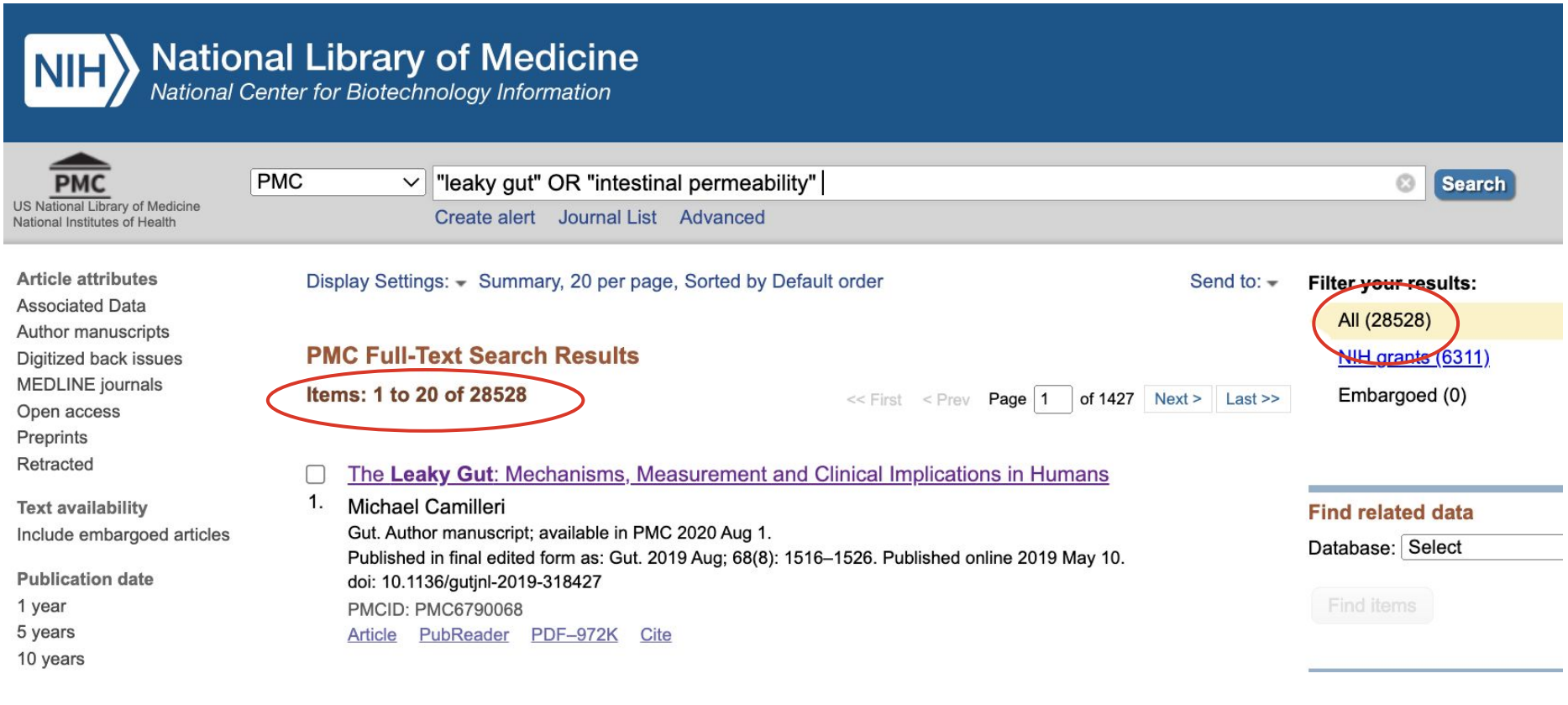
WEBINAR HOST:

Keith Hine MS, RD
VP of Healthcare, Sports & Professional Education
Orgain, LLC

WEBINAR PRESENTER:

Colleen Webb, MS, RDN
Registered Dietitian Nutritionist

Leaky Gut is HOT!



Learning Objectives

At the end of this presentation, participants will be able to...

1. Describe intestinal permeability (“leaky gut”) and its impact on human health.
2. Explain how dietary components and patterns influence the structure and function of the intestinal barrier.
3. Create nutrition interventions intended to improve intestinal permeability and gut barrier function.

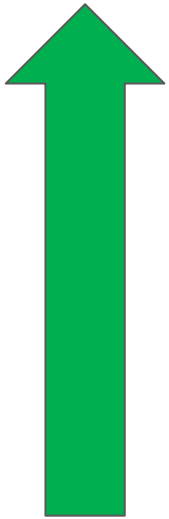
What is NOT Leaky Gut?

…But when that balance (gut microbiota) gets out of whack—say because of chronic stress, chronic constipation, exposure to environmental toxins like pesticides, eating a poor diet, or taking an antibiotic that wipes out a lot those microbes—**the "bad" bacteria cut holes in the fence and some of them, along with food particles and toxins, leak into the bloodstream…**

Source: Healthway

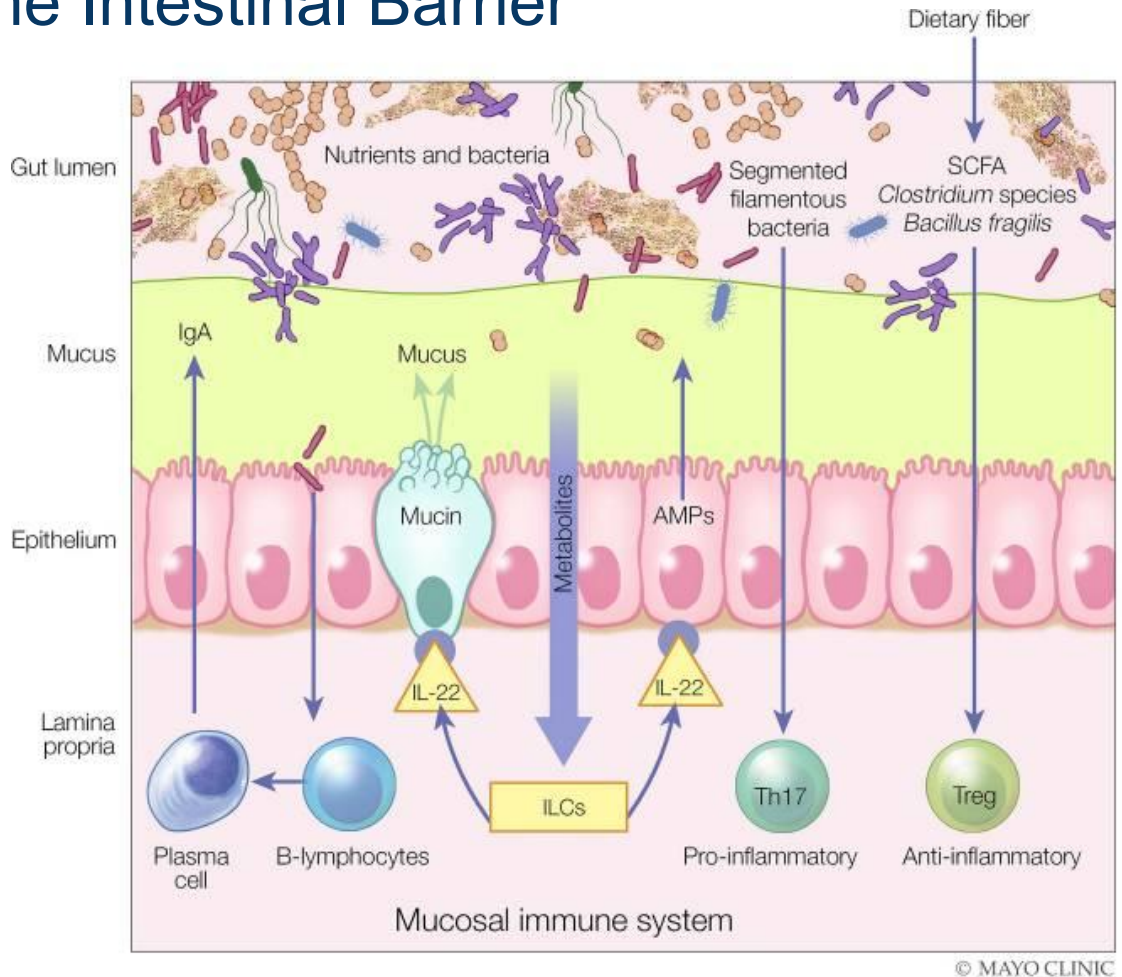
What is Leaky Gut?

- **Reduced barrier function with increased intestinal permeability**
- Permeability: The state or quality of a material or membrane that causes it to allow liquids or gases to pass through it. – Oxford Dictionary



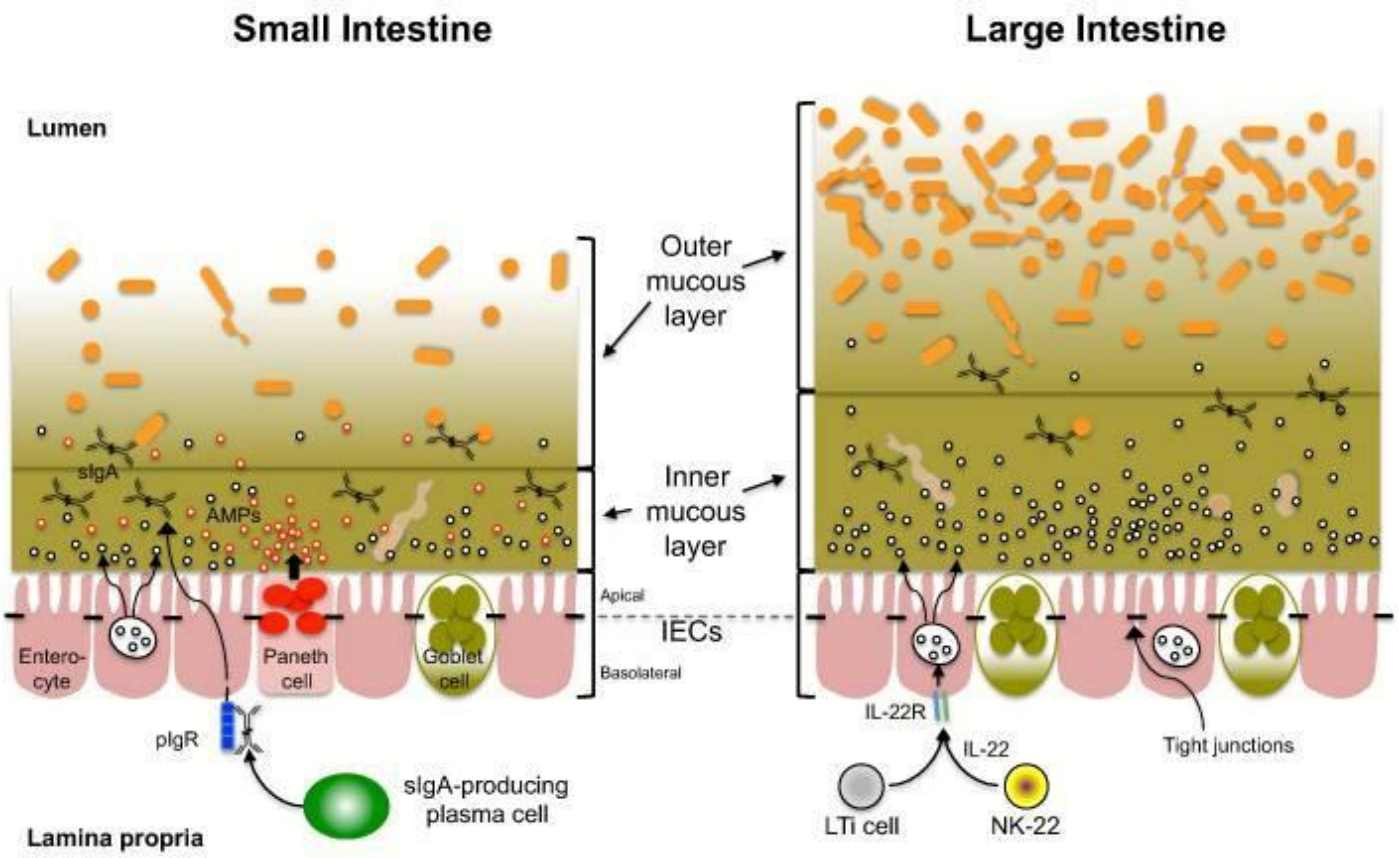
Should Allow In	Should NOT Allow In
Dietary nutrients Electrolytes Amino acids Short chain fatty acids Sugars Water Select microbial metabolites	Luminal microorganisms Microbial toxins (e.g. LPS) Viruses Food antigens Environmental toxins

The Intestinal Barrier

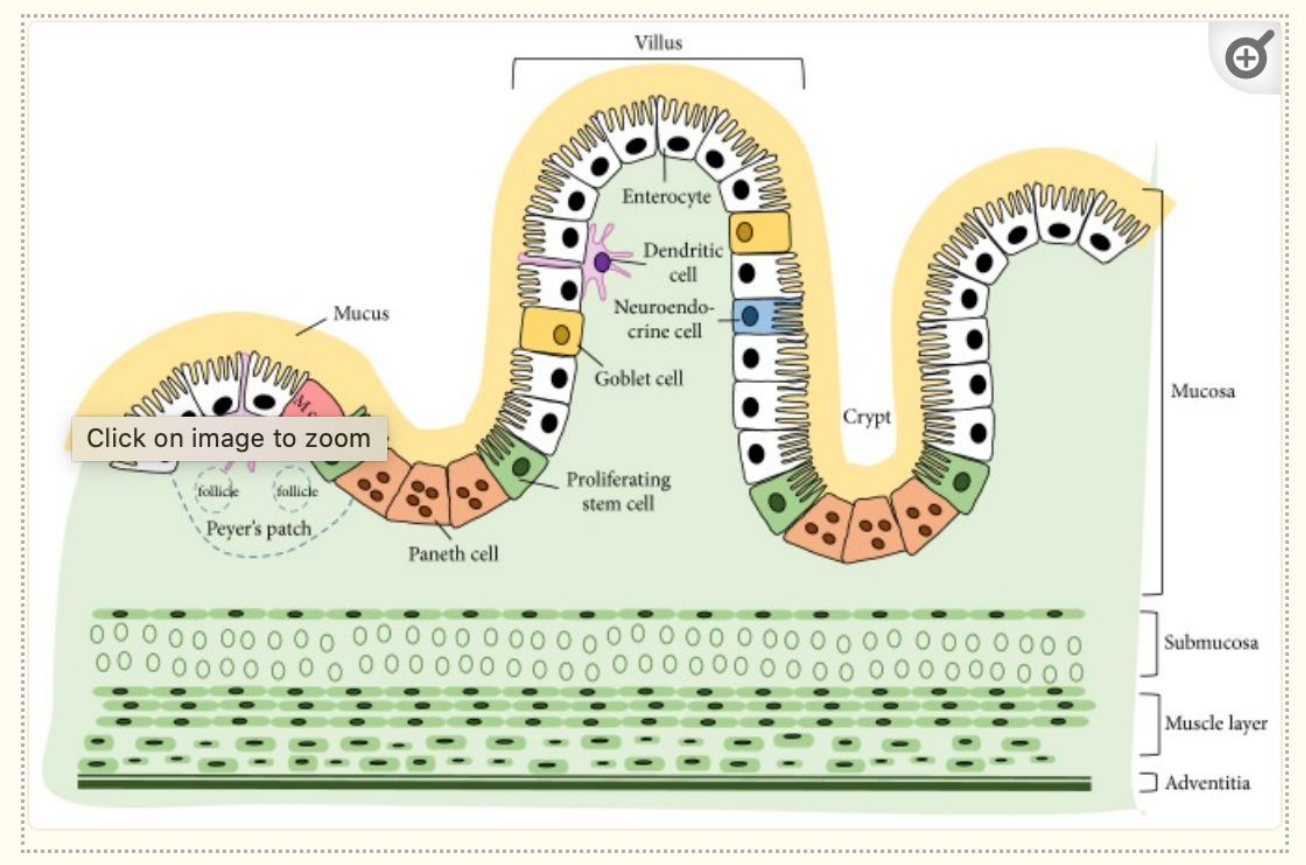


Bile
Gastric acid
Pancreatic juice

Mucus Layer

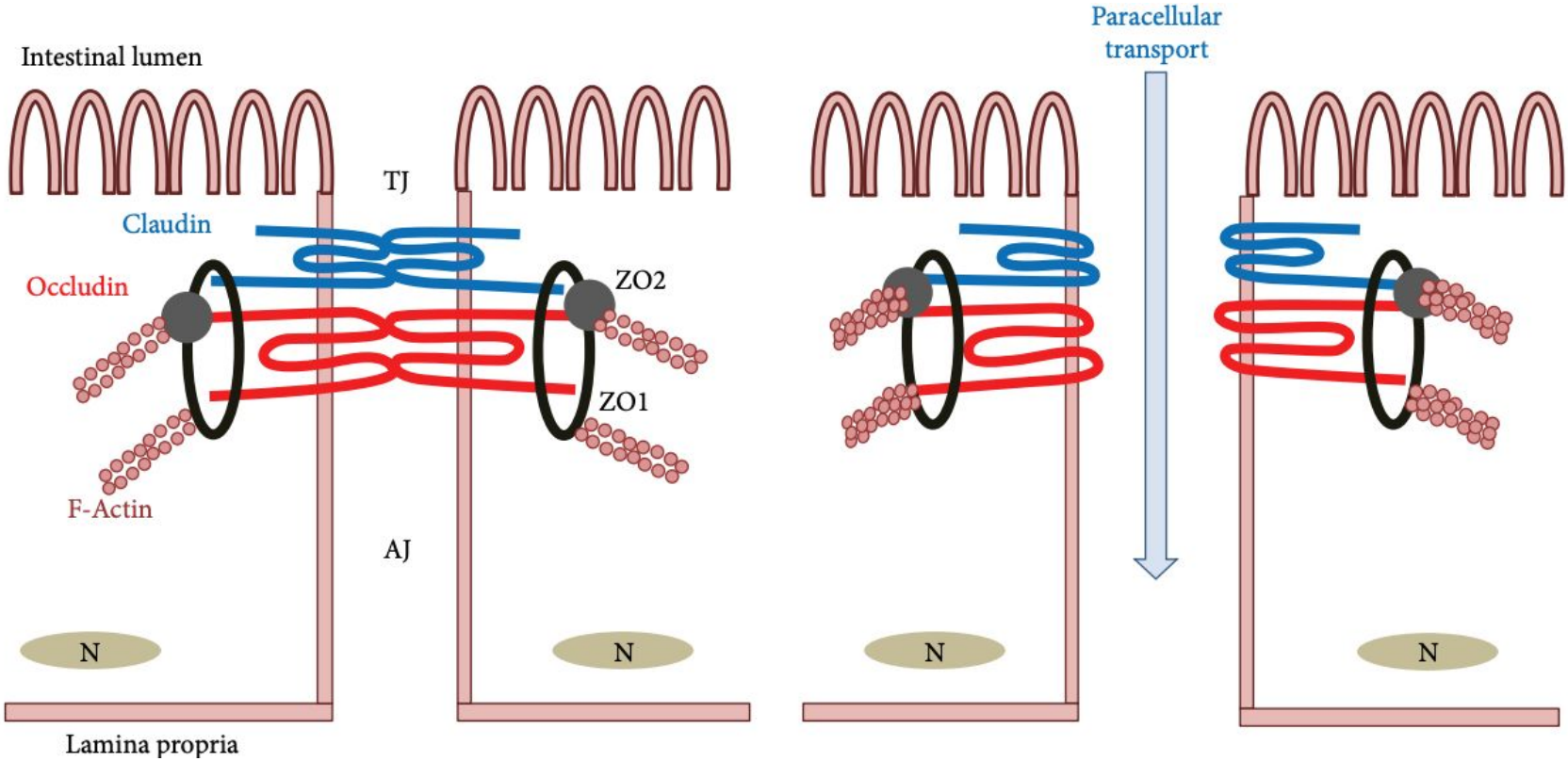

Small Intestine
Large Intestine
Lumen
Outer mucous layer
Inner mucous layer
sIgA
AMPs
Apical
IECs
Basolateral
Entero-cyte
Paneth cell
Goblet cell
pIgR
sIgA-producing plasma cell
Lamina propria
IL-22R
IL-22
Tight junctions
LTi cell
NK-22

The Intestinal Epithelial Barrier



Kong S, et al. Biomed Res Int. 2018.

Tight Junctions

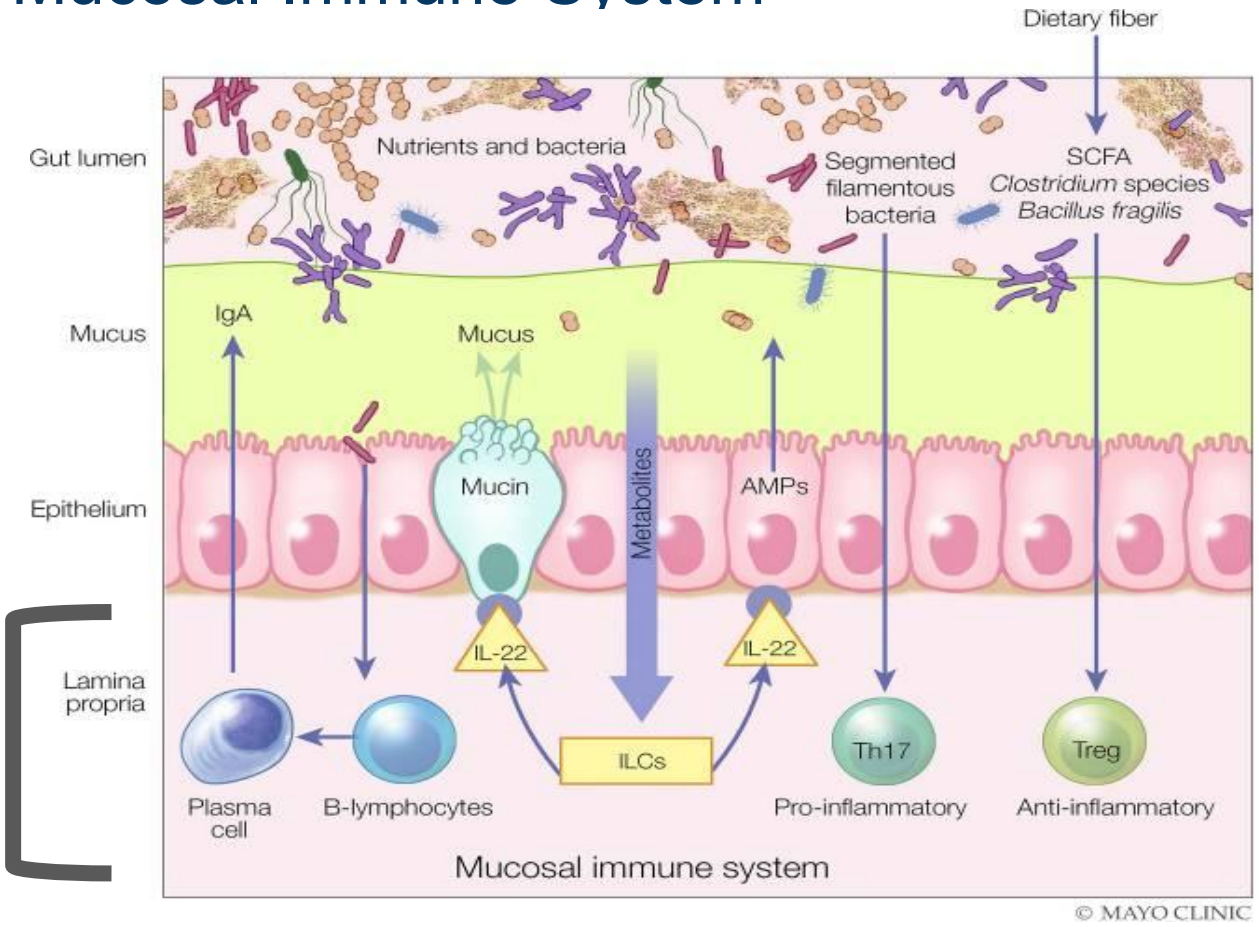


Lee B et al. J Immunol Res. 2018.

Leaky Gut Analogy

Dr. Alessio Fasano

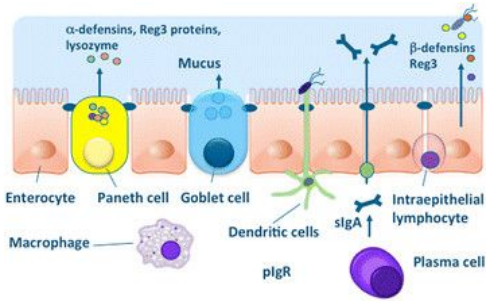
Mucosal Immune System



"Leakiness" through these sublayers occurs through…

1. Mucus degradation
2. Disrupted tight junctions
3. Dysregulation of epithelial cell death

Relationship Between Gut Microbiota and Barrier



- Metabolizes dietary components → active metabolites that impact gut barrier
- Prevents colonization by pathogens
- Balances mucus production
- Influences tight junctions

- Recognizes and tolerates commensal microbes
- Composition of the mucus layer affects the microbiota
- Provides microbes with mucin

Tests for Measuring “Leaky Gut”

Method		Limitations
Orally ingested probe molecules (e.g. lactulose-mannitol)	Assess barrier function	• Variations in the methodologies: urine collection time, sugar solution, study population • Variations in gut transit time, renal fx • Environmental contamination • Uncertainty of normal values
Circulating endotoxins (e.g. LPS, LPS-binding protein)	Markers of impaired barrier function	• Difficult to measure in human blood • Unclear specificity (LBP is promising)
Serum zonulin, intestinal fatty-acid binding protein (I-FABP)	Indicators of epithelial damage	• Commercial zonulin test fail to identify appropriate proteins • Zonulin correlates with BMI
Endoscopic biopsies (e.g. TJ expression, cell analysis)	Can identify breaks in the epithelium	• Invasive • Potentially impacted by sedation
Intestinal biomarkers (e.g. fecal calprotectin, Secretory IgA)		• Unclear specificity

Disorders or Diseases with Intestinal Permeability

Conditions with More Evidence

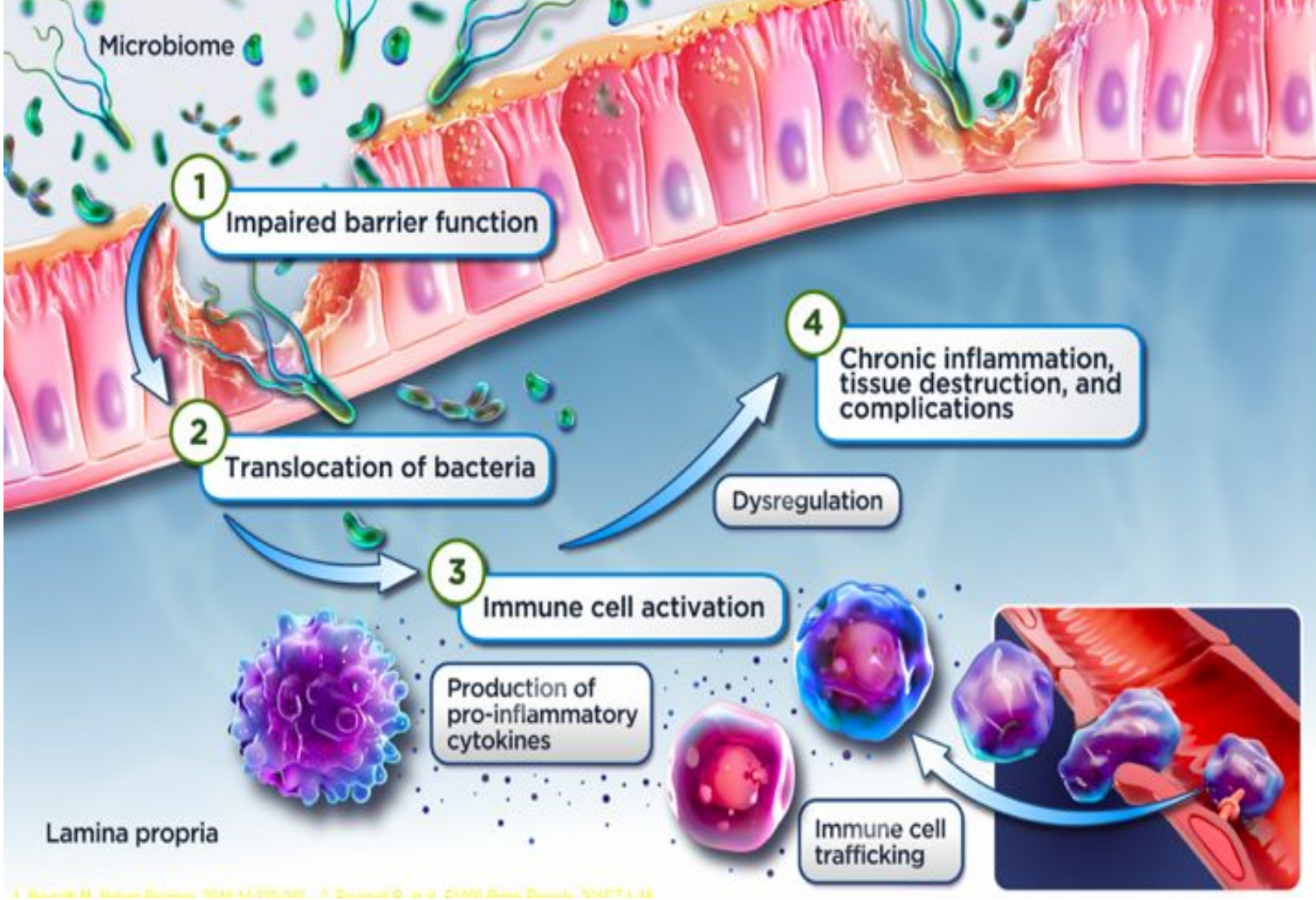
- IBD (Crohn's dz, ulcerative colitis)
- Celiac disease
- Non-celiac gluten sensitivity
- Enteric infections
- HIV / AIDs
- Necrotizing enterocolitis
- IBS

Conditions with Less Evidence

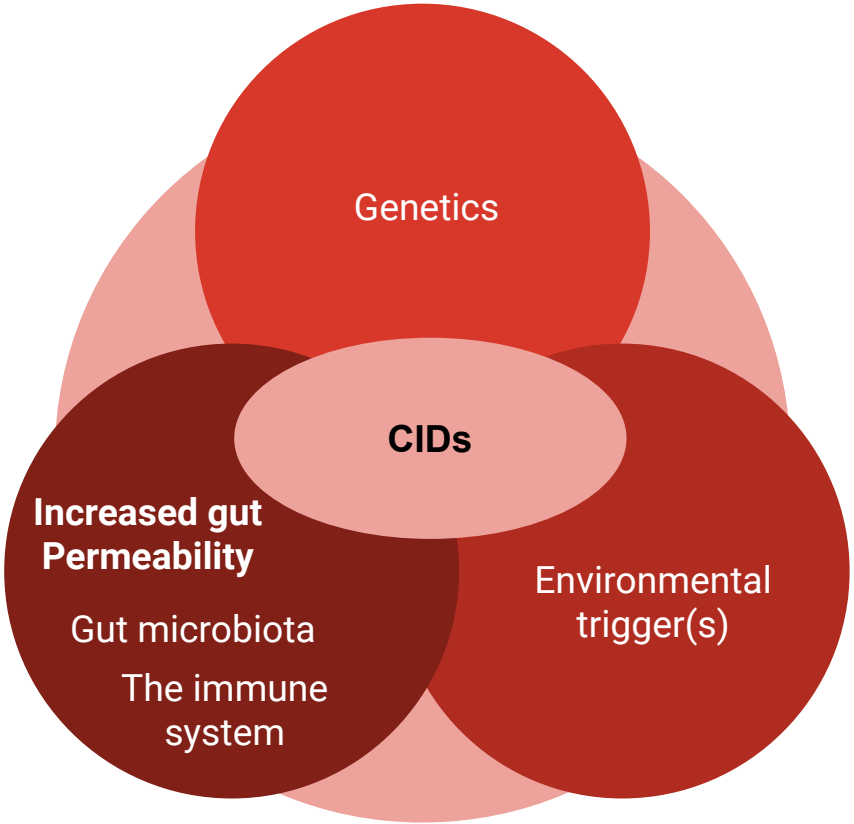
- Aging
- NAFLD
- Parkinson's
- Depression / anxiety
- Ankylosing spondylitis
- Multiple Sclerosis
- Obesity
- Sepsis
- Insulin Resistance
- Diabetes (Types 1 and 2)

Fasano A. 2020
Camilleri M. 2019.

An impaired gut barrier can lead to IBD onset and flares



Hypothesis of Chronic Inflammatory Diseases (CIDs)



How does diet affect the gut barrier?

Dietary Goals for Addressing Leaky Gut

Diet affects the gut barrier via direct interactions with immune and epithelial cells and indirectly by altering gut microbial composition and function.

GOAL: Maintain and or restore normal gut barrier structure and function.

Recommend patients eat foods and follow dietary patterns that strengthen the gut barrier.

Recommend patients limit or avoid foods that negatively impact the gut barrier.

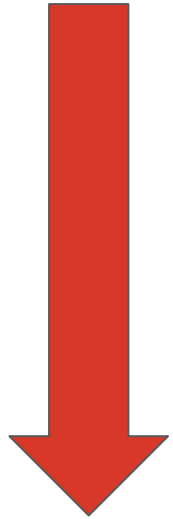
Key Dietary Components Associated with Changes in Gut Permeability

Desirable

- Dietary fiber
- Polyphenols
- Prebiotics
- Probiotics
- Zinc
- Glutamine
- Traditional anti-inflammatory style diets (e.g. Mediterranean)

Less desirable

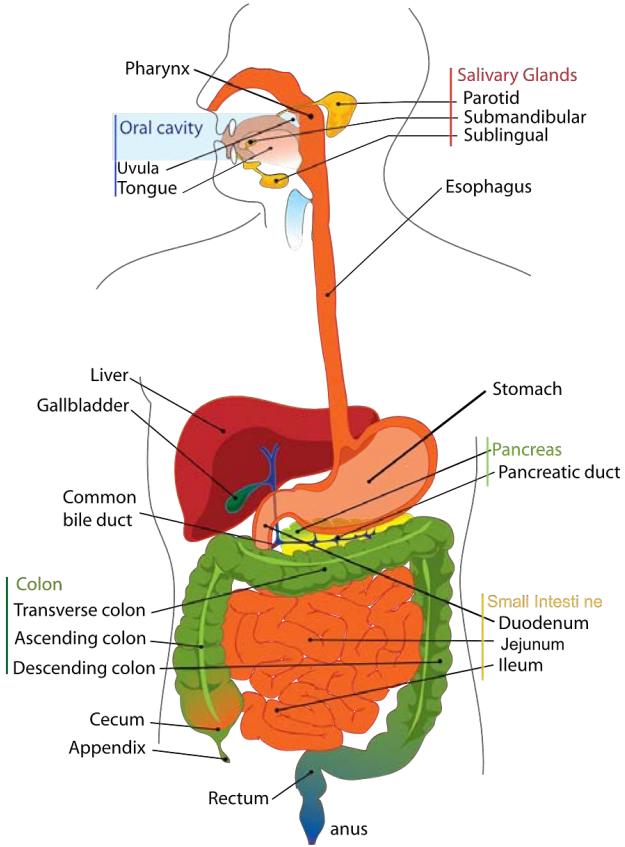
- Saturated fats
- Emulsifiers
- Alcohol
- Western style diet



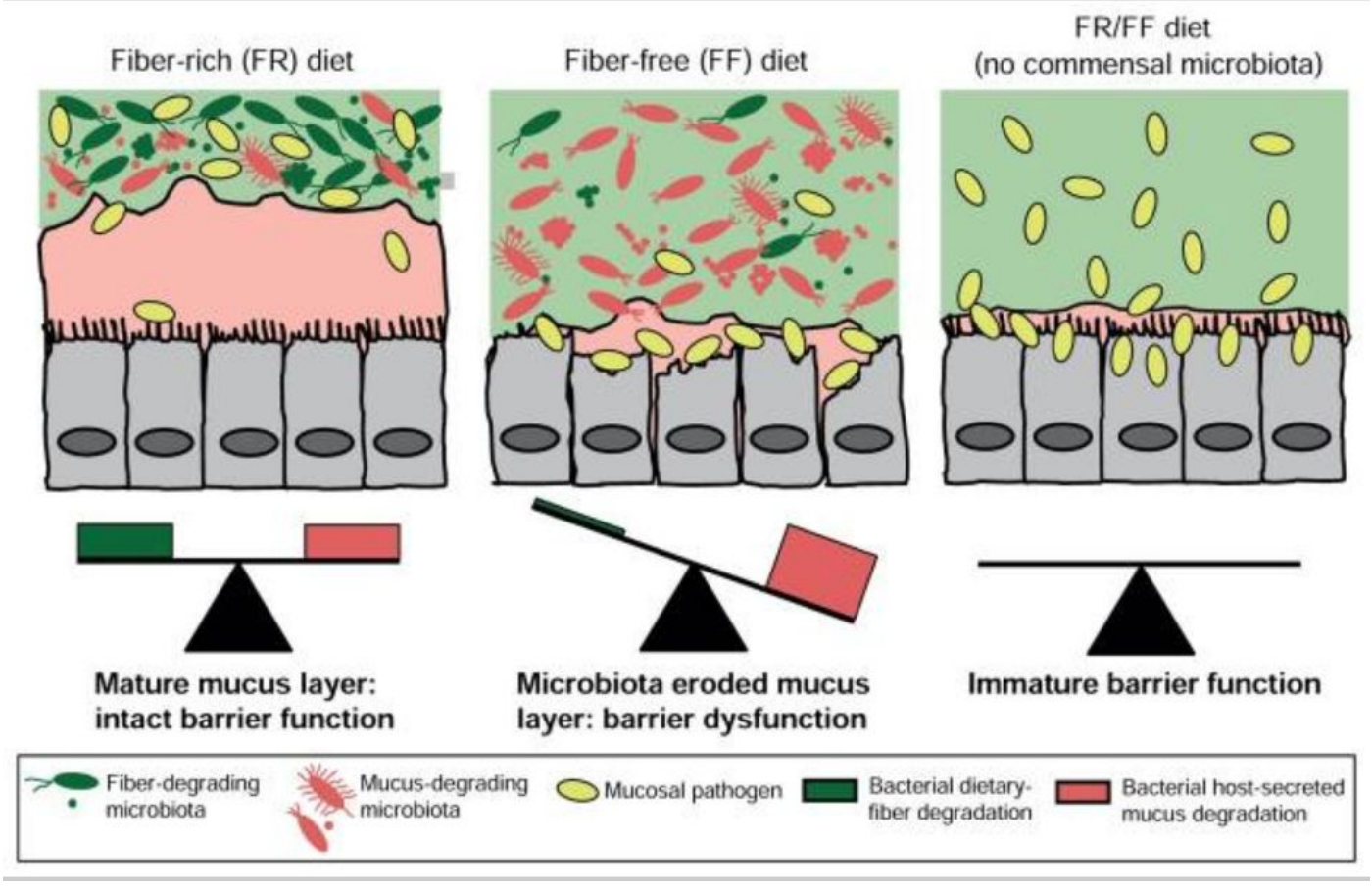
Recommend patients eat foods and follow dietary patterns that strengthen the gut barrier

Dietary Fiber

- Dietary fibers are non-digestible CHO found in plants
- Influence the gut barrier by altering …
  - The mucus layer
  - The gut microbiota
  - Fermentation byproducts

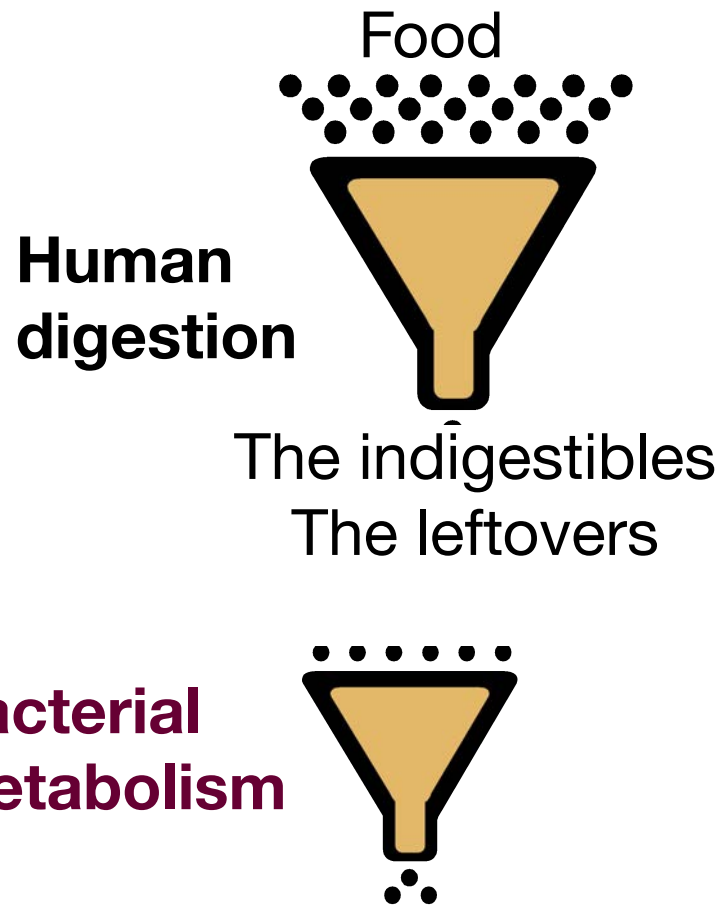


What's to Eat if Fiber Not Available?



Gut Microbial Metabolism

- Obtain energy and nutrients to live and reproduce
- Carry out reactions that human gut enzymes cannot
  - **Fermentation**
  - Denitrification
  - Sulfate reduction
  - Aromatic fission
  - Hydrolysis/deconjugation



Source: Johanna W. Lampe, PhD, RD

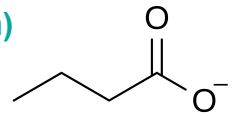
Fermentable Fiber (MACs) is Important for Mucosal Integrity

MACs (microbiota accessible carbs)

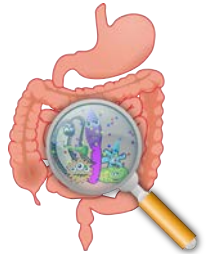
- Legumes/beans
- Nuts/seeds
- Chia, flax
- Oats, buckwheat
- Onions, artichokes
- Cooked and cooled rice/potatoes
- Wheat bran
- Inulin

Beneficial gut microbes

(fermentation)



SCFAs (e.g. butyrate)



Protects mucosal integrity

Silva JPB, et al. *Curr Pharm Des.* 2018

Key GI Benefits of Butyrate

#1 energy source for colonocytes

Strengthens the intestinal barrier

- Increases levels of mucin
- Helps to assemble TJ proteins
- Upregulates defensins

Reduces gut inflammation

Protects against several diseases, including colorectal cancer and IBD

A low fiber diet → Less butyrate → Increased permeability

"The single greatest predictor of a healthy gut microbiome is the diversity of plants in one's diet."

Dr. Rob Knight at DDW 2017

Dietary Recommendations to Help Diversify Fiber Intake

Follow the 1-2-3 Rule

Eat at least **1 vegetable at breakfast** (e.g. smoothie with baby spinach, scrambled eggs with veggies), **2 others at lunch**, and **3 new ones at dinner**.

Aim for 30+ Per Week

Eat **30+ *unique*** plants per week. Choose from vegetables, fruits, legumes, whole grains, nuts, seeds and fresh herbs. Get the whole family involved!

Modify Texture As needed

Gentle High Fiber Foods	Fiber (g)
Avocado, 1 fruit	10
Banana, medium	4
Creamy nut butter, 2 tbsp	3
Sweet potato, no peel, cooked, medium	4
Rolled oats, ½ cup dry	4
Hummus, 2.5 oz	3
Cooked carrots, 1 cup	5
Pureed butternut squash soup, 1 cup	4

Tips for Eating Vegetables on a "Low Fiber Diet"

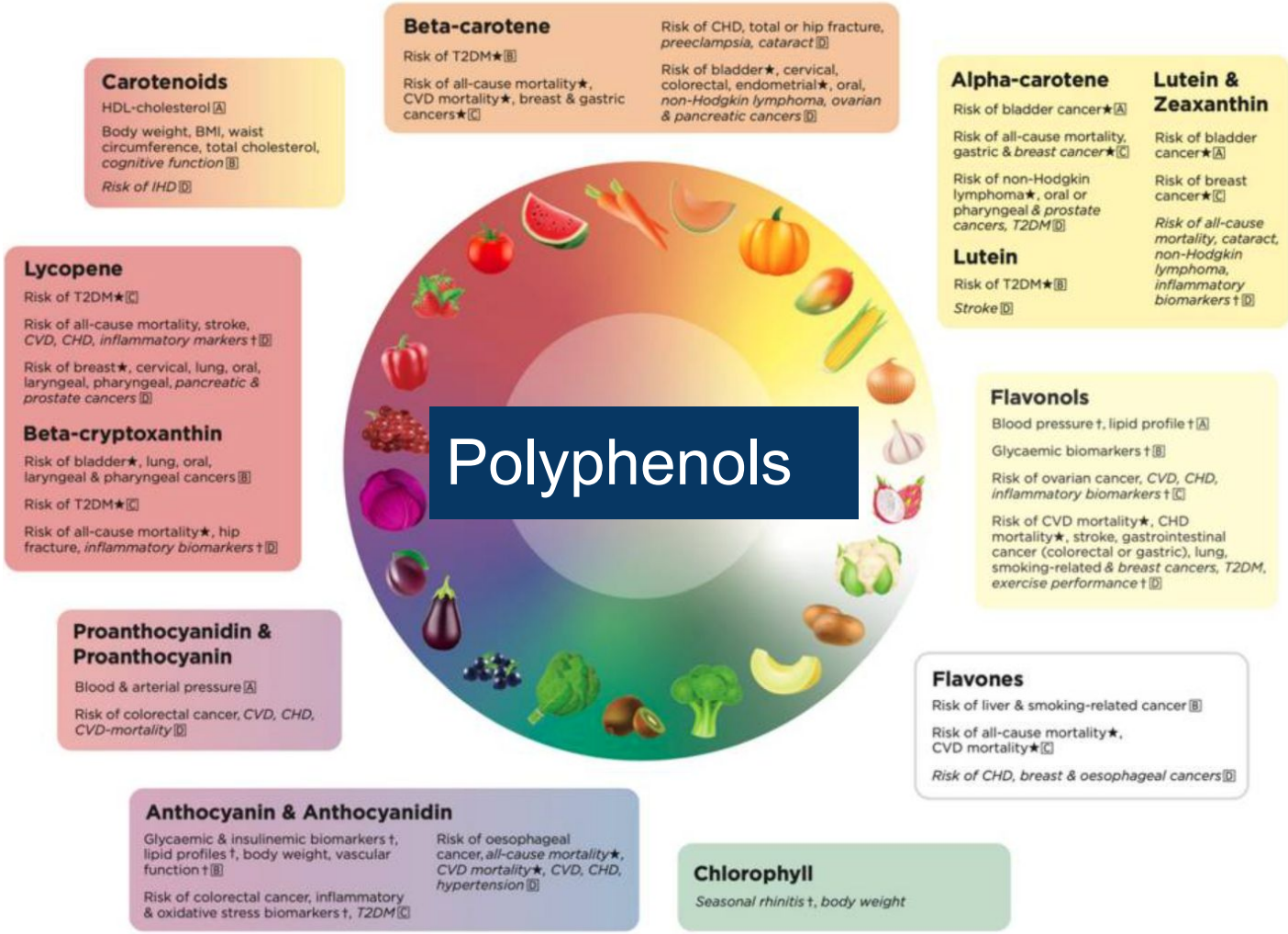
	EXAMPLES	HOW TO PREPARE
Starchy vegetables	• Parsnips • Plantains • Carrots • Cassava / yuka • Taro • Turnips / rutabaga • Sweet potato / yam • Beets	- Cook soft. - Boil and mash. - Roast root vegetables.
Leafy greens	• Spinach, baby spinach • Baby kale • Swiss chard • Collard greens • Bok choy • Choy sum	- Cook soft, such as steamed or lightly sauteed. - Blend into a soup or smoothie.
Others	• Broccoli florets • Green beans • Asparagus tips • Summer and Winter squash • English cucumber	- Remove thick skins and stalks. - Cook until very soft, if applicable - Blend into soup.

The IBD Nutrition Starter Kit for RDNs, Webb, Warren

Fiber Supplements?

- Isolated fiber
- Some are fermentable, others are not
- Fermentable fiber supplements are “prebiotic” fibers
- Most (not all) of these are rapidly fermented

Bottom line: Prebiotic fiber supplements might help improve gut permeability via the production of SCFAs, but they do not take the place of a wide variety of wholesome plant foods



Blumfield M. et al. 2022.

Can a Low FODMAP Diet Affect Gut Permeability?

Table 6 Key dietary components associated with potential to have positive effects on overall gut integrity

Component*	Common food sources
Prebiotic fibre	
Beta glucan	Barley, mushroom, oat
Fructans: Fructo-oligosaccharide Inulin Oligofructose	Asparagus, banana, barley, chicory root, garlic, honey, Jerusalem artichoke, leek, nectarine, onion, scallion, rye, wheat
Galacto-oligosaccharide	Cashew, legume (chickpea, red kidney bean, soybean, split pea), milk, pistachio, squash (butternut, pumpkin)
Pectin	Apple, banana, broccoli, carrot, dried pea, grapefruit, lemon, orange, potato, tomato
Resistant starch	Banana, legume (black bean, dried pea, fava bean, lentil, pinto bean, soybean), whole grain (barley, oat) NOTE: Cooling of cooked starchy food (eg, legume, pasta, potato, rice) increases resistant starch content
Xylo-oligosaccharide	Bamboo shoots and other vegetables, fruit, honey, milk

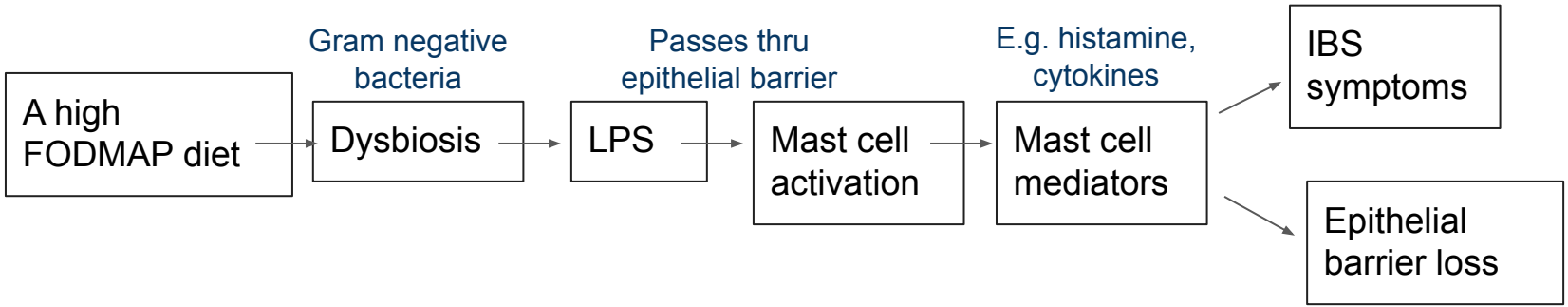
- Effects on gut microbiota are unknown
  - A 4-week low FODMAP diet has been shown to reduce luminal bifidobacteria+

Camilleri M et al. 2022.

Recent Findings Re: FODMAPs and Gut Barrier Fx

In rats, a high FODMAP diet impaired barrier function

- In IBS-D patients, gut barrier function improved after 4 weeks on low FODMAP diet (this correlated with symptom improvement)



Singh et al. 2022.

Probiotics and Leaky Gut

Table 5 Human in vivo studies that have included studies of intestinal barrier function in diseases/models associated with increased permeability

Human studies with probiotics including intestinal permeability/barrier

Probiotic (Ref.)	Study design	# Participants, treatment duration	Effect on permeability	Other effects
Viable vs sonicated probiotics[89]	Randomised, double-blind, placebo-control trial	28 critically ill patients; 7 days	No significant difference in intestinal permeability measured by lactulose: mannitol ratio	
Bifidobacterium adolescentis IVS-1 vs *B. lactis BB12*, +GOS prebiotic, 6 treatment arms[90]	Aspirin challenge; randomised, double-blind, lactose control trial	94 obese (BMI 30–40) patients; 3 weeks	Bifidobacterium IVS-1 but not B. lactis BB-12 reduced permeability (sucralose:lactulose ratio); GOS prebiotic also effective alone	No synergistic effect between prebiotic and probiotic
L. plantarum WCFS1, CIP104448, TIFN101 or placebo[91]	Indomethacin stressor; double-blind, placebo-control, 4-way crossover trial	10 healthy; 7-day oral treatments with 4-week washouts between each	Indomethacin increased lactulose:rhamnose ratio; no difference between baseline and on treatment lactulose:rhamnose ratio for any treatment vs placebo	Integrin pathway and Actinin α4 gene upregulated by *L. plantarum* TIFN 101; Claudin 5 gene downregulated by *L. plantarum* WCFS1; Claudin 19 gene downregulated by *L. plantarum* CIP104448
3-week kefir supplementation compared with 3-week milk supplementation[92]	Crossover intervention study	28 overweight asymptomatic adults	Greater improvement on serum zonulin levels with kefir	Similar improvement in lipid profile and serum glucose with both supplementations. CRP, adiponectin and appetite unaffected

CRP, C reactive protein; GOS, galacto-oligosaccharides.

Camilleri M et al. 2022.

Glutamine and Leaky Gut

- Glutamine deprivation is associated with increased markers of intestinal permeability
- Several animal studies support role for glutamine in maintaining and/or improving gut barrier function
- Select human studies…

Post-infectious IBS-D w/ increased GI permeability (n=54)	**Crohn's patients in remission (n=15)**
5 g TID x 8 weeks → 14-fold greater efficacy for improving IBS symptoms and GI permeability Zhou Q, et al. Gut. 2019.	0.5 g/kg IBW/day x 2 months → improved GI permeability (control group getting whey protein had similar results) Benjamin J, et al. Dig Dis Sci. 2012.

Zinc and Leaky Gut

- Helps to maintain and repair the intestinal barrier
- A zinc deficiency contributes to intestinal inflammation and an impaired gut barrier
- Supplementation with **zinc sulfate** improved gut permeability in patients with quiescent Crohn's disease (n=12) Sturniolo 2001
- In healthy volunteers, supplementation with **zinc carnosine** mitigated NSAID induced changes in gut permeability (n=10, 37.5 mg BID) Mahmood 2007

Recommend our patients avoid/limit foods and dietary patterns that weaken the gut barrier

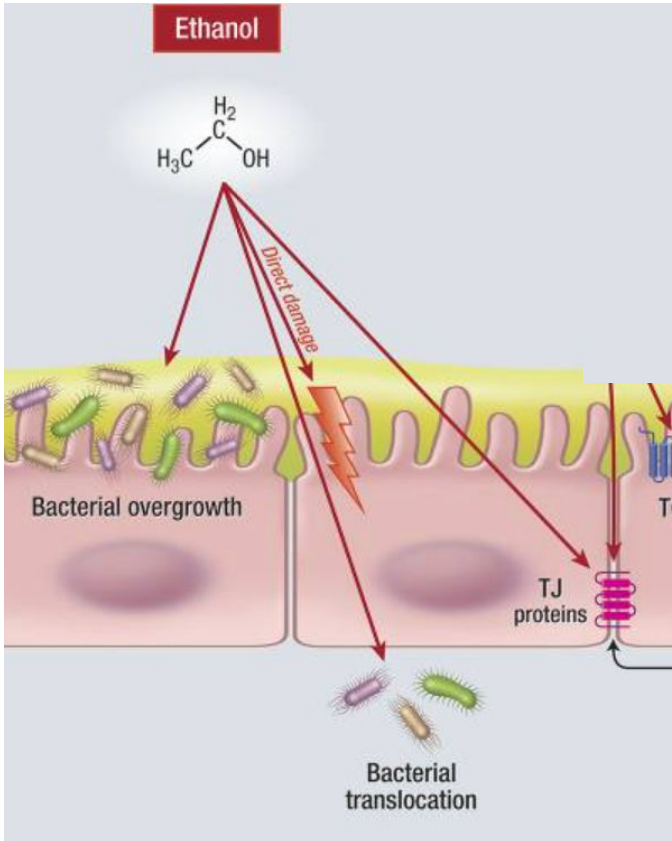
- Alcohol
- Emulsifiers
- High Fat Diet
- Standard American Diet / Western Diet

Alcohol and Gut Permeability

Both acute and chronic alcohol use alter gut permeability.

Potential mechanisms:

- EtOH directly damages epithelial cells
- Alters TJ structures
- Depletes goblet cells (less mucus secretion)
- Changes in the microbiota
- Alters SCFA production and circadian rhythm
- Chronic EtOH → altered microbiota composition, IBO and bacterial translocation

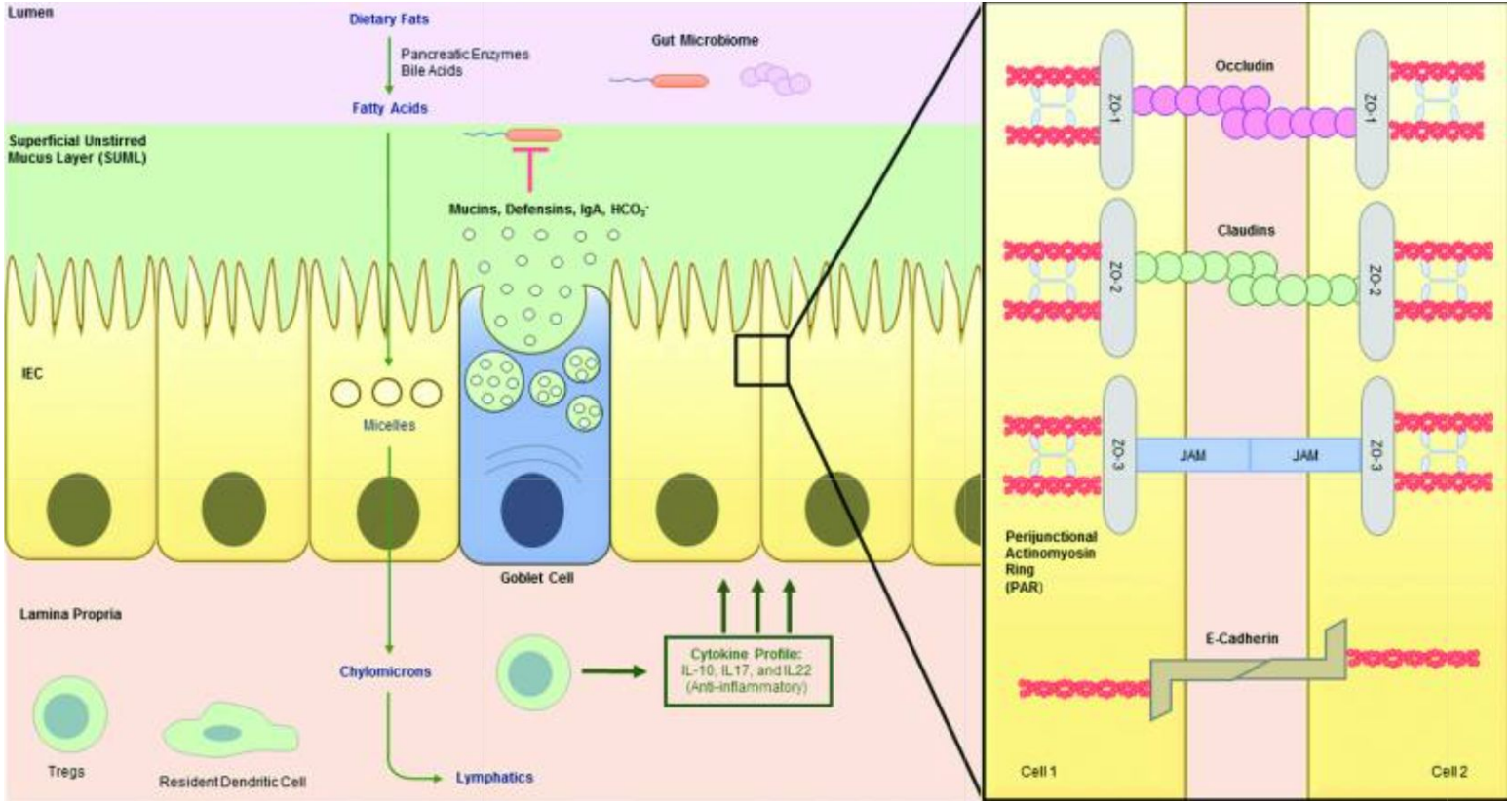


Khoshbin K et al. 2020.

Alcohol: Clinical Application

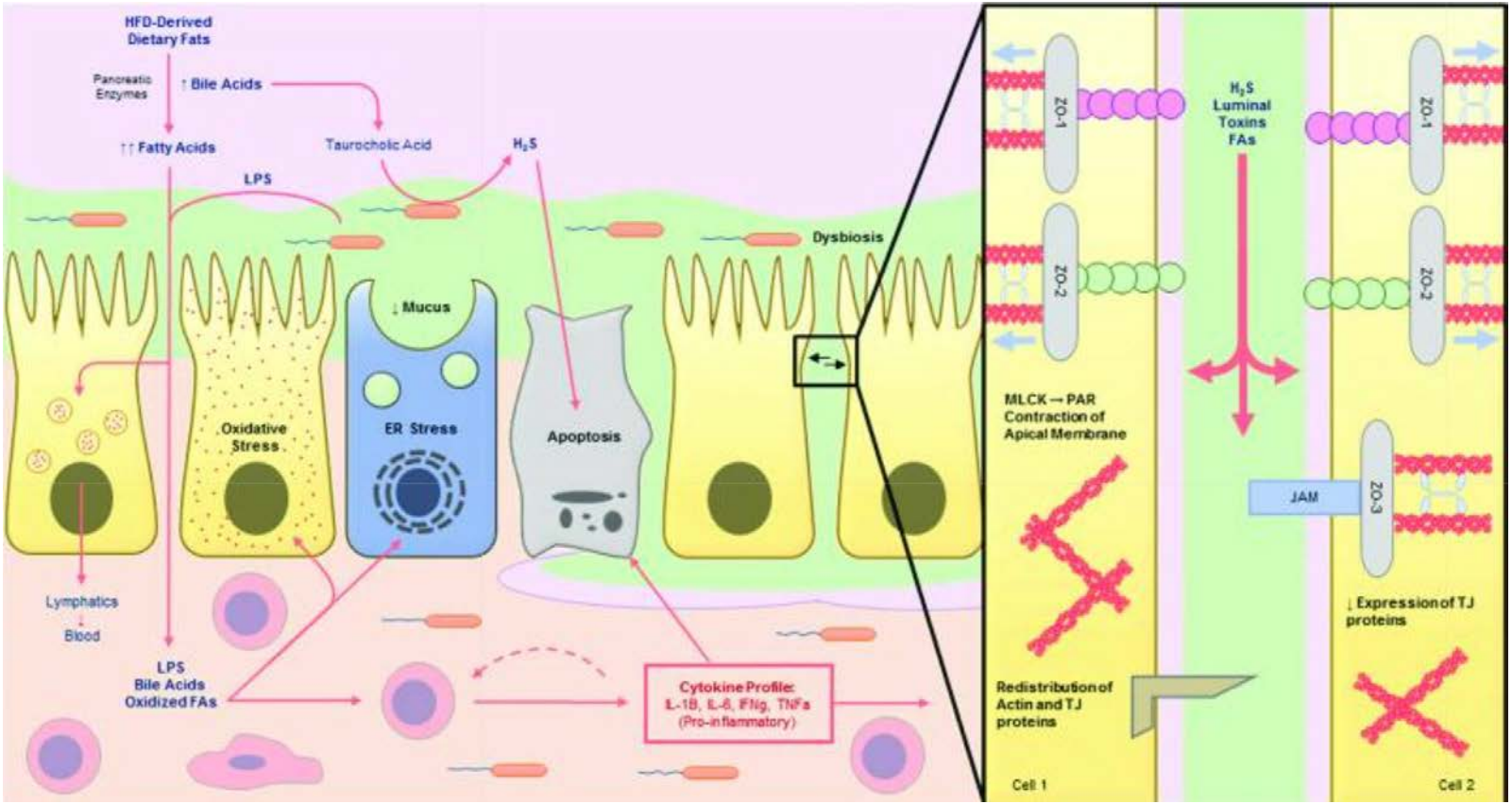
Answering Patients' FAQs	
Can I have *any* alcohol?	• Educate: One serving of alcohol is a/w gut permeability • Check meds for contraindications • For most, recommendations are same as for healthy population
What alcohol is best?	• Red wine has beneficial polyphenols • Potential benefits not reason to start drinking
What alcohol is worst?	• Don't know • However, beer tends to be the most offensive trigger for symptoms

Intestinal Barrier System Under Normal Dietary Conditions



Rohr MW et al. Adv Nutr. 2020.

Intestinal Barrier System Under a Chronic High-Fat Diet (HFD)



Rohr MW et al. Adv Nutr. 2020.

High Fat Diets (HFD) Lead to Gut Permeability

- HFD disrupts the intestinal barrier system via a variety of mechanisms:
  - Reduces “tightness” of TJ proteins
  - Inhibits mucus secretion from the goblet cells
  - Alters the composition and functionality of the gut microbiota
  - Enhances LPS update → metabolic endotoxemia
  - Stimulates the production of bile acids that disrupt the gut barrier and favor bile acid-degrading microbes
  - Promotes pro-inflammatory signaling cascades

Does the type of fat matter?

In humans…

- Lyke et al showed an ^in serum endotoxin (SE) concentration during postprandial period after eating a high-saturated fat meal, decreased SE after n-3 meal and no effect after n-6 meal (n=20 healthy adults)
- Multiple studies have shown how different types of fatty acids produce different changes in gut microbiota

In animals…

- Diet rich in SF increased permeability; fish oil restored barrier function and reduced inflammation
- Diet with n-6 showed ^levels of metabolic endotoxemia and low grade inflammation whereas high levels of n-3 decreased production of LPS and intestinal permeability

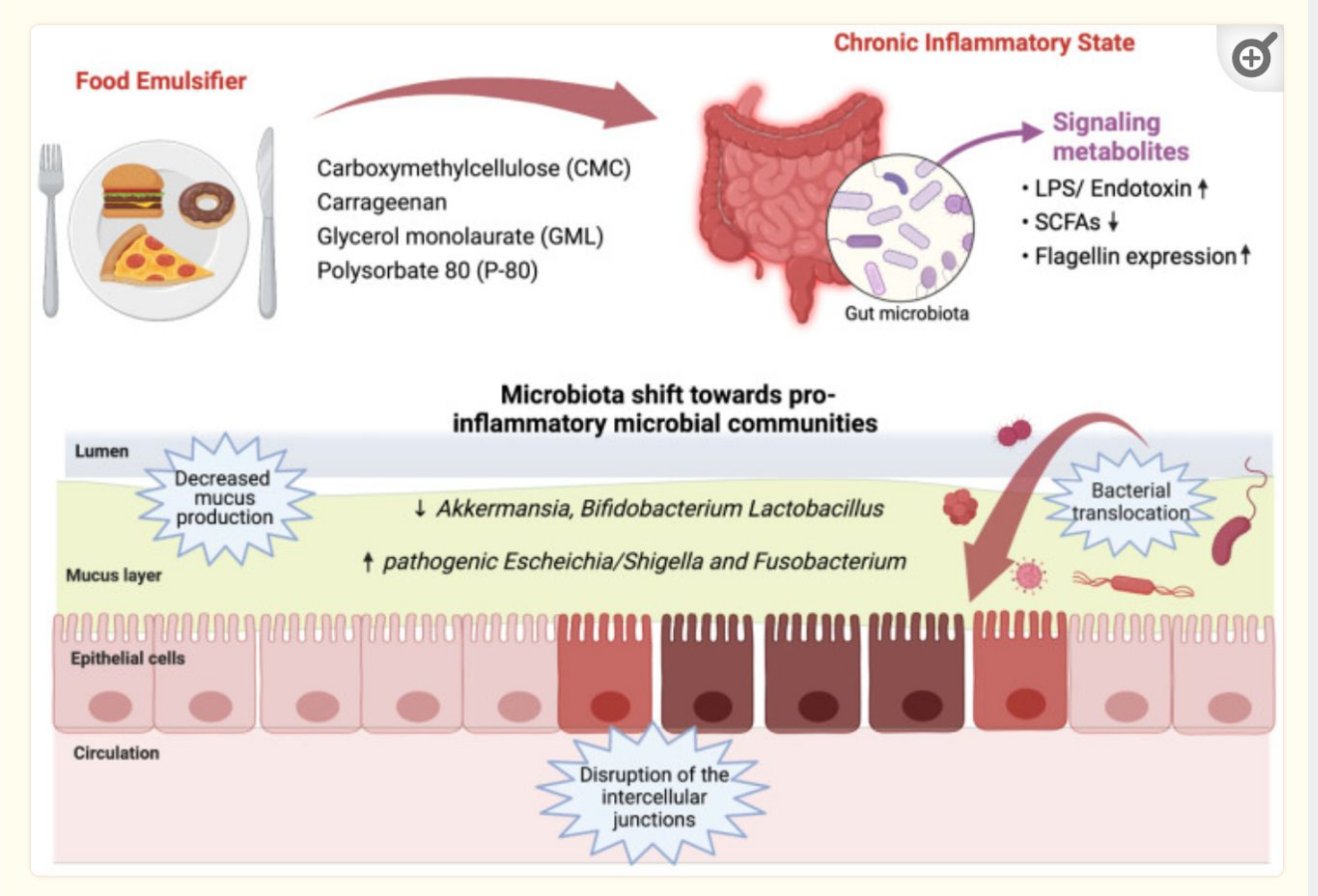
Lyte et al. 2016.
Netto et al. 2018.

Dietary Emulsifiers

- Complex molecules used in food products to improve quality of the final product and extend shelf life

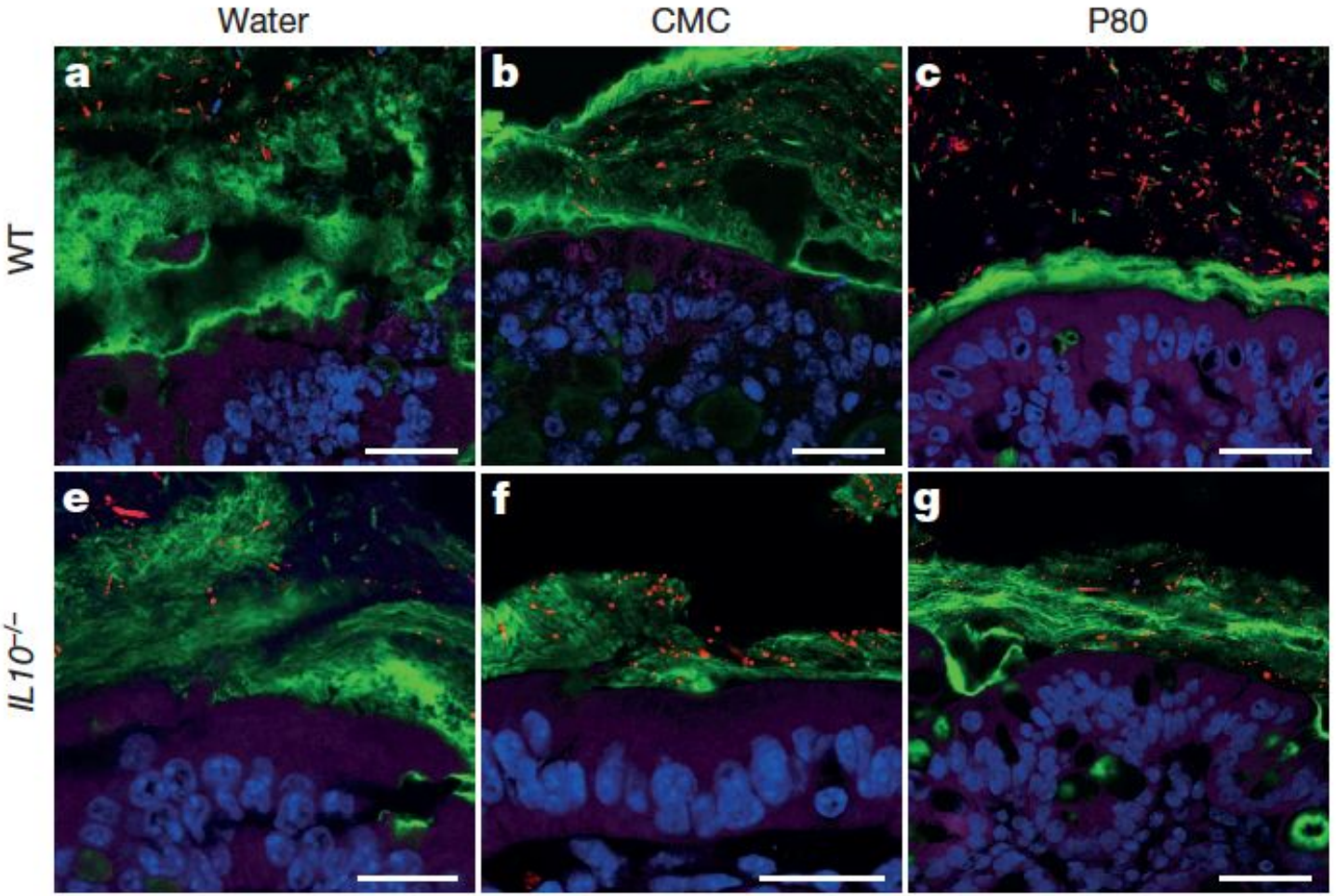
Carboxy-methylcellulose (CMC)	Candies, chewing gums, snack foods, ketchup, and various baked goods
Polysorbate 80 (P80)	Bread, cake mix, salad dressing, frozen desserts, shortening oil, and chocolate
Lecithins	Cottonseed, marine sources, milk, rapeseed, soybeans, and sunflower
Propylene glycol alginate	Salad dressings, ice cream, beer, frozen foods, bakeries, and jelly
Carrageenan	Dairy products, milk alternatives, processed meats, soy-based products, mayonnaise, infant formulas
Gums (Arabic, Xanthan, Guar)	Icing, fillings, soft candy, chewing gum, candy, salad dressings, ketchup
Maltodextrin	

Effect of common emulsifiers on gut microbiota and barrier



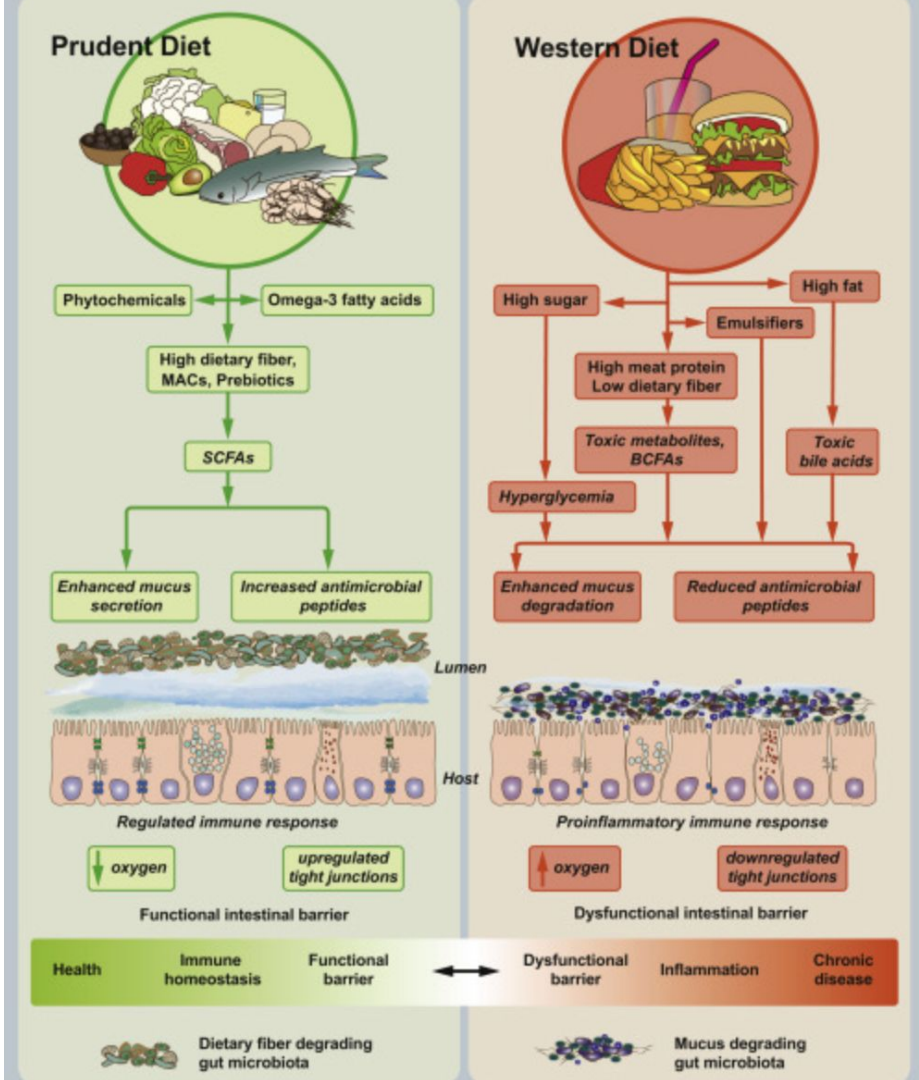
De Siena M et al. 2022.

Dietary Emulsifiers Alter Microbiota Localization, Composition, and Pro-inflammatory Potential



Chassaing et al. Nature. March 2015.

Effect of Prudent vs. Western Diet on Gut Microbiota Composition, Diversity, and Function in Host Physiology



Traditional Anti-inflammatory Diets

MEDITERRANEAN DIET

The Mediterranean Diet reflects a way of eating that is traditional in the countries that surround the Mediterranean, but you don't need to travel any further than your local...

LEARN MORE >

AFRICAN HERITAGE DIET

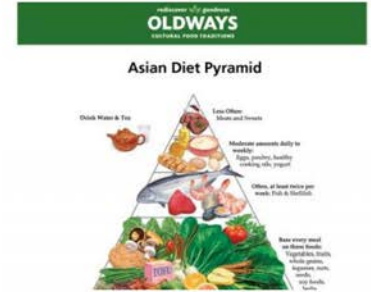
The African Heritage Diet is a way of eating based on the healthy food traditions of people with African roots. This healthy way of eating is powerfully nutritious and delicious, and naturally meets the guidelines experts recommend for supporting good health.

LEARN MORE >

LATIN AMERICAN HERITAGE DIET

The Latin American Diet Pyramid preserves and rivitalizes centuries-old traditions and tastes. Whether you are living in Latin America, of Latin descent but living elsewhere, or whether you simply enjoy the vibrant tastes of Latin culinary traditions, we'll help you learn about the foods...

LEARN MORE >



ASIAN HERITAGE DIET

VEGETARIAN & VEGAN DIET

Gluten and Leaky Gut

- Gluten can trigger zonulin release in everybody
- Zonulin regulates TJs → intestinal permeability
- The gut membrane is selectively permeable, so it's OK if it there is temporary permeability
- Some individuals, including those with celiac dz and NCGS must avoid gluten
- HOWEVER, not everyone needs to avoid gluten. Healthy individuals with a well-balanced microbiota should not have trouble consuming gluten
- **A gluten-free diet is not for everyone**

Collagen and Gelatin and Leaky Gut

- As of yet, there is no research to support collagen supplements for intestinal permeability.
- A small prospective study showed that collagen supplementation 20g/d might improve bloating and mild digestive complaints (n=14, Oct 2022).

- Human studies do not exist to support gelatin supplementation for gut barrier health.
- Animal studies are conflicting. Some suggest improvements in barrier function, others do not.

Key Takeaways for Healthcare Providers

- There is no reliable test or treatment for leaky gut, so beware of “protocols”
- There is no one supplement or quick fix for leaky gut
- To support gut health, encourage patients …
  - Eat a wide variety of wholesome plant-based foods
  - Limit or avoid highly processed foods
  - Limit or avoid alcohol
  - Cut down on NSAIDs
- Help your patients decide if avoiding gluten is in their best interest
- Talk to patients about stress management
- Be prepared to talk about the potential pros and cons of different supplements
- Stay tuned for more research on both dietary and lifestyle recommendations

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Questions?

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