GHAPP

Gastroenterology & Hepatology
Advanced Practice Providers

2020 Third Annual National Conference

November 19-21, 2020

Red Rock Hotel – Las Vegas, NV

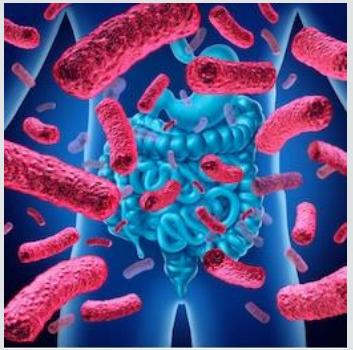
Annenberg Center For Health Sciences at Eisenhower
Imparting knowledge. Improving patient care.

Jointly provided by the Annenberg Center for Health Sciences at Eisenhower and Gastroenterology and Hepatology Advanced Practice Providers.

GHAPP
Gastroenterology & Hepatology Advanced Practice Providers

GHAPP
Gastroenterology & Hepatology
Advanced Practice Providers

Gut Microbiome:
Role in GI and Hepatology



Susan T. Wolgamott, DNP, FNP-C, CTN-B

Digestive Health Center of Michigan

Clinical Research Institute of Michigan

Chesterfield, Michigan

Disclosures

All faculty and staff involved in the planning or presentation of continuing education activities provided by the Annenberg Center for Health Sciences at Eisenhower (ACHS) are required to disclose to the audience any real or apparent commercial financial affiliations related to the content of the presentation or enduring material. Full disclosure of all commercial relationships must be made in writing to the audience prior to the activity. Staff at the Annenberg Center for Health Sciences at Eisenhower and Gastroenterology and Hepatology Advanced Practice Providers have no relationships to disclose.

Disclosures

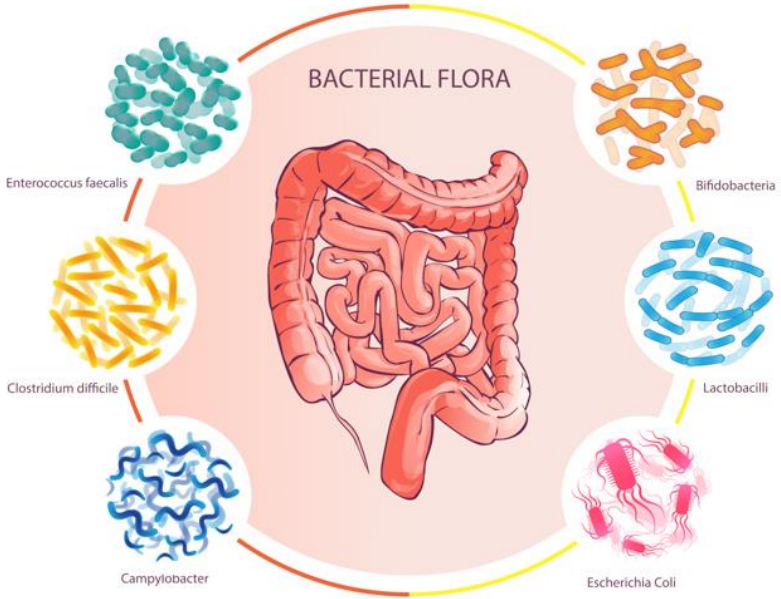
Dr. Susan T. Wolgamott

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

Gut Microbiome



- >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

Shreiner AB et al. *Curr Opin Gastroenterol*. 2015; 31(1):69-75.

Gut Microbiome

- 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

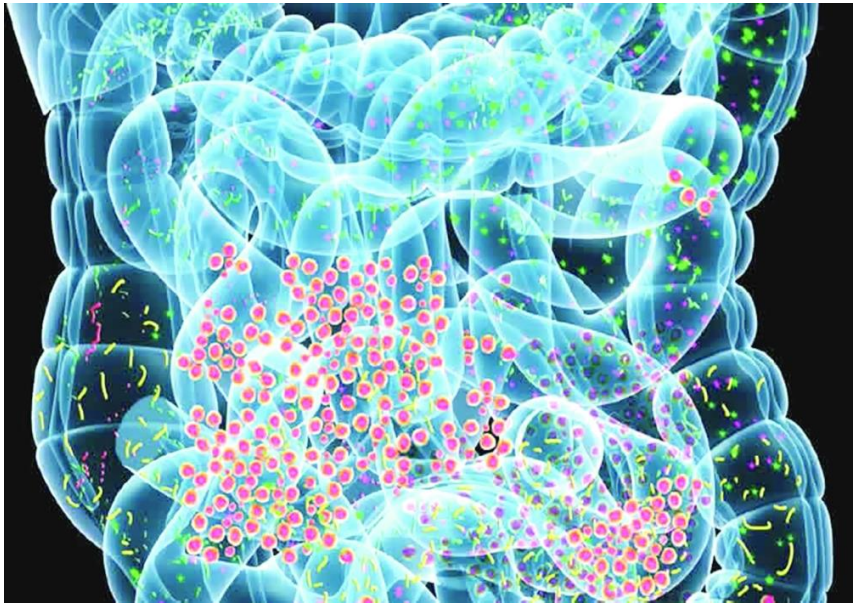
Shreiner AB et al. *Curr Opin Gastroenterol*. 2015; 31(1):69-75.

GHAPP
Gastroenterology & Hepatology
Advanced Practice Providers

Gut Microbiome in Gastroenterology

Dysbiosis

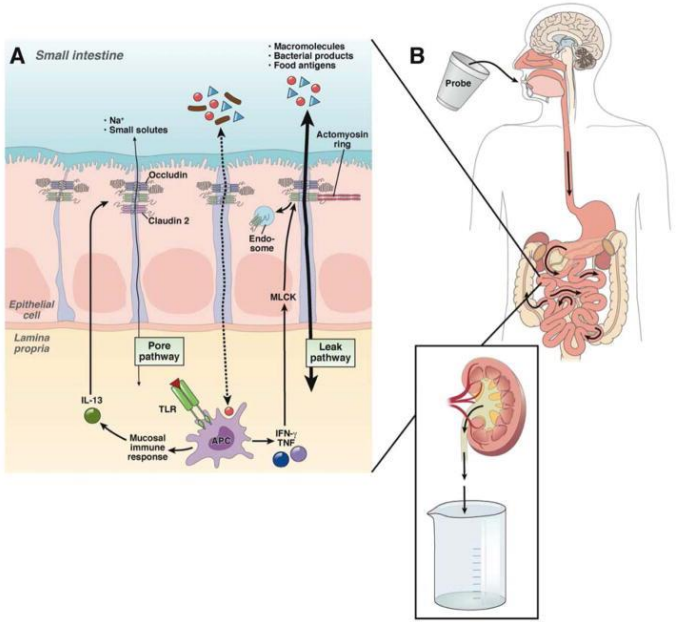
- Disruption to the eustasis
- Variety of symptoms
  - Pain, cramping, bloating, diarrhea
- Identified by origin/symptom prevalence
  - Traveler’s diarrhea
  - SIBO
  - IBS
  - Food poisoning
  - Antibiotic-induced diarrhea
  - Acute gastroenteritis
  - *Clostridium difficile*



Chong PP et al. *Front Microbiol*. 2019; 10:1136. https://doi.org/10.3389/fmicb.2019.01136.

Abnormal Intestinal Permeability & “Leaky Gut Syndrome”

- 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



1. Canadian Society of Intestinal Research. https://badgut.org/information-centre/a-z-digestive-topics/leaky-gut-syndrome/. Accessed 19 Oct 2020; 2. Odenwald MA et al. *Clin Gastroenterol Hepatol*. 2013; 11:1075-83.

Role of Microbiota in Disease: Examining the Evidence

Extensive supporting data

Disease	Human data regarding intestinal permeability	Association supported by animal model(s)?	Prognostic implications of increased permeability	Role of microbiota	Treatment improves disease-associated permeability defects?
IBD	Positive correlation with disease activity; present in some healthy first degree relatives (CD)	Yes[16, 47, 51, 52]	Increased risk of relapse in some studies of CD patients[39, 40]	*Trichuris suis* (whipworm) infection and fecal microbial transplantation clinical trial data are encouraging.[53, 54]	Yes (in patients and experimental models)
Graft vs. Host Disease	Positive correlation of pre-conditioning GI toxicity (presumed to indicate degree of transient barrier loss) with disease activity[57]	Yes[58]	Unknown	Antibiotics reduce disease incidence in patients and experimental animals[59, 60]	Yes (in experimental models)[58]
Type I diabetes	Increased in pre- diabetic and diabetic patients[61]	Yes[62]	Unknown	Changes in microbiome modify incidence of experimental disease.[63, 64]	Unknown
HIV/AIDS	Increased in HIV enteropathy[65]; positive correlation with disease stage[66]	Yes[67]	Unknown	Serum LPS is elevated in patients. Bacterial translocation has been postulated to cause immune activation.[67]	Yes (in patients)[68]
Multiple organ dysfunction syndrome	Correlates with increased disease severity[69]	Yes[70, 71]	Unknown	Controversial	Unknown

Odenwald MA et al. *Clin Gastroenterol Hepatol*. 2013;11:1075-83.

Role of Microbiota in Disease: Examining the Evidence

Some supporting data

Disease	Human data regarding intestinal permeability	Association supported by animal model(s)?	Prognostic implications of increased permeability	Role of microbiota	Treatment improves disease-associated permeability defects?
Irritable bowel syndrome	Increased in diarrhea predominant, post-infectious, and non-post-infectious IBS[72, 73]	No	Unknown	Unknown	Unknown
Celiac Disease	Positive correlation with disease activity[74]; increased in patients and healthy relatives[75]	Yes[76, 77]	Unknown	Unknown	Yes[74]

Odenwald MA et al. *Clin Gastroenterol Hepatol*. 2013;11:1075-83.

Role of Microbiota in Disease: Examining the Evidence

Limited or no supporting data

Disease	Human data regarding intestinal permeability	Association supported by animal model(s)?	Prognostic implications of increased permeability	Role of microbiota	Treatment improves disease-associated permeability defects?
Autism	Increased in patients and relatives; correlates with food intolerance[78]	No	Unknown	Unknown	Unknown
Eczema	Increased in subset of patients; possible correlation with disease activity[79, 80]	No	Unknown	Unknown	Unknown
Psoriasis	Inconclusive	No	Unknown	Unknown	Unknown
Acute pancreatitis	Positive correlation with disease activity[81]	Yes[82, 83]	Unknown	Unknown	Yes (in experimental models)[82, 84]
Parkinson's disease	Increased in subset of patients[85, 86]	No	Unknown	Unknown	Unknown
Fibromyalgia	Increased in subset of patients; correlation with disease activity not studied[87]	No	Unknown	Unknown	Unknown
Depression	Unknown	No	Unknown	Unknown	Unknown

Odenwald MA et al. *Clin Gastroenterol Hepatol*. 2013;11:1075-83.

Role of Microbiota in Disease: Examining the Evidence

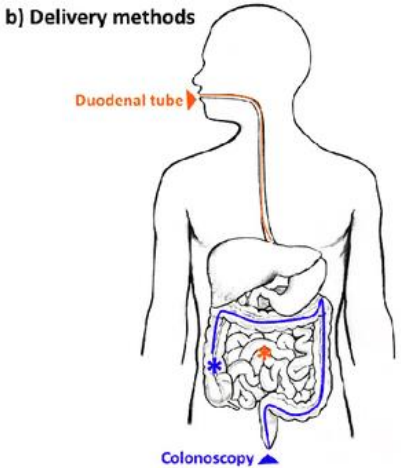
Limited or no supporting data

Disease	Human data regarding intestinal permeability	Association supported by animal model(s)?	Prognostic implications of increased permeability	Role of microbiota	Treatment improves disease-associated permeability defects?
Chronic Fatigue Syndrome	Unknown	No	Unknown	Unknown	Unknown
Asthma	Increased in asthmatic patients; no correlation with disease activity[89]	No	Unknown	Hypothesized to provide possible protective role[90]	No
Multiple Sclerosis	Increased in subset of patients; normal in remission[91]	No	Unknown	Reduced experimental disease in germ free mice[92]	Unknown
Rheumatic diseases (RA, AS)	Increased in patients[93]; NSAID treatment is confounding factor[94]	No	Unknown	Symptoms correlate with germ-free status in rat model[95]; Gut flora worsens disease in mouse models.[96]	Unknown
NAFLD	Positive correlation with disease activity[97, 98]	No	Unknown	Correlation in humans.[97] Strong association in mice.[99, 100]	Unknown
Alcoholic cirrhosis	Increased in subset of patients; correlation with disease activity not studied[101]	No	Unknown	Postulated to be the source of LPS that leads to liver damage and inflammation.[102]	Unknown

Odenwald MA et al. *Clin Gastroenterol Hepatol*. 2013;11:1075-83.

Fecal Microbiota Registry/Transplant

- 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



Kelly C et al. *Gastroenterology*. 2020;158(7):1881-1898.

AGA Summary of Recommendations on Probiotic Use

	Recommendation	Strength of recommendation	Quality of evidence
1	In patients with *C difficile* infection, we recommend the use of probiotics only in the context of a clinical trial.	No recommendation	Knowledge gap
2	In adults and children on antibiotic treatment, we suggest the use of *S boulardii*; or the 2-strain combination of *L acidophilus* CL1285 and *L casei* LBC80R; or the 3-strain combination of *L acidophilus*, *L delbrueckii* subsp *Bulgaricus*and *B bifidum*; or the 4-strain combination of *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B bifidum*, and *S salivarius* subsp *thermophilus* over no or other probiotics for prevention of *C difficile* infection.	Conditional	Low
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.	No recommendation	Knowledge gap

Su GL et al. *Gastroenterology*. 2020;159(2):697-705.

AGA Summary of Recommendations on Probiotic Use

	Recommendation	Strength of recommendation	Quality of evidence
4	In adults and children with pouchitis, we suggest the 8-strain combination of *L paracasei* subsp *paracasei*, *L plantarum*, *L acidophilus*, *L delbrueckii* subsp *bulgaricus*, *B longum* subsp *longum*, *B breve*, *B longum* subsp *infantis*, and *S salivarius* subsp *thermophilus* over no or other probiotics.	Conditional	Very low
5	In symptomatic children and adults with irritable bowel syndrome, we recommend the use of probiotics only in the context of a clinical trial.	No recommendations	Knowledge gap
6	In children with acute infectious gastroenteritis, we suggest **against** the use of probiotics.	Conditional	Moderate

Su GL et al. *Gastroenterology*. 2020;159(2):697-705.

AGA Summary of Recommendations on Probiotic Use

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

Su GL et al. *Gastroenterology*. 2020;159(2):697-705.

Prebiotics/Synbiotics

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

Chong PP et al. *Front Microbiol*. 2019; 10:1136. https://doi.org/10.3389/fmicb.2019.01136.

Antibiotics/Xenobiotics

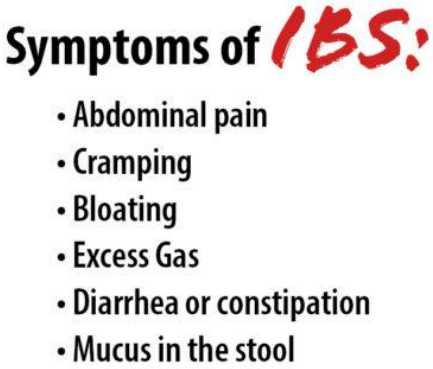
- Overuse/over prescribing
  - Most common source of injury to eustasis
  - Killing both pathogenic and commensal
  - Reshaping ecology with functional consequences
  - Effects on diseases
    - Malnutrition, obesity, diabetes, *C difficile*
- Non-absorbable antibiotics
  - Rifaximin/rifamycin
  - Neomycin

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

1. Das A et al. *PLoS ONE*. 2016; 11(10):e0163099. https://doi.org/10.1371/journal.pone.0163099;
2. Langdon A et al. *Genome Medicine*. 2016; 8(1): 39. https://doi.org/10.1186/s13073-016-0294-z.

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



Chong PP et al. *Front Microbiol*. 2019; 10:1136. https://doi.org/10.3389/fmicb.2019.01136.

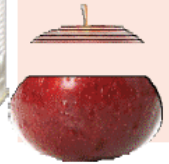
FODMAP/Polyphenols

Foods suitable on a low-fodmap diet

fruit	vegetables	grain foods	milk products	other
fruit banana, blueberry, boysenberry, canteloupe, cranberry, durian, grape, grapefruit, honeydew melon, kiwifruit, lemon, lime, mandarin, orange, passionfruit, pawpaw, raspberry, rhubarb, rockmelon, star anise, strawberry, tangelo Note: if fruit is dried, eat in small quantities	**vegetables** alfalfa, bamboo shoots, bean shoots, bok choy, carrot, celery, choko, choy sum, endive, ginger, green beans, lettuce, olives, parsnip, potato, pumpkin, red capsicum (bell pepper), silver beet, spinach, squash, swede, sweet potato, taro, tomato, turnip, yam, zucchini **herbs** basil, chili, coriander, ginger, lemongrass, marjoram, mint, oregano, parsley, rosemary, thyme	**cereals** gluten-free bread or cereal products **bread** 100% spelt bread **rice** **oats** **polenta** **other** arrowroot, millet, psyllium, quinoa, sorgum, tapioca	**milk** lactose-free milk*, oat milk*, rice milk*, soy milk* *check for additives **cheeses** hard cheeses, and brie and camembert **yoghurt** lactose-free varieties **ice-cream substitutes** gelati, sorbet **butter substitutes** olive oil	**tofu** **sweeteners** sugar* (sucrose), glucose, artificial sweeteners not ending in '-ol' **honey substitutes** golden syrup*, maple syrup*, molasses, treacle *small quantities

Eliminate foods containing fodmaps

excess fructose	lactose	fructans	galactans	polyols
fruit apple, mango, nashi, pear, tinned fruit in natural juice, watermelon **sweeteners** fructose, high fructose corn syrup **large total fructose dose** concentrated fruit sources, large serves of fruit, dried fruit, fruit juice **honey** corn syrup, fruisana	**milk** milk from cows, goats or sheep, custard, ice cream, yoghurt **cheeses** soft unripened cheeses eg. cottage, cream, mascarpone, ricotta	**vegetables** artichoke, asparagus, beetroot, broccoli, brussels sprouts, cabbage, eggplant, fennel, garlic, leek, okra, onion (all), shallots, spring onion **cereals** wheat and rye, in large amounts eg. bread, crackers, cookies, couscous, pasta **fruit** custard apple, persimmon, watermelon **miscellaneous** chicory, dandelion, inulin, pistachio	**legumes** baked beans, chickpeas, kidney beans, lentils, soy beans	**fruit** apple, apricot, avocado, blackberry, cherry, longon, lychee, nashi, nectarine, peach, pear, plum, prune, watermelon **vegetables** cauliflower, green capsicum (bell pepper), mushroom, sweet corn **sweeteners** sorbitol (420) mannitol (421) isomalt (953) maltitol (965) xylitol (967)



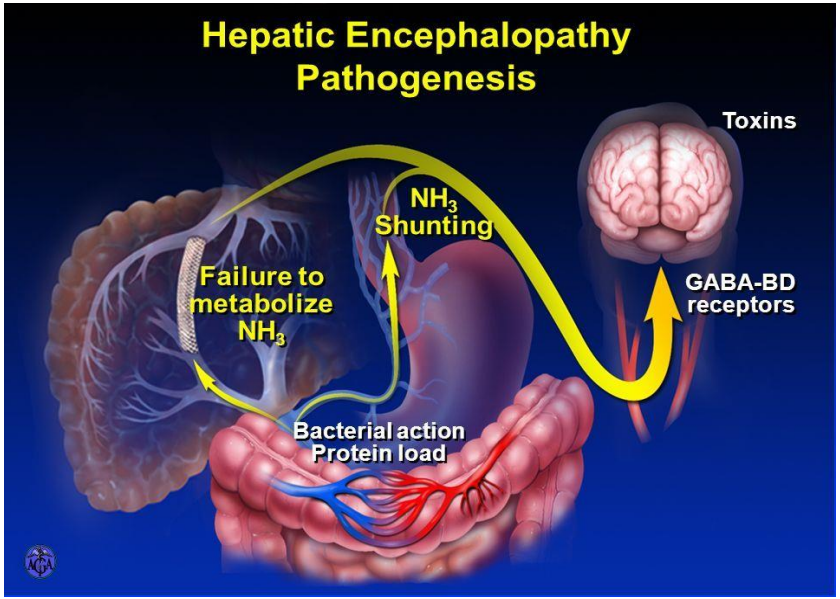
1. Chong PP et al. *Front Microbiol*. 2019; 10:1136. https://doi.org/10.3389/fmicb.2019.01136.
2. Staudacher HM et al. *Proc Nutr Soc.* 2016; 75(3): 306–318.

GHAPP
Gastroenterology & Hepatology
Advanced Practice Providers

Gut Microbiome in Hepatology

Hepatic Encephalopathy

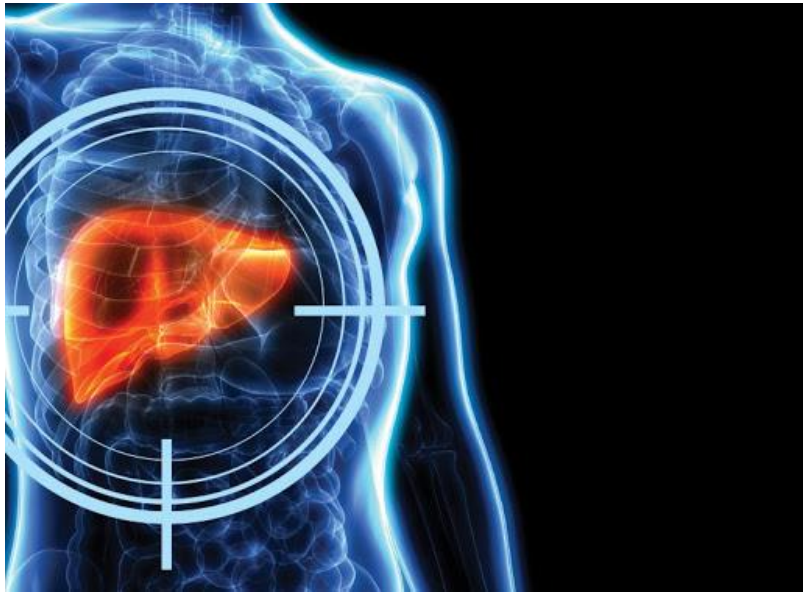
- Function of ammonia levels and alterations in microbiota
- High ratio of healthy to pathogenic bacteria
- Microbiota secrete biologically active compounds
  - Inhibit pathogens
  - Metabolism of toxic compounds (eg, ammonia)
- Fecal microbiota evolve with increasing Child-Pugh and MELD scores
  - Stool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



Rai R et al. *J Clin Exper Hepatol.* 2015; 5(Suppl 1): S29–S36.

Hepatic Encephalopathy

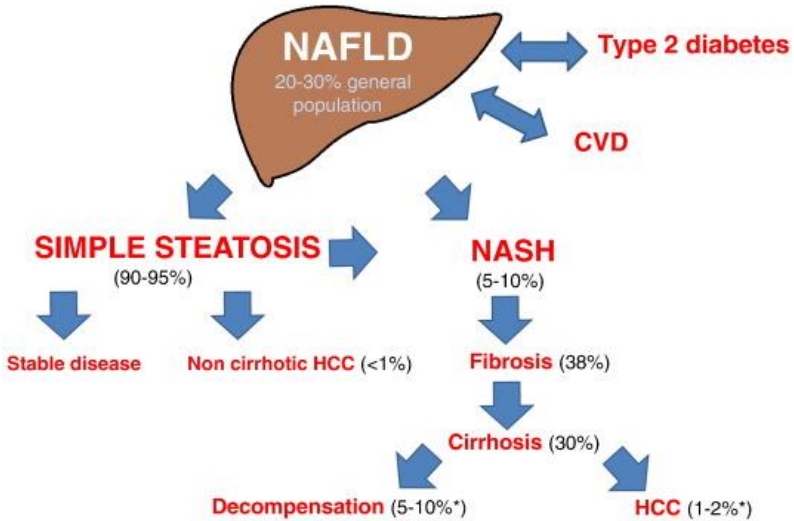
- Gut-Liver Axis
  - 70% of Portal circulation from the gut
  - Absorption/metabolism of nutrition/drugs
  - Lack of bile acid homeostasis results in diarrhea and bacterial overgrowth
  - Cirrhosis decrease GI motility increasing infection risk (eg, SBP)
- Lactulose – No change in fecal microbiota w/ treatment or withdrawal
- Rifaximin – Modest changes in fecal and mucosal microbiota
- Combined positive symptom response
  - Increased microbial metabolic function
  - Improved dysbiosis



Rai R et al. *J Clin Exper Hepatol.* 2015; 5(Suppl 1): S29–S36. .

NAFLD

- 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



1. Aron-Wisnewsky J et al. *Gastroenterology.* 2020;158(7):1881-1898. 2. Milosevic et al. *Int J Mol Sci.* 2019; 20(2):395.
3. Estes C et al. *Hepatology*. 2018; 67(1):123-131.

NAFLD

Low to mild fibrosis

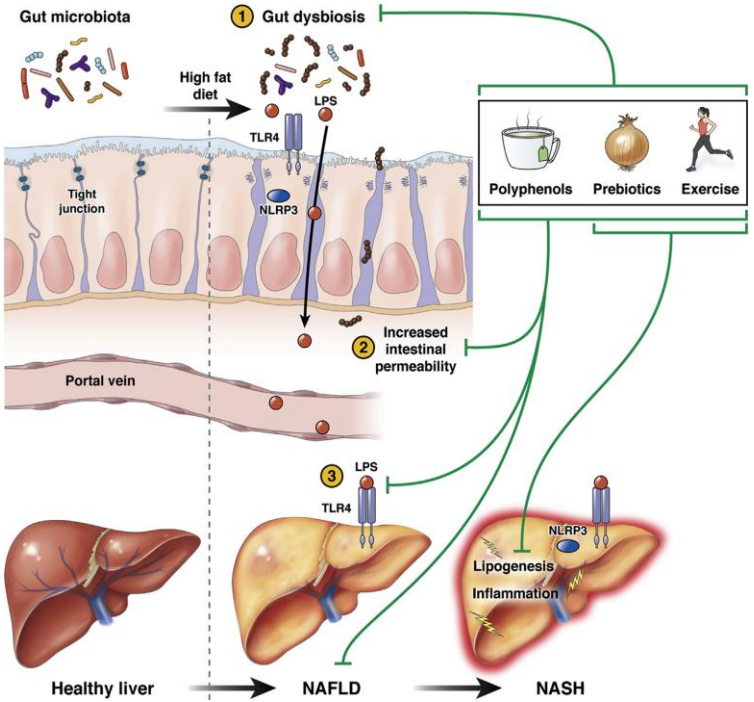
- Frequently associated with ↑ Proteobacteria (phylum level)
- *Rikenellaceae* and *Rumminoccaceae* are ↓ (family level)
- *Escherichia* and *Dorea* are ↑↑ while *Anaerosporobacter, Coprococcus, Eubacterium, Faecalibacterium* and *Prevotella* are ↓ (genera level)

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)

1. Aron-Wisnewsky J et al. *Gastroenterology.* 2020;158(7):1881-1898. 2. Milosevic et al. *Int J Mol Sci.* 2019; 20(2):395.

NAFLD



- 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

1. Aron-Wisnewsky J et al. *Gastroenterology.* 2020;158(7):1881-1898. 2. Milosevic et al. *Int J Mol Sci.* 2019; 20(2):395.

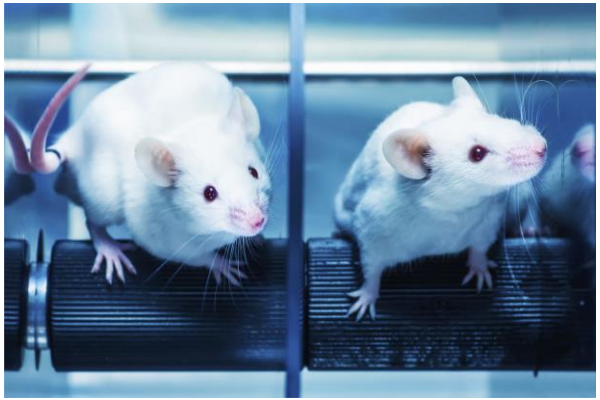
NAFLD

- 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

1. Aron-Wisnewsky J et al. *Gastroenterology.* 2020;158(7):1881-1898. 2. Milosevic et al. *Int J Mol Sci.* 2019; 20(2):395.

FMT – Obesity Mice Trials

- 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

Pérez-Matute P et al. *Sci Rep.* 2020; 10(1):1–14.

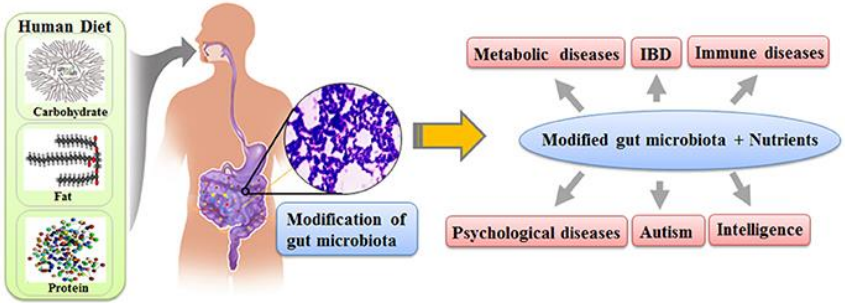
FMT-TRIM Human Trial

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

Yu E et al. *PLoS Medicine.* 2020; 17(3), e1003051.

Pipeline



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

References

Aron-Wisnewsky, J., Warmbrunn, M., Nieuwdorp, M., & Clément, K. Nonalcoholic fatty liver disease: Modulating gut microbiota to improve severity? *Gastroenterology.* 2020; (New York, N.Y. 1943), 158(7), 1881-1898.doi:10.1053/j.gastro.2020.01.049.

Canadian Society of Intestinal Research. Debunking the Myth of 'Leaky Gut Syndrome'. 2018. https://badgut.org/information-centre/a-z-digestive-topics/leaky-gut-syndrome/ Accessed 19 Oct 2020.

Chong, P. P., Chin, V. K., Looi, C. Y., Wong, W.F., Madhavan, P., & Yong, V. C. The Microbiome and Irritable Bowel Syndrome - A Review on the Pathophysiology, Current Research and Future Therapy. *Frontiers in Microbiology*. 2019;10,1136. https://doi.org/10.3389/fmicb.2019.01136.

Das A, Srinivasan M, Ghosh TS, Mande SS Xenobiotic Metabolism and Gut Microbiomes. *PLoS ONE*. 2016; 11(10): e0163099. https://doi.org/10.1371/journal.pone.0163099.

Estes, C., Razavi, H., Loomba, R., Younossi, Z., & Sanyal, A. Modeling the Epidemmic of Nonalcoholic Fatty Liver Disease Demonstrates an Exponential Increase in Burden of Disease. *Hepatology*. 2018; 67(1), 123-131.

Kelly, C. et al. Fecal Microbiota Transplant is Highly Effective in Real World Practice: Initial Results from the FMT National Registry. *Gastroenterology*. 2020; Volume 158, Issue 7,1881,1898. DOI: 10.1053/j.gastro.2020.01.049.

Langdon, A., Crook, N., & Dantas, G. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. *Genome Medicine*. 2016; 8(1), 39. https://doi.org/10.1186/s13073-016-0294-z.

References

Le Roy T, Llopis M, Lepage P, Bruneau A, Rabot S, Bevilacqua C, et al. Intestinal microbiota determines development of non-alcoholic fatty liver disease in mice. *Gut*. 2013; 62(12):1787–94. doi: 10.1136/gutjnl-2012-303816, 23197411.

Menees, S., & Chey, W. The gut microbiome and irritable bowel syndrome. 2018; F1000Research, 7, F1000 Faculty Rev 1029.https://doi.org/10.12688/f1000research.14592.1.

Milosevic, I., Vujovic, A., Barac, A., Djelic, M., Korac, M., Radovanovic Spurnic, A., Gmizic, I., Stevanovic, O., Djordjevic, V., Lekic, N., Russo, E., & Amedei, A. Gut-Liver Axis, Gut Microbiota, and Its Modulation in the Management of Liver Diseases: A Review of the Literature. *International Journal of Molecular Science*s. 2019; 20(2), 395. https://doi.org/10.3390/ijms20020395.

Pérez-Matute, P., Íñiguez, M., de Toro, M., Recio-Fernández, E., & Oteo, J. A. Autologous fecal transplantation from a lean state potentiates caloric restriction effects on body weight and adiposity in obese mice. *Scientific Reports*. 2020; 10(1), 1–14. https://doi.org/10.1038/s41598-020-64961-x.

Rai, R., Saraswat, V. A., & Dhiman, R. K. Gut microbiota: its role in hepatic encephalopathy. *Journal of Clinical and Experimental Hepatology*. 2015; 5(Suppl 1), S29–S36. https://doi.org/10.1016/j.jceh.2014.12.003.

Shreiner, A. B., Kao, J. Y., & Young, V. B. The gut microbiome in health and in disease. Current opinion in gastroenterology; 2015; 31(1), 6975. https://doi.org/10.1097/MOG.0000000000000139.

References

Staudacher, H. M., & Whelan, K. Altered gastrointestinal microbiota in irritable bowel syndrome and its modification by diet: probiotics, prebiotics and the low FODMAP diet. *The Proceedings of the Nutrition Society*. 2016; 75(3), 306–318. https://doi.org/10.1017/S0029665116000021.

Su, Grace L. et al. Clinical Practice Guidelines on the Role of Probiotics in the Management of Gastrointestinal Disorders. *Gastroenterology*. 2020; Volume 159, Issue 2, 697 -705. https://doi.org/10.1053/j.gastro.2020.05.059.

Yu, E. W., Gao, L., Stastka, P., Cheney, M. C., Mahabamunuge, J., Torres Soto, M., Ford, C. B., Bryant, J. A., Henn, M. R., & Hohmann, E. L. Fecal microbiota transplantation for the improvement of metabolism in obesity: The FMT-TRIM double-blind placebo controlled pilot trial. *PLoS Medicine*. 2020; 17(3), e1003051. https://doi.org/10.1371/journal.pmed.1003051.