



Long Covid-19 Foundation



Long Covid Coalition Conference

The Gut-Brain Axis in Covid-19

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The Gut-Brain Axis in Covid-19

Topics presented:

- 1-An overview of the gut microbiome and its systemic effects**
- 2-How the gut microbiome impacts brain function and repair**
- 3- Covid-19 alters the gut microbiome**
- 4-The gut microbiome impacts the course of Covid-19 and the risk of Long Covid**
- 5-The gut as a reservoir for persistent SARS-CoV-2 infection**
- 6-Therapeutic modulation of the gut microbiome to prevent and reverse Long Covid**

Homo sapiens

Despite human diversity and complexity, our species has only about 25,000 functioning genes



Rice

Which appears to have far less complexity and diversity, is the fruit of this plant...



Oryza sativa

*which has 46,000 genes that
have evolved over
15 million years*

*How do humans
manage to do so
much with so little?*



The human microbiome

supplies about 4 million genes...

Genes are the template for creating proteins.

Two major types of protein:

- Structural

- Enzymes (catalysts of biochemical reactions)



The gut microbiome is
your body's largest
and most diverse
ecosystem

About 100 trillion microbes,
95% of the total

More microbial cells than all
your human cells



Understand the Microbiome By Answering Two Basic Questions

- Who's there?
- What do they do?

What do gut microbes do?

- Alter, create, destroy, recycle
 - Nutrients
 - Toxins
 - Hormones
- Make nutrients more or less bioavailable
- Stimulate immune responses
- Modify systemic metabolism
- Alter gut motility
- Compete with pathogens
- Activate the enteric nervous system, which connects directly with the CNS
- Influence protein function in brain and muscle

They do this through their Structure and Function

- Structural components are recognized by the innate immune system's pattern recognition receptors
- Microbial metabolism of host secretions and ingested substances yields products that impact human cellular function.

The gut microbiome shapes human physiology

- Over 90% of the chemicals circulating in your blood originate with your gut microbiome
- Some of these substances are neurotoxins
 - Ammonia
 - D-lactic acid
- Some of these substances trigger systemic inflammation, which effects the brain
 - LPS (cell wall lipopolysaccharides)
 - Peptidoglycans
- Some of these substances are anti-inflammatory and stimulate tissue repair
 - Butyrate, which stimulates synthesis of BDNF (brain derived neurotropic factor) in laboratory animals
- Some substances may be helpful or harmful, depending on concentration
 - H₂S (hydrogen sulfide)
 - Propionate

[The Gut Microbiome and the Brain](#)

Leo Galland, J Med Food 17; 12: 1–12 (2014)

Who's There?

- Bacteria, a thousand different species/person
- Viruses, mostly phages that inhabit bacteria
- Fungi, mostly yeasts, about 15 species
- Archea, primitive producers of methane
- Protozoa (one-celled animals)
- Helminths (worms)

Taxonomy: the organization of taxa, now confirmed by DNA sequencing

- Kingdom
- Phylum
- Class
- Order
- Family
- Genus
- Species
- Strain

Complexity and Diversity of the Microbiome

- Bacteria and Archea (which look alike) have separate kingdoms
- Lactobacilli and Bifidobacteria, similar probiotics, are in separate phyla
 - Humans and eels are in the same phylum
- Different strains of the same species may have divergent, even opposite, effects
 - *Bacteroides fragilis* strains may prevent autism or promote colon cancer

Diversity and Balance

Create a Healthy Ecosystem

- Health is usually associated with a greater variety of taxa at all levels
- Health is usually associated with a greater evenness in the richness of different taxa
- Groups of unrelated taxa support one another by creating interdependent feeding networks called syntrophic clusters
- The microbiome consists of complex, dynamic microbial communities
- Bacteriophages increase complexity by altering the functions and the lifespans of the bacteria they infect

Keystone species

Major taxa that support other species to hold it all together

Examples:

Faecalibacterium prausnitzii, a major producer of butyrate, which supports growth of Bifidobacteria

Akkermansia muciniphila, which feeds on mucus and stimulates the colonic immune system



Faecalibacterium prausnitzii, a keystone species depleted in CFS/ME

- *F prausnitzii* is major butyrate producer that supports growth of Bifidobacterial spp
- CFS is associated with reduction in *Faecalibacterium prausnitzii* and other species frequently described as anti-inflammatory, decreased bacterial diversity, increase in pro-inflammatory *Enterobacteriaceae* (gram negative aerobes).
- Elevation of blood markers of microbial translocation: LPS, LBP, and sCD14, indicating increased intestinal permeability (“Leaky gut”)

Nagy-Szakal et al. Fecal metagenomic profiles in subgroups of patients with myalgic encephalomyelitis/chronic fatigue syndrome. *Microbiome*. 2017

Giloteaux et al. Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome. *Microbiome*. 2016 Jun 23;4(1):30.

DYSBIOSIS

An imbalance or instability among the many organisms of the microbiome that alters the ecosystem, creating undesirable effects on the health of the host

Stress Can Create Dysbiosis

- Stress hormones like adrenaline and noradrenaline selectively encourage the growth of some pathogenic bacteria like *E coli*
- Adrenalin, in addition, can make bacteria like *E coli* produce more toxins
- Toxic bacteria break down the intestinal barrier
- Barrier breakdown (leakiness) allows greater penetration of these toxins into your body
- Meditative practice and yoga can reverse this chain of events

Inflammation and Dysbiosis: a Vicious Cycle

- Inflammation increases the concentration of nitrates in the inflamed tissue by increasing synthesis of nitric oxide
- A high nitrate environment changes bacterial growth patterns
- Anti-inflammatory bacteria are stunted
- Pro-inflammatory bacteria are stimulated
- Their growth creates more inflammation and maintains a high nitrate concentration

SARS-CoV-2 in the Gut Creates Dysbiosis

- SARS-CoV-2 enters cells through attachment to and destruction of the vital enzyme ACE-2
- ACE-2 in the gut acts as a chaperone for amino acid absorption
- Enteric ACE2 deficit impairs tryptophan absorption
 - depletes serotonin
 - diminishes synthesis of defensins
 - produces gut bacterial dysbiosis

IMPACT OF COVID-19 ON THE GUT MICROBIOME PERSISTS FOR MANY MONTHS

- **Decreased bacterial diversity, increased pro-inflammatory species.** Gu et al. Alterations of the Gut Microbiota in Patients with COVID-19 or H1N1 Influenza. Clin Infect Dis. 2020
- **Increased fungal richness: *C. albicans*, *C. auris*, *Aspergillus flavus*.** Zuo, et al. Alterations in Fecal Fungal Microbiome of Patients With COVID-19 During Time of Hospitalization until Discharge. *Gastroenterology*. 2020
- ***Enterococcus faecalis*, potent inducer of gamma-interferon, associated with increased mortality.** Ward et al. Intestinal and oral Microbiomes Are Robust Predictors of COVID-19 Severity, the Main predictor of COVID-19-Related Fatality. MedRxIV 2020
- **Keystone depleted species: *Faecalibacterium prausnitzii*,** Zuo et al, Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization, *Gastroenterology* (2020). Yeoh et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. *Gut* 2021.

Gut Microbiome at Disease Onset Predicts Development of PASC

- Gut microbiome of patients with PASC were characterized by lower levels of *Faecalibacterium prausnitzii* and higher levels of *Ruminococcus gnavus*, *Bacteroides vulgatus*.
- Butyrate-producing bacteria, especially *Faecalibacterium prausnitzii* and *Bifidobacterium pseudocatenulatum* showed the largest inverse correlations with PASC at 6 months.

Liu et al, Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome, *Gut* (2022). DOI: [DOI: 10.1136/gutjnl-2021-325989](https://doi.org/10.1136/gutjnl-2021-325989)

DOES PERSISTING VIRAL INFECTION CONTRIBUTE TO PASC?

- Stool may contain SARS-CoV-2 for months after respiratory samples become negative
- Persisting viral RNA has been reported in multiple tissues at autopsy or surgery, weeks or months after disease onset
- Some patients experience marked improvement of PASC after vaccination, anti-viral drugs and/or monoclonal antibody therapy. These are individual case reports
- Patients with NeuroPASC have impaired function of T-effector memory lymphocytes, an immune deficit seen with persistent antigenic stimulation

Visvabharathy et al. Neuro-COVID long-haulers exhibit broad dysfunction in T cell memory generation and responses to vaccination. medRxiv [Preprint]. 2021 Oct 29:2021.08.08.21261763.

A Program for Reversing PASC-associated Dysbiosis: Increase Butyrate and *F. prausnitzii*

- A high fiber, polyphenol-rich diet increases growth of *F. prausnitzii*
- Adherence to a Mediterranean diet elevates fecal levels of *F. prausnitzii*. Gutiérrez-Díaz et al. J Agric Food Chem. 2017 Jan 25;65(3):586-595.
- Prebiotic oligosaccharides (FOS, GOS) increase *F. prausnitzii*, hippocampal BDNF in rats. [Magsood](#), Stone The Gut-Brain Axis, BDNF, NMDA and CNS Disorders op cit.
- Resveratrol inhibits *Enterococcus faecalis*, alters gut/lung microbiome to limit superantigen-induced respiratory inflammation. Chan MM. Antimicrobial effect of resveratrol on dermatophytes and bacterial pathogens of the skin. Biochem Pharmacol. 2002. Hu et al. The Bidirectional Interactions between Resveratrol and Gut Microbiota: An Insight into Oxidative Stress and Inflammatory Bowel Disease Therapy. Biomed Res Int. 2019 . Alghetaa et al. Resveratrol-mediated attenuation of superantigen-driven acute respiratory distress syndrome is mediated by microbiota in the lungs and gut. Pharmacol Res. 2021

REVERSING GUT BACTERIAL DYSBIOSIS IN PASC

- **RCTs: *Bifidobacterium longum* BB536 and *Bacillus coagulans* GBI30 increase *F. prausnitzii*, subdue inflammation.** Odamaki et al. Influence of *Bifidobacterium longum* BB536 intake on faecal microbiota in individuals with Japanese cedar pollinosis during the pollen season. *J Med Microbiol.* 2007. Lau et al. . *Bifidobacterium longum* BB536 alleviated upper respiratory illnesses and modulated gut microbiota profiles in Malaysian pre-school children. *Benef Microbes.* 2018. Nyangale et al. *Bacillus coagulans* GBI-30, 6086 Modulates *Faecalibacterium prausnitzii* in Older Men and Women. *J Nutr.* 2015. Nyangale et al. . Effect of prebiotics on the fecal microbiota of elderly volunteers after dietary supplementation of *Bacillus coagulans* GBI-30, 6086. *Anaerobe.* 2014
- **Prebiotic oligosaccharides (FOS, GOS) increase *F. prausnitzii*, hippocampal BDNF in rats.** [Maqsood](#), Stone The Gut-Brain Axis, BDNF, NMDA and CNS Disorders op cit.
- ***Bacillus subtilis* B-7092 (Tundrex/Vetom/Subalin) secretes α -IFN, which is virucidal for SARS-CoV-2.** Kumari et al. Type I interferon susceptibility distinguishes SARS-CoV-2 from SARS-CoV. *bioRxiv* 2020
- **Resveratrol inhibits *Enterococcus faecalis*, alters gut/lung microbiome to limit superantigen-induced respiratory inflammation.** Chan MM. Antimicrobial effect of resveratrol on dermatophytes and bacterial pathogens of the skin. *Biochem Pharmacol.* 2002. Hu et al. The Bidirectional Interactions between Resveratrol and Gut Microbiota: An Insight into Oxidative Stress and Inflammatory Bowel Disease Therapy. *Biomed Res Int.* 2019 . Alghetaa et al. Resveratrol-mediated attenuation of superantigen-driven acute respiratory distress syndrome is mediated by microbiota in the lungs and gut. *Pharmacol Res.* 2021

The Gut Microbiome and Cytotoxic T-Lymphocytes (CTLs)

- CTLs play important roles in recovery from viral infection
- CTLs are critical for vaccine-induced protection against Covid-19
- Lactobacillus consumption through yogurt, fermented foods, or as a supplement increases number and activity of CTLs. Meyer et al Ann Nutr Metab. 2006;50(3):282-9. Ashraf & Shah Crit Rev Food Sci Nutr. 2014;54(7):938-56.
- *Lactobacillus plantarum* reduced infection after major abdominal surgery by 70%
 - Rayes Z Gastroenterol. 2002 Oct;40(10):869-76.
- *Lactobacillus plantarum* improved gut barrier function, decreased growth of gut pathogens and improved clinical outcomes of patients with pancreatitis
 - Qin et al Eur J Clin Nutr. 2008 Jul;62(7):923-30..

Enhancement of T-effector memory cells (TEMs), a type of CTL

- Important for prolonged immune memory following viral infection and immunization
- TEMs thrive on fatty acid oxidation, availability of butyrate and presence of *Lactobacilli*
- Diet: high fiber, adequate fat, low sugar, fermented food daily (yogurt, sauerkraut, kimchi)
- L-carnitine 500-1000 mg bid
- Black raspberry concentrate 1 tablespoon daily
- *Lactobacillus plantarum*

Dietary Factors Impact Bacteriophage Activity

- Polyphenols, especially bioflavonoids, disable or kill bacteriophages, inducing structural damage to the capsid, inhibiting bacteriophage activity and infectivity.
- Oregano oil suppresses multiple types of prophages, preventing their cellular entry and impact on bacteria
- The natural sweetener stevia, promotes multiple species phage responses, increasing their impact on bacteria.

Marongiu et al. Dietary Modulation of Bacteriophages as an Additional Player in Inflammation and Cancer. *Cancers (Basel)*. 2021 Apr 23;13(9):2036.

Can polyphenols or oregano prevent or reverse PASC by inhibiting bacteriophage activity?