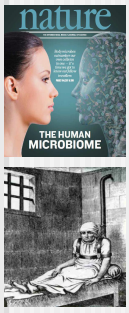
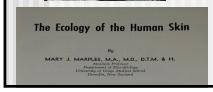


The Human Microbiome



-Implications for day to day practice

-Every patient's microbiome is different

-The human body has 10x more microbial cells than human cells.

-You have the ability to impact your patients microbiome.

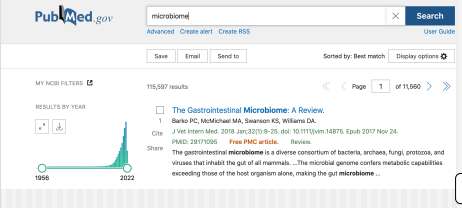
1

- **Gerald T. Simons, PA-C**
- **Clinical Assistant Professor**
  - **Stony Brook PA Program**
- Surgical PA
- AASPA
  - Past President
  - Wound Care Instructor
  - Board of Directors
- **No disclosures. No financial interests**
- **No commercial associations**

2

Interest in the microbiome

- Patients are asking more about the microbiome
- More than 28,000 articles on the microbiome in the last 5-6 years
  - Many are quality RCT-DB studies



April 9 2022

3

Question 1

- Do you currently recommend probiotics in your practice:
  - A. Yes, for all patients
  - B. For patients on antibiotics
  - C. For patients with acute gastroenteritis
  - D. Not yet, that's why I'm here!

4

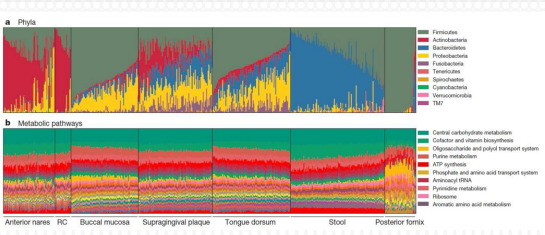
Vocabulary-1

- The human **microbiota**
  - The bacteria, viruses, fungi, and other single-celled animals that live in the body.
  - Our collective organism!
- The **microbiome**
  - All of the genes/genomes inside these microbial cells
  - "gene content"

Fun fact:
BM= loss of 1/3 of microbiome Sender, et.al 2016

5

NIH Human Microbiome Project

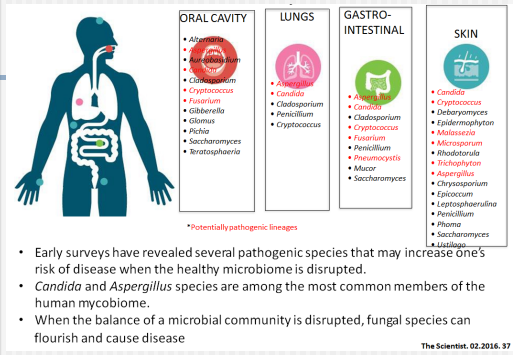


HMP, Nature 2012

- Each site is different in terms of its predominant microbial types
- No core microbiome at every site for everyone
- Considerable variation in health
- Unique fingerprints at each site for individuals
- Generally similar functionality
- Loss and gain of functions at the individual level with strains

6

The Human Microbiome



- Early surveys have revealed several pathogenic species that may increase one's risk of disease when the healthy microbiome is disrupted.
- *Candida* and *Aspergillus* species are among the most common members of the human mycobiome.
- When the balance of a microbial community is disrupted, fungal species can flourish and cause disease

The Scientist. 02.2016. 37

Theory- check for candida/fungal infection in chronic disease?

7

Vocabulary-2

- Human Superorganism
  - Human cells
  - Microbial symbionts
    - 37 trillion human cells & 40 trillion bacteria!
      Sender, et.al. 2016
    - 40 trillion human cells & 100 trillion microbial cells
      Mayo, 2021

8

VOCABULARY -3

- Symbionts: Symbiotic relationship
  - bacteria that are helpful and won't harm the host.
- Commensals: Bacteria will have no effect
  No detriment or benefit
- Probiotics:
  Viable/live microbial feed/microorganisms that reach the target in active form. They exert a positive health effect on the host.
- Prebiotics:
  A food source used by us (the host) to produce probiotics.
- Synbiotic: PROBIOTICS + PREBIOTICS
  - A therapeutic mixture of pre- and probiotics

Swanson KS, Gibson GR, Hutkins R, et al. Nat Rev Gastroenterol Hepatol. 2020;17(11)

9

Vocabulary 4 Psychobiotics

- Live bacteria that directly and indirectly produce positive effects on neuronal functions by colonizing into the intestinal flora with anxiolytic and antidepressant activities
  - Adv Exp Med Biol. 2019;1192:565-581
- Psychobiotics can be geared for depression, anxiety, OCD, eating, sleep
- Many neuro & psych patients have gut symptoms!
- More research needed

10

Vocabulary-5

- Dysbiosis
  - Imbalance in the gut microbiome
  - enrichment of Proteobacteria is a common feature in immunosuppressed patients
    - associated with IBD &CFS
      - *Nature.com 2 April 2019*
- SIBO: Small Intestinal Bacterial Overgrowth
  - Excessive aerobic and anaerobic microbes that are normally present in the colon.
  - Bloating, flatulence, abdominal discomfort, or diarrhea.

UpToDate 8 April 2022

11

Our way of thinking ….

- MICROBES are BAD & cause DISEASE
  - They colonize & infect
- Detected by microscopy and cultured
- Characterized by growth on specific media, sensitivity to antibiotics
  - They need to be killed with
    - Antiviral
    - Antibiotic
    - Antiparasitic
    - Antifungal

BUT…

12

NEW WAY OF THINKING

- Your patient is not just one organism!
- Antibiotics in infants and toddlers can have long term implications on health
  - Asthma, IBD, Obesity *(Vallianou, 2021)*
- It can take weeks for the gut to recover from a standard course of oral antibiotics
- Every patient is its OWN unique microbiota
- Most of our organisms are non-pathologic
  - even beneficial!
- Humans are like moveable, warm-blooded diverse coral ecosystems
  - Symbiosis & commensals

13

What we know today

- Changes in our basic bacterial balance can cause or exacerbate disease including premature birth, bowel disease, mood and memory changes, and circadian rhythms.
- Diet changes & lifestyle (processed foods, excess showering) can enhance or inhibit our microbiome
- PAs can take simple steps to include the microbiome in their daily care of patients.
- Every patient has their own unique microbial fingerprint
- It is a ever evolving field and the data changes regularly.

14

What impacts our microbiome

- Birth method
  - C-section vs vaginal
- Antibiotic exposure
  - Especially early in life
- Genetics
- Stress
- Infections
  - SIBO
- Frequency of showering
- Hygiene Hypothesis
  - Excessive showering
  - Excessive hand antisepsis
- Sex
- Age
- Diet
  - Intake of prebiotics
  - Intake of probiotics
  - SIBO
  - Hepatic disease

15

Acquiring our microbiome

- Sterile womb hypothesis-Uterus is sterile
  - Birthing process is the first exposure & seeding of a neonate to microbes, and subsequent interactions shape and seed the neonate's microbial communities
  - C section vs vaginal delivery
  - Within a MONTH of birth, the microbial genome outnumbers human genes **150:1**
  - Breast feeding vs bottle
    - Breast feeding enhances infants gut microbiome
  - Outdoor play.

PLoS Biol, 2013, Vol 11(8)

16

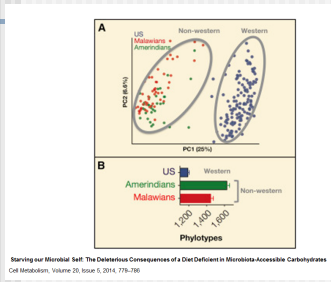
Cesarean Section Delivery Increases Child's Risk of:

- Allergic Rhinitis
- Asthma
- Celiac Disease
- Type I Diabetes
- Inflammatory Bowel Disease

PLoS Biol, 2013, Vol 11(8): e1001631

17

Diet: Western Microbiota is less diverse than Non-Western Populations



Starving our Microbial Self: The Deleterious Consequences of a Diet Deficient in Microbiota-Accessible Carbohydrates
Cell Metabolism, Volume 20, Issue 5, 2014, 779–786

-Poor diet =
Poor gut microbiome!
-Western diet+
Less diversity

& BaAka rainforest hunter-gathers
Gomez Cell Reports, 2016

Americans &
Fiber deficiency.

18

Question 2:

The current USDA recommendations for fiber intake are:

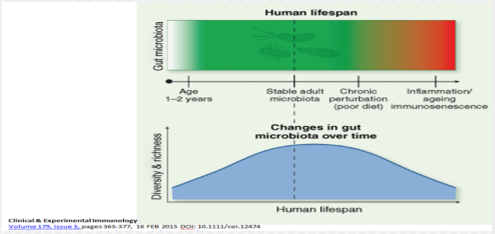
A. 10-16gm a day
B. 15-22 grams a day
C. 20-25 grams a day
D. 25 to 38 grams a day

"It is both compelling and daunting to consider that dietary intervention at an individual or population level could reduce rates of psychiatric disorders." AJP 2010

19

Age: The gut microbiota during the human lifespan

Age & inflammation reduces microbial diversity
Theory: Affects gut- brain axis

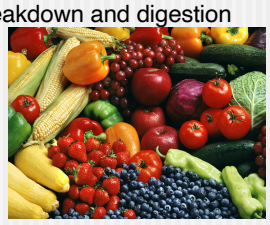


Fun fact: Kissing for 10 sec transfers an average of 80 million bacteria

20

Food allergy/food sensitivity

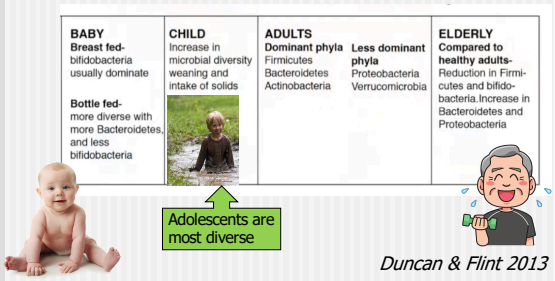
- Why do some patients tolerate some foods better than other?
- Evidence supports role of microbial diversity in food breakdown and digestion



21

Age: The microbiome over a lifetime

- Fetus: usually sterile



Duncan & Flint 2013

22

Akkermansia microbe M vs F

There have been many reports on the roles of intestinal flora and intestinal environment in health promotion and disease prevention. Beneficial bacteria such as *Bifidobacterium* and lactic acid-producing bacteria have been shown to improve the intestinal environment, and yield a good effect on metabolism, immunity and nerve response. In this review, in addition to these beneficial bacteria, we introduced *Akkermansia muciniphila* as a next-generation beneficial microbe. Several reports indicate that *Akkermansia muciniphila* affects glucose metabolism, lipid metabolism, and intestinal immunity, and that certain food ingredients such as polyphenols may increase the abundance of *Akkermansia muciniphila* in the gut.

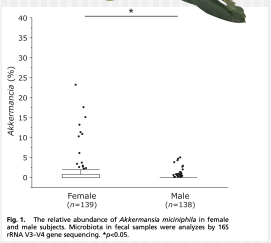


Fig. 1. The relative abundance of *Akkermansia muciniphila* in female and male subjects. Microbiota in fecal samples were analyzes by 16S rRNA V3-V4 gene sequencing. *p<0.05.

& Vaginal microbiota may have Systemic effects

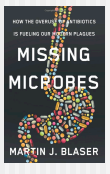
Naito, J. Clin. Biochem. Nut. July 2018 Vol 63

23

Antibiotic exposure: Kills of beneficial bacteria

- Our normal, symbiotic microbiome does not recover completely from antibiotics
- Can be replaced in the long term by resistant organisms
- Overuse of antibiotics could be fueling the dramatic increase in conditions such as obesity, type 1 diabetes, inflammatory bowel disease, allergies and asthma, which have more than doubled in many populations

Stop the killing of beneficial bacteria



Blaser; Nature, 2011, Vol 476: 393-394

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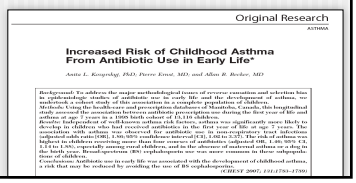
Antibiotic exposure: Childhood asthma

- Independent of known asthma risk factors, asthma was significantly more likely to develop by age 7 in children who had received antibiotics in the first year of life.
  - Chest, Vol 131: 1753-1759


Original Research

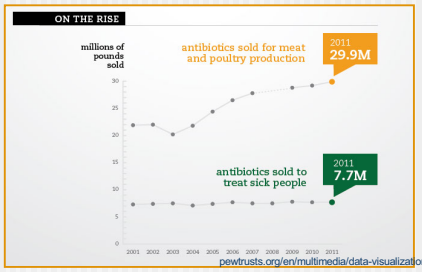
ASTHMA

Increased Risk of Childhood Asthma From Antibiotic Use in Early Life*

Anita L. Kozyrskyj, PhD; Pierre Ernst, MD; and Allan B. Becker, MD

25

Antibiotic use
- 40% of adults
- 70% of all children in the U.S. take antibiotics every year (CDC)



Tip: Antibiotics in the first 6 months of life increases rate of obesity *(Carding, May 2015)*

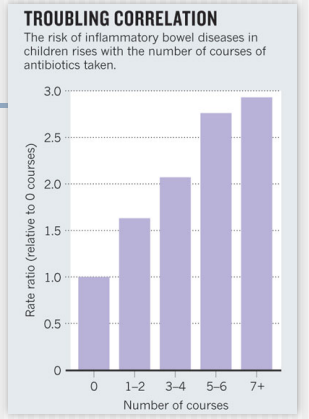
26

Antibiotic exposure:

-Inflammatory bowel

-Allergies

Dejea PLOS 2015



Blaser; Nature, 2011, Vol 476: 393-394

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Human Microbiome

- Skin
- Nasal
- Ocular
- Mouth
- Pharynx
- Gut
- Vaginal

Research continues to evolve.

Microbes have a 4/5 billion year history of success.

Many live in us and on us.

28

Ocular microbiome

- Ocular microbiota
  - Many commensal & pathogenic species present on the eye.
- The ocular surface is continuously exposed to the environment and harbors various commensals
- Evidence suggests that ocular disease progression is associated with altered gut microbial composition
- Emerging evidence has shown that gut microbiota may play an essential role in the development of uveitis
- probiotic eye–drops treatment improves symptoms and signs in patients affected by keratoconjunctivitis (N=6) *Iovieno Inves Opto Vis Sci 2016*
- *Mycobacterium tuberculosis* associated with ocular inflammation *Weinstein and Pepple, 2018*

29

Oral Microbiota

Dentures
Bridges
Retainers

- >700 species
- Critical to maintain
  - Homeostatic balance
  - Proper balance = less oral disease
- Commensals
- Symbiotics
- Pathogens
  - & Biofilms
  - & opportunistic

30

Oral microbiome

- Encourage brushing after each meal
- Alcohol free mouthwash
  - Esp. for patients with dry mouth syndromes
- Low sugar diet reduces caries
- Fiber- improves microbiome
- Dairy- improves microbiome
- AVOID SMOKING
  - Increases biofilm
  - Increases acidity of the oropharynx

Cigarettes typically contain

Bacillus Clostridium

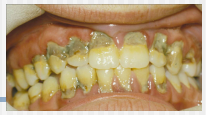
31

Oral Microbiome

- Strong link between gingivitis and CV disease
- Alcohol consumption
  - Increases *strep mutans*
  - Ethanol converts to acetaldehyde (carcinogen!)
- Red Wine
  - Antimicrobial aspects in the mouth
  - Less strep = less cavities
  - Less Strep Pyogenes = less pharyngitis

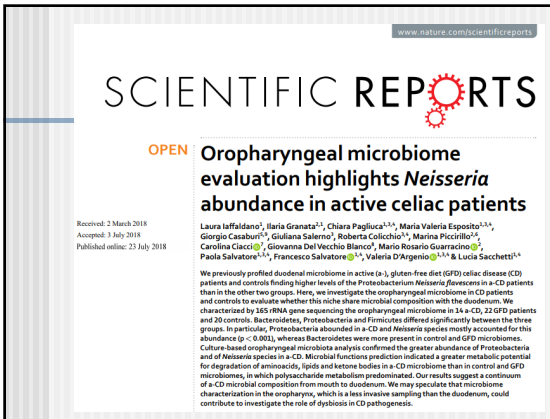
32

Oral Microbiome



- Periodontal inflammation
  - Diabetes
  - Rheumatoid arthritis
  - SLE
- All have increased risk of periodontal disease
- Can trigger or exacerbate systemic inflammation.
- Monitor CRP, ADVISE panel

33



www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

Oropharyngeal microbiome evaluation highlights *Neisseria* abundance in active celiac patients

Received: 2 March 2018
Accepted: 3 July 2018
Published online: 23 July 2018

Laura Iaffaldano[1], Ilaria Granata[2,3], Chiara Pagliuca[1,3,4], Maria Valeria Esposito[2,3,4], Giorgio Casaburi[2,3], Giuliana Salerno[2], Roberta Colicchio[1,4], Marina Piccirillo[1,4], Carolina Ciacci[5], Giovanna Del Vecchio Blanco[5], Mario Rosario Guarracino[2], Paola Salvatore[1,3,4], Francesco Salvatore[1,4], Valeria D'Argenio[1,3,4] & Lucia Sacchetti[1,4]

We previously profiled duodenal microbiome in active (a-), gluten-free diet (GFD) celiac disease (CD) patients and controls finding higher levels of the Proteobacterium *Neisseria flavescens* in a-CD patients than in the other two groups. Here, we investigate the oropharyngeal microbiome in CD patients and controls to evaluate whether this niche share microbial composition with the duodenum. We characterized by 16S rRNA gene sequencing the oropharyngeal microbiome in 14 a-CD, 22 GFD patients and 20 controls. Bacteroidetes, Proteobacteria and Firmicutes differed significantly between the three groups. In particular, Proteobacteria abounded in a-CD and *Neisseria* species mostly accounted for this abundance ($p < 0.001$), whereas Bacteroidetes were more present in control and GFD microbiomes. Culture-based oropharyngeal microbiota analysis confirmed the greater abundance of Proteobacteria and of *Neisseria* species in a-CD. Microbial functions prediction indicated a greater metabolic potential for degradation of aminoacids, lipids and ketone bodies in a-CD microbiome than in control and GFD microbiomes, in which polysaccharide metabolism predominated. Our results suggest a continuum of a-CD microbial composition from mouth to duodenum. We may speculate that microbiome characterization in the oropharynx, which is a less invasive sampling than the duodenum, could contribute to investigate the role of dysbiosis in CD pathogenesis.

34

Poor oral health linked to

- Pneumonia
- Pancreatic disease
- CV disease/atherosclerosis
- Colorectal cancer
  - Higher levels of *Aggregatibacter actinomycetemcomitans*
- Esophageal cancer
- Pancreatic cancer
  - Both have higher levels of *Porphyromonas gingivalis*

35

Vaginal microbiome

- An intricate & dynamic microecosystem that constantly undergoes fluctuations throughout the lifespan, especially during the menstrual cycle.
- Diverse bacteria and fungi in vaginal canal
- A healthy vaginal microbiome is dominated by *Lactobacillus* which produce various antimicrobial compounds.
  - Create lactic acid & keep pH low
  - Occupy space & prevents pathologic species from residing
  - Reduce inflammation

36

Vaginal Microbiome

- Anaerobes can contribute to vaginal dysbiosis
- Bacterial vaginosis is characterized by the decline in *Lactobacillus* & marked increase in the concentration of anaerobic microbes.
- If tx BV or candida, check for both and test pH
- Consider boric acid vaginal suppositories

Xiaodi, Frontiers in Cellular and Infection Microbiology, Vol=11, 2021
Auriemma et.al Frontiers in Cell Infe Microbiology Vol =11 2021

37

Skin microbiome

- A natural ecosystem that supports the growth of microorganism
  - Marples, The Ecology of the Human Skin, 1965
- Changes through the lifespan
  - Teenage acne (the ultimate skin dysbiosis)
  - Less diversity as we age
- Skin dysbiosis can contribute to local and systemic inflammation and exacerbate delays in wound healing.
  - Decreased diversity= more staph

38

Skin microbiome by location

- Naturally supports the growth of micro-organisms
- Location
  - Greatest fungal populations: toes, groin, axilla
- Sebaceous sites- low diversity
  - Cutibacterium & Corynebacterium
- Moist areas-Medium diversity
  - Staph & Corynebacterium
- Dry areas- highest diversity!
  - Proteobacteria & Bacteroides

Grice, Nature reviews Micro 2011 | Grice, Kong, Science 2009

39

Atopic dermatitis a classic study of the microbiome

- High population of staph during AD flare
  - *Kong et al Genome Res 2021*
  - Tip: compare w nasal staph
- "Atopic March"
  - Most with severe AD have asthma/allergies
  - Incidence of "march" from AD to asthma has doubled in the last 33 years

40

Skin microbiome & Primary immunodeficiency

- Colonized with atypical microbiota
  - *Serratia*
  - *Gammaproteobacteria*
- Atopic dermatitis, eczema, primary immunodeficiency, diabetic ulcers, and Hyper IgE syndrome all have abnormal skin microbiome

Julia Oh

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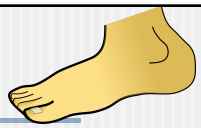
Skin dysbiosis and DM foot ulcers



- About 25% of DM suffer from a chronic wound
- Skin dysbiosis plays a role in delay of healing
- The core microbiome consisted of bacteria *Alcaligenes*, *Pseudomonas*, *Burkholderia*, and *Corynebacterium* in decreasing order
- The core microbial community varies with wound severity, polymicrobial species distribution is individual specific, antibiotic susceptibility varies.
- The "DFU100 cohort"
  - 100 patients uninfected plantar DFU
  - Sharp debridement

Ercolini 2020
Kalan 2019

42

Skin microbiome- take home

- Most people do not need to shower daily
- Excessive use of antimicrobial hand gels & washes reduce diversity
- Most major skin conditions have an altered microbiome
  - Oatmeal application/bath and Epsom salt baths may help *(personal observations)*
- It's ok for kids (and adults) to get dirty!
- Look for microbiome focused cosmetics

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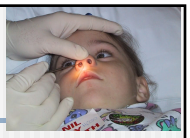
Nasal Microbiome

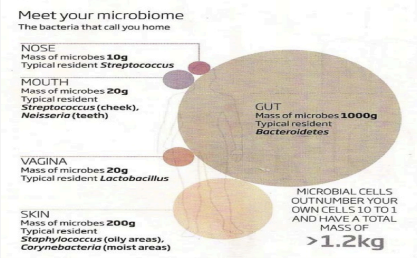


- Initial filter for airborne particles
- Alterations in nasal microbiome
  - Chronic rhinosinusitis
    - Consider candida/fungal & biofilm disease
  - Asthma
  - Polyps
  - Allergic rhinitis
  - Many with COVID also have bacterial co-infection
    - Dimitri-Pinheiro proposes idea of nasal probiotics
    - Allergy Rhinology Jan 2020

44

Gut microbiome

- A human gut can hold 2 kg of microbes including 1,000 species of bacteria.



45

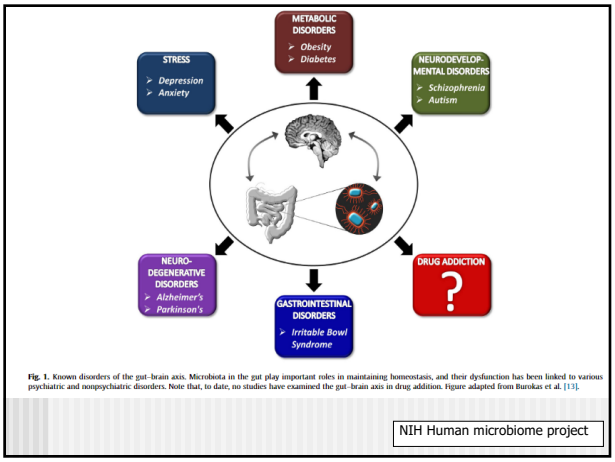


Fig. 1. Known disorders of the gut–brain axis. Microbiota in the gut play important roles in maintaining homeostasis, and their dysfunction has been linked to various psychiatric and nonpsychiatric disorders. Note that, to date, no studies have examined the gut–brain axis in drug addition. Figure adapted from Burokas et al. [13].

NIH Human microbiome project

46

Gut Microbiome function 1 Immune function

- The GI tract is a vast frontier
- The ultimate portal of entry into the body.
- It's lumen is filled with a complex mixture of nutrients
  - Its an attractive "culture medium" for microbes.
- Intestine is constantly working to distinguish between potentially harmful microorganisms versus benign antigens that occur in food.
- Intestine also has a special need for immune surveillance against malignancy. Thus, the rapid rate of proliferation of intestinal epithelial cells, coupled with exposure of these cells to potential toxins in the intestinal lumen, renders the epithelium uniquely sensitive to cell transformation.
- PROTECTS AGAINST INFECTION

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Gut microbiome function-2

- Synthesize vitamins & metabolites
  - Vit K, biotin, vitamin B_{12}, folic acid, and thiamine.
  - Low levels? Think of the gut!
- Maintenance of gut barrier
- Immune modulation
- Digestion & metabolism:
  - energy and nutrient extraction
  - Gut breaks down EVERY ORAL MED!
  - Chronic fatigue?
  - Malabsorption

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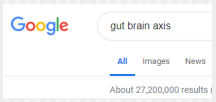
Gut microbiome-3

- Gut-brain
- Intestinal development
- Epithelial turnover
- Peristalsis
- Micronutrient
- Drug metabolism
- Blood flow



"I have a gut feeling"
"I have butterflies in my stomach!"

49

Gut-brain connections
George Porter Phillips

- Early 1900's Bethlem Royal Hospital (London)
- Patients with melancholia had constipation & "general clogging of the metabolic processes"
  - brittle nails, thin hair and pallor.
- It was thought these symptoms were caused by depression
- He removed all meat (except fish) and gave them fermented milk (keifer) which contains lactobacillus
- N=18 patients
  - 11 were cured completely
  - 2 others showing significant improvement.
  - Birth of PSYCHOBIOTICS!

50

1910

Try it!

The Treatment of Melancholia by the Lactic Acid Bacillus. (1) By J. George Porter Phillips, M.B., B.S. (Lond.), M.R.C.S., L.R.C.P., Assistant Physician, Bethlem Royal Hospital.

Melancholia, with its attendant constipation and faulty alimentation, lends itself at once to a dietetic form of treatment.

Whether the constipation is dependent on defective innervation and is a direct symptom of melancholia or is the initial cause of this mental disturbance, it matters not so far as our endeavours in treatment are concerned.

It is obvious that the melancholiac, in the acute stages of his illness, struggles against great odds owing to the following facts: His alimentation is defective, his excretions are diminished, and, moreover, his whole system is in a state of auto-intoxication. In other words there is a general clogging of the metabolic processes. The disturbance of the alimentary tract tends to form a vicious cycle hindering the nervous system from obtaining an efficient and pure food supply.

We have ample evidence of this impaired metabolism with its toxæmia. The patient has a sallow, muddy complexion, a dry skin, a parched, furred tongue, a high-tension pulse,

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Mood, Anxiety, OCD

- ASK ABOUT GUT FUNCTION IN PSYCH AND NEURO PATIENTS
- *Lactobacillus plantarum*
  - IBS patients:
  - Significantly reduced their anxiety and improved their quality of life
- *Bifidobacterium longum*
  - Show to help depression, reduces cortisol, address obsessions, compulsions, paranoia, anxiety.
- GABA: main inhibitory and relaxing neurotransmitter
  - Studies suggest that *lactobacillus rhamnosus* may reduce anxiety by changing the expression of GABA receptors

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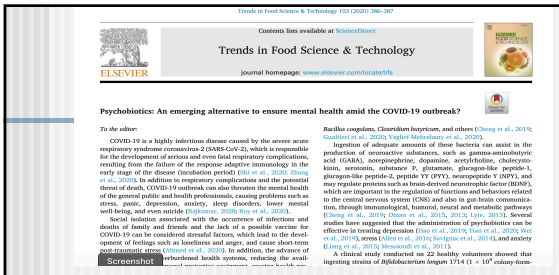

- *Lactobacillus gasseri* was effective in recovering from fatigue and in relieving anxiety and depressed mood in university students and improved mental status and sleep quality in young students exposed to chronic stress (N=49)

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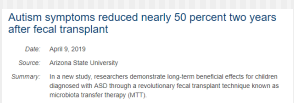
2019 Autism & Gut-brain

- 70% have GI complaints
- Microbiota transfer therapy (FMT)
- 45% reduction in abnormal language, social interaction and behavior at two years post-treatment
- "We are finding a very strong connection between the microbes that live in our intestines and signals that travel to the brain,"
- "Two years later, the children are doing even better, which is amazing."



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Assessing the gut microbiome

- What can you do on a day to day basis?
- PE:
  - Thick white coated tongue
  - Abdominal distension/tympany
- Lab:
  - IgA
  - CRP
  - Stool culture
  - ? Advanced stool testing

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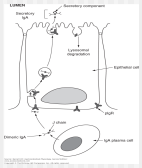
IgA serum levels

- IgA: Secreted across the intestinal epithelium
- Key marker of gut mucosal health
- Low IgA associated with
  - Autoimmunity
  - Celiac
  - Asthma (wow!)
  - SIBO
  - Allergies
  - Alpha gal persistence *(personal observation)*



Gastrointestinal Physiology, 2e, 2014

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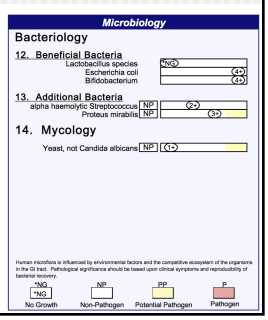
Stool testing

- Basic cultures
  - pH
  - WBC
  - Culture



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Stool testing for probiotics/Microbiome

Gut Microbiome and Metabolic Health	Genus/Species	Abundance	Previous	Rating	Potential Associated Risk*
	Lactobacillus reuteri	LOW ↓		★★★★	
	Lactobacillus casei	OPTIMAL ↔		★★★	
	Lactobacillus paracasei	OPTIMAL ↔		★★★★★	
	Methanobacteriales	OPTIMAL ↔		★	
	Bifidobacterium Animalis	OPTIMAL ↔		★★★★	Obesity
	Methanobrevibacter smithii	OPTIMAL ↔		★★★★	
	Staphylococcus	OPTIMAL ↔		★★★	
	Blautia	OPTIMAL ↔		★★	
	Oscillospira	OPTIMAL ↔		★★★★★	
	Alistipes	OPTIMAL ↔		★★★	
	Roseburia	LOW ↓		★★★★★	
	Eubacterium	LOW ↓		★★★★★	Type II Diabetes
	Eggerthella	OPTIMAL ↔		★★★★★	

Potential Risk Mitigation Choices

Probiotics

Consider taking probiotics containing Lactobacillus reuteri, Lactobacillus paracasei, Lactobacillus rhamnosus, and Bifidobacterium animalis.

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Gut Microbiome and Nutrition I	Genus/Species	Abundance	Previous	Rating	Potential Associated Risk*
	Bifidobacterium bifidum	OPTIMAL ↔		★★★★	
	Bifidobacterium longum	OPTIMAL ↔		★★★★	
	Lactobacillus plantarum	OPTIMAL ↔		★★★	K Vitamins and B Vitamins Production affected
	Bifidobacterium breve	OPTIMAL ↔		★★★★	
	Bifidobacterium adolescentis	OPTIMAL ↔		★★★★	
	Bacillus subtilis	OPTIMAL ↔		★★	Vitamin K2 production affected
	Lactobacillus reuteri	LOW ↓		★★	
	Propionibacterium freudenreichii subsp. shermanii	OPTIMAL ↔		★★	Vitamin B12 production affected
	Lactobacillus fermentum	OPTIMAL ↔		★★	

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Lets look at

- Probiotics for specific disease states

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Probiotics for IBS

63 RCTs Studying IBS and probiotics

Most favorable (or at least no harm!)

- Irritable bowel syndrome =crampy pain, gassiness, bloating and changes in bowel habits.
- *B. regularis*
  - **16 RCTs = benefit in IBS-C**
- Whorwell:
  - Encapsulated *bidifido. infantis* in women w IBD
  - **Placebo controlled N= 363**
  - >20% improvement w a dose of 10^8
- Guglielmetti:
  - Adequate relief reported in 47% (11% in placebo)
  - Improved global symptom score, pain, distension/bloati stool urgency.

Whorwell etal 2006 AJGI 1581-1590

Guglielmetti S, et al. RCT: Bifidobacterium bidfidum MIMBb75 significantly alleviates IBS and improves QOL-a DBPCS. Aliment Pharmacolo Ther. 2011. 33(10)

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Inflammatory bowel Disease

- Hygiene hypothesis
- Less microbial diversity
  - Less stability
  - Especially in IBD patients receiving repeated antibiotics
- Activation of specific species (i.e. E. Coli)
- Depletion of mucous layer- low IgA
- Inflammation & elevated CRP
- Hot debate: Cause vs effect

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Inflammatory bowel & Primary sclerosing cholangitis

- Strong correlation
- Share immune mediated pathways
  - Mertz, Ann Gastroenterol. 2019 Mar-Apr; 32(2)
- Patients with PSC have less microbial diversity
- E. Coli levels are correlated with Alk Phos levels
- Enhancement of the microbiome with diet, probiotics, and fecal transplant are under study with early promising results
  - *Sabino, etal, Gut 2016*

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Gut microbiome and amyloid deposits

SCIENTIFIC REPORTS

OPEN

Gut microbiome alterations in Alzheimer's disease

Nicholas M. Vogt[1], Robert L. Kerby[2], Kimberly A. Dill-McFarland[2], Sandra J. Harding[1], Andrew P. Merluzzi[1], Sterling C. Johnson[3,4,5], Cynthia M. Carlsson[3,4,5], Sanjay Asthana[3,5], Henrik Zetterberg[1,6,7,8], Kaj Blennow[1,8], Barbara B. Bendlin[3,4] & Federico E. Rey[2]

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Accepted: 27 September 2017
Published online: 19 October 2017

Alzheimer's disease (AD) is the most common form of dementia. However, the etiopathogenesis of this devastating disease is not fully understood. Recent studies in rodents suggest that alterations in the gut microbiome may contribute to amyloid deposition, yet the microbial communities associated with AD have not been characterized in humans. Towards this end, we characterized the bacterial taxonomic composition of fecal samples from participants with and without a diagnosis of dementia due to AD. Our analyses revealed that the gut microbiome of AD participants has decreased microbial diversity and is compositionally distinct from control age- and sex-matched individuals. We identified phylum- through genus-wide differences in bacterial abundance including decreased Firmicutes, increased Bacteroidetes, and decreased *Bifidobacterium* in the microbiome of AD participants. Furthermore, we observed correlations between levels of differentially abundant genera and cerebrospinal fluid (CSF) biomarkers of AD. These findings add AD to the growing list of diseases associated with gut microbial alterations, as well as suggest that gut bacterial communities may be a target for therapeutic intervention.

Alz Disease: low firmicutes & bidifidobacterium, increased bacteroides

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Role in Cancer therapy

CellPress

Cancer Cell
Perspective

The Influence of the Gut Microbiome on Cancer, Immunity, and Cancer Immunotherapy

Vancheswaran Gopalakrishnan,[1,3] Beth A. Helmink,[1,3] Christine N. Spencer,[2] Alexandre Reuben,[1] and Jennifer A. Wargo[1,2,*]

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https://doi.org/10.1016/j.ccell.2018.03.015

The microbiome is receiving significant attention given its influence on a host of human diseases including cancer. Its role in response to cancer treatment is becoming increasingly apparent, with evidence suggesting that modulating the gut microbiome may affect responses to numerous forms of cancer therapy. A working knowledge of the microbiome is vital as we move forward in this age of precision medicine, and an understanding of the microbiome's influence on immune responses and cancer is key. It is also important to understand factors influencing the gut microbiome and strategies to manipulate the microbiome to augment therapeutic responses.

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Probiotics and HTN

BP reduction -Consumption of milk fermented with *Lactobac* = modest **reductions in blood pressure**, due to the ACE inhibition-like peptides produced during fermentation.

- "Consuming probiotics may improve BP by a modest degree, with a potentially greater effect when baseline BP is elevated, multiple species of probiotics are consumed, the duration of intervention is ≥8 weeks, or daily consumption dose is ≥10^{11} CFUs"
  - *S. Khalesi, Hypertension, Oct 2014*
- "We're some way from being able to tell you exactly which yogurt to eat to try to promote lower blood pressure, but I think that being able to provide that sort of information is the long-term hope—gather all of the puzzle pieces, and put them together,"
  - *J. L. Pluznick. Ph.D, Johns Hopkins 2020*

66

NAFLD

J Gastroenterol (2020) 55:142–158
https://doi.org/10.1007/s00535-019-01649-8

The Japanese Society of Gastroenterology

REVIEW

Intestinal microbiome and NAFLD: molecular insights and therapeutic perspectives

Haiming Hu[1] · Aizhen Lin[2] · Mingwang Kong[1] · Xiaowei Yao[1] · Mingzhu Yin[1] · Hui Xia[1] · Jun Ma[1] · Hongtao Liu[1]

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Obesity & metabolic syndrome

- Low levels of Bacteroidetes in obesity
- Elevated Actinobacteria in obese
- Higher levels
  - glycoside hydrolases
  - Carb binding
  - Polysaccharide lyases
- Obese patients consider supplementation with Bacteroides
  - They are firmicutes dominant

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Colon Cancer

- Inflammatory disease
  - Low fiber high risk
  - Diverticular disease high risk
- High fecal fats
- "Dysbiosis has been associated with the development of colorectal cancer. Gut microbiota is involved in the metabolic transformations of dietary components into oncometabolites and tumor-suppressive metabolites that in turn affect CRC development." *Chattopadhyay 2021*
- Increased wall permeability, direct introduction of microbes fueling inflammation

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Celiac persistent disease

- Persistent disease despite strict dietary changes
- Higher levels of *Proteobacteria*
- Lower levels of *firmicutes*
- Overall less diversity
- Consider SIBO, dysbiosis
  - I have had success in resistant Celiac with probiotics and rifaximin.

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Nutrition Research 87 (2021) 1–12

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/NTR

ELSEVIER

Review Article

Probiotics: A potential immunomodulator in COVID-19 infection management

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[b] Academy of Scientific and Innovation Research (AcSIR), Ghaziabad, Uttar Pradesh 201002 India

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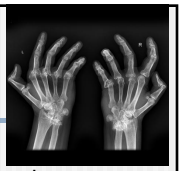
Rheumatoid



- Bacteria is present on mucosal surfaces which alter local and system host response & trigger inflammation
  - Mycoplasma
  - ACR.org: low dose minocin
  - Roadback foundation
- Gene alone can't fully explain RA
- Theory under research: bacteria shares pro-inflammatory proprieties & act as a trigger.

Brisca Current Opio Rheum 2014, Deja, PNAS 2015. radiopaedia.org

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Manipulating the gut microbiome: overview

- Can be beneficial!
- Lifestyle
- Diet
- Prebiotics- help stimulate growth
- Probiotics (Psychobiotics) planting new strains
- Appropriate antimicrobials –eliminate pathogenic strains
- Fecal transplant replacing strains

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Supporting the Microbiome

- Lifestyle: Adequate sleep & exercise frequently
- Take probiotics
  - Lactobacilli (multiple species)
  - Bifidobacterium (multiple species)
- Minimize:
  - Refined carbohydrates
  - Meds: NSAIDs & PPIs- esp. in psych patients!
  - Alcohol
  - Antibiotics– especially in kids!
    - Theory – esp. in kids born via C-section!

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Supporting The Microbiome: Diet

- The food we eat can support good microbes
  - These microbes can alter taste receptor signaling & further impact our intake
- Eat a variety of fresh plant based foods
  - Eat the colors
  - Plant based diet have a much more diverse microbiome (Wu Science 2011, David Nature 2013)
- Consume prebiotic fibers:
  - Pectin, inulin, asparagus, garlic, onions, leeks, bananas
- Eat fermented foods:
  - Kombucha, fresh sauerkraut, kimchi, yogurt, ACV

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AGA recommendation 2020

Conditional recommendation low evidence

- Probiotics during antibiotic therapy to prevent C.diff
  - Cochran N=995
  - Probiotics reduced the overall risk of *C difficile* infection vs placebo
  - 2-species combo: *L acidophilus* & *L casei*
  - 3-strain combo *L acidophilus, L delbrueckii B bifidum*
  - 4-strain combo of *L acidophilus, L delbrueckii B bifidum*, and *S salivarius*

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AGA recommendation 2020

Conditional recommendation high evidence

- Preterm <37 weeks & low birth weight
- A combination of *Lactobacillus* and *Bifidobacterium* and *B longun infantis*;
- or *L casei* and *B breve*;
- or *L rhamnosus*, *L acidophilus*, *L casei*, *B longum infantis*, *B bifidum*, and *B longum longum*;
- for prevention of NEC

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L-Glutamine

- Essential for gut microbiome support
- Monitor IgA levels
- Most abundant amino acid

in the body and is necessary for the maintenance of many metabolic functions. Under situations of stress, physiological demands increase, triggering a need for glutamine supplementation.

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Restoring the gut microbiome

- FMT
  - directly change the recipient's gut microbiome to normalize the composition and gain a therapeutic benefit.
  - Hx traced back to the 4th century
  - 2013 FDA approval for recurrent and refractory *C diff*
  - the range of FMT applications extended rapidly and broadly not only in GI but also in extra-gastrointestinal diseases

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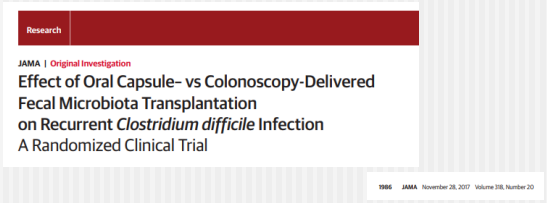
Restoring the microbiome


Research

JAMA | Original Investigation

Effect of Oral Capsule– vs Colonoscopy-Delivered Fecal Microbiota Transplantation on Recurrent *Clostridium difficile* Infection

A Randomized Clinical Trial

Frozen: immediate avaibility & ability to mix donors
Fresh vs frozen: no clinical difference, *Lee JAMA 2016*

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FMT: Dysbiotic states under study

- IBD*
- IBS*
- Chronic functional constipation
- Obesity
- Diabetes
  - RCTs support
- Multiple Sclerosis*
- Parkinson's Disease
- Anxiety
- Rheumatoid arthritis
- Depression
- Chronic fatigue*
- Eosinophlic and allergy disease
- Immune TP

*Many case series supports

Smits, Gastroenterology 2015
Lee, Gastro & Hepatology 2015

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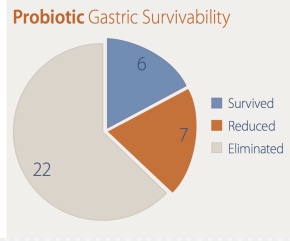
"Good Probiotics"

- Need to get to the gut, especially the colon
  - *Redding University an Standards Agency*



Look for enteric coated probiotics, and doses in the BILLIONS!

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Probiotic 'prescription'

- Look for probiotics in the BILLIONS!
- **Look for strain names on the label!**

Proprietary Blend *Lactobacillus acidophilus* La-14® *Bifidobacterium longum* BI-05™ *Lactobacillus plantarum* Lp-115®	409 mg (50 Billion CFU†)

Xymogen

Lactobacillus acidophilus (LA-14)	12 Billion CFU*	**
Lactobacillus acidophilus (LA-1)	10 Billion CFU*	**
Bifidobacterium lactis (BL-04)	15 Billion CFU*	**
Bifidobacterium lactis (Bi-07)	7 Billion CFU*	**
Lactobacillus paracasei (LPC-37)	3 Billion CFU*	**
Lactobacillus rhamnosus (HN001)	3 Billion CFU*	**

** Daily Value (DV) not established

Masters Formula
Not an endorsement

No financial interest

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Look for Multi-Probiotic strains

Research emerging on potential benefits of multiple probiotic strains as a health supplement as opposed to a single strain.

1. ProBio GI, Des Bio
2. Omnibiotic AB-10
3. Acidophilus Pearls
   Lactobacillus acidophilus, Bifidobacterium longum
4. *Kyo-Dophilus*
   Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium longum
5. *Symprove live activated probiotic*
   Lactobacillus plantarum, Lactobacillus acidophilus, Lactobacillus Casei, var. Rhamnosus, Enterococcus faecium.

Not an endorsement
No financial interest

84

Probiotics are GRAS

- More than 60 human studies since 2008
- Many RCTs/DB
- 60 strains evaluated
- No morbidity

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Probiotics- Cautions

- **Avoid in children with acute infectious gastroenteritis!**
  (AGA – moderate evidence 2020)
- Can be an unnecessary expense in those who do not require them.
- Diet enriched with soluble, but not insoluble, fiber induced HCC in dysbiotic mice (Inulin) *Singh et al., 2018, Cell 175, 679–694*
- Some probiotics supplements have been associated with infections in patients who are immunocompromised.
  - skin rash, fever, bloody stools etc.
- Rare cases cause bloating, diarrhea, abdominal pain.
- Not all claims on the label are true!
- Severe pancreatitis (Lancet 2008)
- Immunocompromised patients: Lactobacillus bacteremia- rare!
- Sometimes interact with immunosuppressive drugs leading to life threating conditions.
- BUYER BEWARE!

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Key points

- We are living in the age of decreasing microbial diversity
  - May explain many diseases.
- The microbiome is equivalent to another functioning organ in the body.
- Encourage 25-35 grams of fiber a day
- Diversity diet with more colorful veggies
- Elderly have least diversity, more at risk for candida, C. diff, and dysbiosis.
- Gut microbiome plays a strong role in the Gut-brain connection- consider psychobiotics.
- Limit long term PPI
- Limit antibiotic use in our youngest patients
- Probiotics for obesity, diabetes, IBD

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Question 3

Studies suggest that antibiotic use stresses our gut microbiome and triggers an increase incidence of

A. Obesity & type 1 diabetes
B. Long term viral illnesses
C. Melanomas & skin cancers
D. Kidney stones & UTIs

Blaser (2011) & Becattini (2016)

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Question 4

- Which of the following is TRUE regarding our gut microbiome?
  A. A gut populated with *Firmicutes* is associated with a **lower BMI.**
  B. Children born by c-section have a **lower** rate of allergies and metabolic diseases.
  C. Long term PPIs **do not** alter the gut microbiome.
  D. Bacteria populating the gut microbiota can secrete **large amounts** of amyloids and lipopolysaccharides.

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References-1

- Toscano M, de Vecchi E, Microbiological and genetic identification of some probiotics proposed for medical use in 2011. J Chemother. 2013;25(3):156–61.
- Goldstein EJC, Citron DM, Claros MC, Tyrrell KL. Bacterial counts from five over-the-counter probiotics: are you getting what you paid for? Anaerobe. 2014; 25:1–254.
- Sanders ME, Klaenhammer TR, Ouwehand AC, Pot B, Johansen E, Heimbach JT, et al. Effects of genetic, processing, or product formulation changes on efficacy and safety of probiotics. Ann N Y Acad Sci. 2014;1309:1–18. pmid:24571253
- Grzeskowiac L, Isolauri I, Salminen S, Gueimonde M. Manufacturing process influences properties of probiotic bacteria. Brit J Nutr. 2011;105:887–894. pmid:21059281
- Vanhee LM, Goemé F, Nelis HJ, Coenye T. Quality control of fifteen probiotic products containing *Saccharomyces boulardii*. J Appl Microbiol. 2010;109(5):1745–52.
- Johnson CL, Versalovic J. The Human Microbiome and its Potential Importance to Pediatrics. Pediatrics. 2012;129(5):950-960.
- Lin A, Bik E, Costello E, et al. Distinct distal gut microbiome diversity and composition in healthy children from Bangladesh and the United States. PLoS One. 2013;8(1):e53838.
- Tyakht A, Kostryukova E, Popenko A, et al. Human gut microbiota community structures in urban and rural populations in Russia. Nature Communications. 2013;4:2469.
- Mani V, Hollis JH, and Gabler NK. Dietary oil composition differentially modulates intestinal endotoxin transport and postprandial endotoxemia. Nutrition & Metabolism. 2013;10:6.
- Sanz Y, Olivares M, Moya-Perez A, Agostoni C. Understanding the role of gut microbiome in metabolic disease risk. Pediatric Research. 2015;77:236-244.

90

References-2

- Nagpal R, Kumar M, Yadav AK, et al. Gut microbiota in health and disease: an overview focused on metabolic inflammation. Benef Microbes. 2016;7(2):181-94.
- Cryan JF, O'Mahony SM. The microbiome-gut-brain axis: from bowel to behavior. Neurogastroenterol Motil. 2011;23:187–192.
- Okeke F, Roland BC, Mullin GE. The Role of the Gut Microbiome in the Pathogenesis and Treatment of Obesity. Glob Adv Health Med. 2014;3(3):44-57.
- Karlsson FH, Fak F, Nookaew I, et al. Symptomatic atherosclerosis is associated with an altered gut metagenome. Nat Commun. 2012;3:1245.
- Semenkovich CF, Danska J, Darsow T, et al. American Diabetes Association and JDRF Research Symposium: Diabetes and the Microbiome. Diabetes. 201;64(12):3967-3977.
- Alcock J, Maley CC, Aktipis CA. Is eating behavior manipulated by the gastrointestinal microbiota? Evolutionary pressures and potential mechanisms. BioEssays. 2014;36(10):940-949.
- Rieder R, Wisniewski PJ, Alderman BL, et al. Microbes and mental health: A review. Brain Behav Immun. 2017: S0889-1591(17):30016-8.
- "Survival of Probiotics in Simulated Gastric Fluid." Food Science Center Report. Silliker Labs. RPN 16663. August 24, 2013.
- Gibson GR, Rouzaud G, Brostoff J, et al. An evaluation of probiotic effects in the human gut: microbial aspects. Final Technical report. FSA project ref G01022.
- Larsen N, Michaelsen K, Paerregaard A, et al. A comparative study on adhesion and recovery of potential probiotic strains of Lactobacillus spp. by in vitro assay and analysis of human colon biopsies. Microb Ecol Health Dis. 2009;21(2):95-99.
- Prakash S, Tomaro-Duchesneau C, Saha S, et al. The Gut Microbiota and Human Health with an Emphasis on the Use of Microencapsulated Bacterial Cells. J Biomed Biotechnol. 2011;2011:981214.
- Li N, Russell W, Douglas-Escobar M, et al. Live and heat-killed Lactobacillus rhamnosus GG: Effects on proinflammatory and anti-inflammatory cytokines/chemokines in gastrostomy-fed infant rats. Pediatr Res. 2009;66(2): 203-7.
- Lefevre M, Racedo SM, Ripert G, et al. Probiotic strain Bacillus subtilis CU1 stimulates immune system of elderly during common infectious disease period: a randomized, double-blind placebo-controlled study. Immun Ageing. 2015;12:24.
- Serra CR, Earl AM, Barbosa TM, et al. Sporulation during Growth in a Gut Isolate of Bacillus subtilis. J Bacteriol. 2014;196(23):4184-4196.

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Reference 3

Gastroenterology 2020;159:697–705

CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guidelines on the Role of Probiotics in the Management of Gastrointestinal Disorders

Grace L. Su,[1,2] Cynthia W. Ko,[3] Premysl Bercik,[4] Yngve Falck-Ytter,[5,6] Shahnaz Sultan,[7] Adam V. Weizman,[8] and Rebecca L. Morgan[9]

[1]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan; [2]Gastroenterology Section, Veterans Administration Ann Arbor Healthcare System, Ann Arbor, Michigan; [3]Division of Gastroenterology, University of Washington Medical School, Seattle, Washington; [4]Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada; [5]Division of Gastroenterology, Case Western Reserve University, Cleveland, Ohio; [6]Louis Stokes Veterans Affairs Medical Center, Cleveland, Ohio; [7]Division of Gastroenterology, University of Minnesota, Minneapolis, Minnesota; [8]Division of Gastroenterology, Mount Sinai Hospital, Department of Medicine, University of Toronto, Toronto, Ontario, Canada; and [9]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

This document presents the official recommendations of the American Gastroenterological Association (AGA) on the role of probiotics in the management of are not considered drugs in the United States or Europe, the regulatory status is not the same as would normally accompany a pharmaceutical product. The industry is

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Reference -4
Psychobiotics & sad mood

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood ☆

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Thank you!

AASPA American Association of Surgical Physician Assistants

- Remember you are not alone & you are what you eat!
- I hope you come to share my excitement for the microbiome!
- "It is reasonable to propose that the composition of the microbiome and its activities are involved in most, if not all, of the biological processes that constitute human health and disease"
  Martin J Blaser, MD
  J Clin Invest. 2014;124(10):4162-4165
- Any questions or comments?

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