THE PROBIOTIC PRESCRIPTION

AAPA Virtual CME meeting

May 2021

"All disease begins in the gut." – *Hippocrates*

"Should I take a probiotic? Which one?" - *Most of our patients*

1

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- Clinical Assistant Professor
  - **Stony Brook PA Program**
- Surgical PA
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  - BOD
- **PA**
  - **Morrison Health, NY**
- **No disclosures.**
- **No commercial associations**

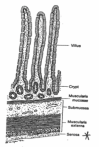
Stony Brook Southampton Hospital

Stony Brook School *of* Health Technology and Management

AASPA

2

MY INTEREST



- I have a 23 year interest in the GI tract.
- It began simply as a surgical/technical interest- how to resect the bowel, staple, suture and scope it. As time when on, I became more interested in its physiology, neurologic innervation, absorption etc.
- I'm always excited to talk about the gut microbiome to anyone who will listen!
- I've come to realize that the gut
  - is a key part of our immune system & overall ecosystem
  - oral medication can alter its function
  - nutrition can affect and is affected by its role.
  - Probiotics are an important prescription for many

3

THE PROBIOTIC PRESCRIPTION

- **Description**
- Typing 'probiotics' into Google gives you > 56 million hits. As patients read more about the role of probiotics in treatment and prevention of disease, the topic comes up regularly in everyday practice. Clinicians must be prepared to discuss the role of probiotics and describe appropriate use. Clinicians should also understand when probiotics may not be beneficial or indicated.

- **Learning Objectives**
- At the end of this session, participants should be able to:
  - Recognize the role of the gut microbiome in human health
  - Define a prebiotic, probiotic, psychobiotic, and synbiotic
  - Compare and contrast the two major strains of probiotics: Lactobacillus and Bifidobacterium
  - Describe the appropriate use of probiotics during antibiotic administrations well as for dysbiosis, enteritis, Inflammatory bowel, and for mood
  - Recognize that research is evolving, and explain to patients the proper use of probiotics

4

T/F

1. In RCTs & meta-analysis, **probiotics** have been shown to reduce the amount of antibiotic associated diarrhea.
2. In RCTs & Meta-analysis, **prebiotics** have been shown to reduce the amount of antibiotic associated diarrhea.
3. All patients can benefit from probiotic use in a capsule form.
4. In patients with significant immune deficiency, probiotics may be harmful.
5. Cardiology PAs use probiotics for cholesterol and blood pressure lowering abilities.
6. The best probiotics are refrigerated to preserve potency.
7. Most probiotic prescribing is not supported by RCTs.
8. The most expensive probiotics are the highest quality.

5

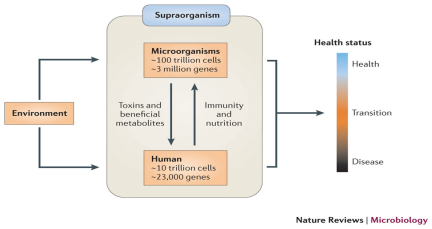
REVIEW

To understand probiotics, review the gut microbiome.

- Human microbiota
  - The specific bacteria, viruses, fungi, and other single-celled animals that live in the body.
  - Our collective organism!
  - AKA: The ecological community of bacteria that lives on and within us
- Microbiome
  - All of the genes/genomes inside these microbial cells
  - "gene content"
- Dysbiosis
  - Imbalance in the gut microbiome
  - High levels of Proteobacteria
    - Gram-negative bacteria. Escherichia, Salmonella, Vibrio, Helicobacter, Yersinia, Legionellae
  - *UpToDate*
  - AAPA2020 Gut microbiome lecture

6

Human-Microbiota Supraorganism



Nature Reviews | Microbiology

Nature Reviews Microbiology 11, 639–647 2013

- The gut lining is the 'frontline' where our immune system recognizes the enemy!
- Ratio of human to non human cells is 10:1

7

FACTORS AFFECTING THE INTESTINAL MICRO ECOSYSTEM

- Antibiotics exposures
  - Especially under the age of 2
- Microbial infections
- Diet (highly processed, low fiber foods)
- Chronic diarrhea
- Stress
- Chlorinated water
- Radiation and chemotherapy
- Birth by c-section

8

WHAT WE EAT AFFECTS OUR MICROBIOME

- One day of strict animal or plant based diet will alter our microbiome
- High fiber = more prevotella
- High fat/high protein = more bacteroides
- both are members of Bacteroidetes family

30gm a day!

- Eating PREBIOTICS feeds out gut microbiome
- Fiber – not broken down by digestive enzymes, so they make it to our colon and can be fermented by gut bacteria into something GOOD
- Most Americans do not get enough fiber (about 16gm a day)
- Best prebiotic fiber:
  - Beans, veggies, berries

9

WHAT WE EAT AFFECTS OUR MICROBIOME

- Jan 11 2021
- A. O'Conner

The New York Times

How the Right Foods May Lead to a Healthier Gut, and Better Health

A diet full of highly processed foods with added sugars and salt promoted gut microbes linked to obesity, heart disease and diabetes.

10

THE AMERICAN GUT PROJECT

- The more different plant types a person eats, the higher the microbial diversity of the gut. Persons who ate 30 or more different plant types a week, had microbiomes that were more diverse than those of people who ate only 10 plant types or less per week.
- The administration of antibiotics lowered the microbial diversity of the gut.
  - The diversity of the molecules found in people who had taken antibiotics, was much higher than in people who haven´t taken antibiotics for > a year.
- Unexpected: detection of agricultural antibiotics in people who claimed that they haven't taken antibiotics in the year prior to their sample collection. This means that with the meat we eat, we still might take up antibiotics which harm our microbiome.
- UK seemed to have a higher microbial diversity than people form the US.
- Link between the composition of the microbiome and depression. The samples proved to be consistent in the US and UK populations. This shows that the microbiome and disease strongly influence each other, independent of the environment the person lives in.

- UC San Diego, 2018

11

PROBIOTICS: A HISTORY

4000 BC Old Testament (Genesis 18:8)
Abraham owed his longevity to the consumption of sour milk.

76 BC Plinius recommended fermented milk for gastritis/gastroenteritis

Early 20th century, Russian noble prize winner and father of modern immunology, Elie Metchnikoff, of the Pasteur institute, first conceptualize probiotics. He proposed that the acid producing bacteria in fermented milk products could prevent "fouling" in the colon and if consumed regularly, lead to a longer, healthier life

12

GUT-BRAIN CONNECTIONS
GEORGE PORTER PHILLIPS

- Early 1900's Bethlem Royal Hospital (London)
- Patients with melancholia had constipation and "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 game them fermented milk (keifer) which contains lactobacillus
- N=18 patients
  - 11 were cured completely
  - 2 others showing significant improvement.
  - Birth of PSYCHOBIOTICS!

13

1920's *Lactobacillus acidophilus can* restores the positive effect of "healthy gut flora"

1930's. Minoru Shirota (Japan) developed a fermented milk product with a special strain of *Lactobacillus casei*.

1953 Kollath first coined the word "probiotics" as "being necessary for life"

1992 Currently accepted definition of probiotics by Havenaar et al

1995 First definition of prebiotics (Gibson and Roberfroid)

14

VOCABULARY -1

- Symbionts: Symbiotic relationship (bacteria that are helpful and won't harm the host)
- Commensals: Bacteria will have no effect
  Not a detriment or benefit
- Biotics: adjective
  A term that is functionally equivalent to "bacteria"
  "relating to or resulting from living things"

15

VOCAB-2

- Probiotics:
  - Viable/live microbial feed/microorganisms that reach the intestine in active form. They exert a positive health effect on the host by improving its intestinal microbial balance (i.e. enhancing or restoring our gut microbiome)
  - A probiotic must have sufficient LIVING bacteria that survive food processing, and these surviving bacteria must have a benefit to human health
- Prebiotics:
  - A food source used by us (the host) to produce probiotics.
  - Most common: nondigestible carbs
- Antibiotics:
  - Substances especially made by bacteria and fungi, that kills or arrest the growth of other bacteria

16

SYNBIOTICS

- PROBIOTICS + PREBIOTICS
- A therapeutic mixture of pre- and probiotics
- Foods containing the combination of probiotics and prebiotics
- Improved survival in upper GI tract and more efficient implantation.
- New definitions as of 2020:
- Synergistic synbiotic is a synbiotic in which the substrate is designed to be selectively utilized by the co-administered microorganism(s).
- Complementary synbiotic is a synbiotic composed of a probiotic combined with a prebiotic, which is designed to target autochthonous microorganisms. Minimum criteria for the existing probiotic and prebiotic must be met for both components of a complementary synbiotic.

- *Swanson KS, Gibson GR, Hutkins R, et al. The International Scientific Association for Probiotics and Prebiotics consensus statement on the definition and scope of synbiotics. Nat Rev Gastroenterol Hepatol. 2020;17(11):687-701*

17

WHAT MAKES AN EFFECTIVE PROBIOTIC?

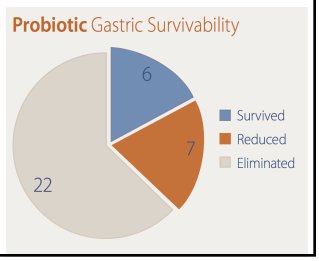
- Able to survive the passage through the stomach in a large enough number.
- Able to attach to the intestinal epithelia and colonize.
- Able to maintain good viability.
  - Many good quality probiotics are stable at room temp!
- Able to utilize the nutrients and substrates in a normal diet.
- Non pathogenic and non toxic.
- Capable of exerting a beneficial effect on the host.
- Stability of desired characteristics during processing, storage and transportation.
- Anti-inflammatory, antimutagenic, immunostimulatory.
- *A probiotic that can successfully bind and colonize in the gut to restore health will likely be a strain naturally found in our healthy human gut microbiome

18

"GOOD PROBIOTICS"

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

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



19

PROBIOTIC ADVANTAGES/BENEFITS

1. Produce lactic acid- lowers the pH of intestines and inhibiting *Clostridium*, *Salmonella*, *Shigella*, *E. coli*, etc.
   - There are **82 RCT's** on the use of probiotics and reducing ABX associated diarrhea (N= >11,000)
     - Meta-analysis : Probiotics= overall benefit, NNT = 13 (Hempei et al, JAMA 2021 May 9 Vol 307
     - Meta- analysis: N= > 3800, Drinking *Lactob. Casei* = 21% risk reduction in Cdiff, no adverse reactions, NNT= 5, "moderate strong evidence" (Johnson etal, 2012 Ann Int. Med)
   - Probiotics normalize the colonic microbiota during antibiotic use
   - Prevention of antibiotic-associated D:
     - *Saccharomyces boulardii* I-745
     - *Lactobacillus acidophilus*
2. Enhance nutrient use & stimulate enzyme production

   Aid absorption of minerals, especially calcium, due to increased intestinal acidity.
3. Production of β- D- galactosidase enzymes that break down lactose.

20

PROBIOTIC ADVANTAGES/BENEFITS

4. Balance the gut microbiome

   Produce a wide range of antimicrobial substances -acidophilin and bacteriocin.

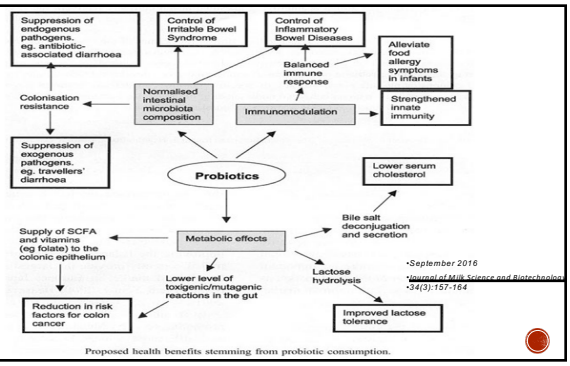
   These help control abnormal bacterial growth.

   Act as barriers to prevent harmful bacteria from colonizing the intestines.

5. Produce vitamins as part of their metabolism

   Especially vitamin B and vitamin K

21



Proposed health benefits stemming from probiotic consumption.

- September 2016
- Journal of Milk Science and Biotechnology
- 34(3):157-164

22

6. **Colon cancer –** ***Lactobacillus bulgaricus)***may help prevent colon cancer by preventing the breakdown of enzymes (**β- glucuronidase**) that contribute to the growth of cancer causing agents.

Decreases the production of a variety of carcinogenic metabolites.

7. **Lowering cholesterol –more than 15 studies**

Probiotics inhibit bile's reabsorption in the gut, which would enters the blood as cholesterol. Patients with high cholesterol, taking *L. reuteri* for 9 wks lowered total cholesterol by 9% and LDL by 12%

Jones ML, Martoni CJ, Prakash S. Cholesterol lowering and inhibition of sterol absorption by Lactobacillus reuteri NCIMB 30242: a randomized controlled trial. Eur J Clin Nutr. 2012

Wang reviewed 32 studies:

Compared to controls TC was significantly reduced in probiotics group.

Specific strains also significantly reduced serum TC:

L acidophilus and B lactis

VSL#3

L plantarum

Wang L, Guo MJ, Gao Q,Yang JF,Yang L, Pang XL, Jiang XJ. The effects of probiotics on total cholesterol: A meta-analysis of randomized controlled trials. Medicine (Baltimore). 2018 Feb;97(5)

23

PROBIOTICS AND HTN

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

- "The present meta-analysis suggests that 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 $\geq 10^{11}$ 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*

24

9. 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]

25

10. TREAT/MITIGATE ALLERGY

1. Degradation enteral antigens.
2. Normalization of the properties of aberrant indigenous microbiota and of gut barrier functions.
3. Regulation of the secretion of inflammatory mediators, and promoting development of the immune system.
4. Prevents food allergy by promoting endogenous barrier mechanisms and alleviating intestinal inflammation.
5. Stimulating immune response and reduction of serum IgE levels.
6. Reduction of cytokine response.
7. Future: Probiotic nasal spray/rinse ?

26

11. Immune support

    Promote antibody formation

12. Regular digestion

    about 1/3 of our stool weight is beneficial bacteria (rationale for fecal transplants)

13. Weight loss

    Eating yogurt with *Lactobacillus fermentum* or *Lactobacillus amylovorus* reduced body fat by 3–4% over 6 wks

    A study of 125 overweight investigated the effects of *Lactobacillus rhamnosus* on weight loss & weight maintenance. Women taking the probiotics lost 50% more weight over 3 months, compared with those taking a placebo pill. They also continued to lose weight during the weight maintenance phase.

    In one well-designed study, 114 adults with obesity were given *Lactobacillus sakei* or a placebo for 12 wks.

    Probiotic = significant decreases in both body fat mass and waist circumference

    Lim S, et.al Effect of Lactobacillus sakei, a Probiotic Derived from Kimchi, on Body Fat in Koreans with Obesity: A Randomized Controlled Study. Endocrinol Metab (Seoul). 2020 Jun;35(2):425-434.

    Sanchez M, et.al A. Effect of Lactobacillus rhamnosus CGMCC1.3724 supplementation on weight loss and maintenance in obese men and women. Br J Nutr. 2014 Apr 28;111(8)

    Kadooka, et.al. 2010Euro J Clin Nutr, 64, 636

27

14. Reduction in the common cold

More than 15 studies on probiotics and reduction and treatment of common cold and influenza.

2015 Cochran review: probiotics reduce cold frequency & duration N=37270 (DB/RCT)

*Better than Vit C

15. Prevention of COVID-19

16. Treatment adjunct of COVID-19

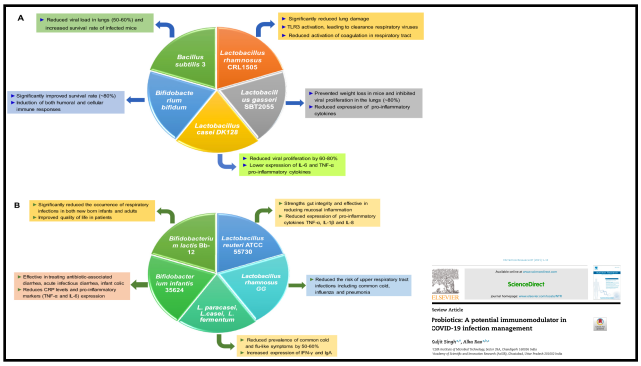
Review Article

Probiotics: A potential immunomodulator in COVID-19 infection management

Kuljit Singh[a,f], *Alka Rao*[a,b,*]

[a] CSIR-Institute of Microbial Technology, Sector 39A, Chandigarh 160036 India
[b] Academy of Scientific and Innovation Research (AcSIR), Ghaziabad, Uttar Pradesh 201002 India

28



29

PROBIOTICS AND VIRAL INFECTION REDUCTION

- "Probiotic bacteria can hinder the adsorption process via directly binding to the virus and inhibiting entry into epithelial cells.
- Binding of probiotic bacteria to the epithelial surface can cause steric hindrance and block the virus's attachment to the host cell receptor.
- Probiotic bacteria releases antimicrobial substances (such as bacteriocins, biosurfactants, lactic acid, hydrogen peroxide, nitric oxide, organic acids) and intestinal mucins from mucosal cells, which can effectively inhibit virus proliferation.
- Virus neutralized by secretory antibodies like IgA.
  - *Kuljit Singh,Alka Rao, Probiotics: A potential immunomodulator in COVID-19 infection management, Nutrition Research, Elsevier, March 2021*

30

17. INFLUENZA VACCINE EFFECTIVENESS

- 212 subjects in 3 groups
- Double blind, RCT
- Given bb-12, L. casei, or placebo
- Daily x 6 weeks
- After two weeks, given flu vaccine
- Vaccine specific Ig measured at 6 weeks
- Probiotic group much more robust response!
- These specific probiotics may improve immune response!!

Br J Nutr. 2012 Mar;107(6):876-84. doi: 10.1017/S0007114511004205. Epub 2011 Sep 7.

Evaluation of the immune benefits of two probiotic strains Bifidobacterium animalis ssp. lactis, BB-12® and Lactobacillus paracasei ssp. paracasei, L. casei 431® in an influenza vaccination model: a randomised, double-blind, placebo-controlled study.

Rizzardini G[1], Eskesen D, Calder PC, Capetti A, Jespersen L, Clerici M

31

18. MOOD, ANXIETY, OCD

- *Lactobacillus plantarum*
  - When given to patients with IBS
  - 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

References at the end

32

Trends in Food Science & Technology 103 (2020) 386–387

Contents lists available at ScienceDirect

Trends in Food Science & Technology

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

Psychobiotics: An emerging alternative to ensure mental health amid the COVID-19 outbreak?

To the editor:

COVID-19 is a highly infectious disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is responsible for the development of serious and even fatal respiratory complications, resulting from the failure of the response adaptive immunology in the early stage of the disease (incubation period) (Shi et al., 2020; Zhang et al., 2020). In addition to respiratory complications and the potential threat of death, COVID-19 outbreak can also threaten the mental health of the general public and health professionals, causing problems such as stress, panic, depression, anxiety, sleep disorders, lower mental well-being, and even suicide (Rajkumar, 2020; Roy et al., 2020).

Social isolation associated with the occurrence of infections and deaths of family and friends and the lack of a possible vaccine for COVID-19 can be considered stressful factors, which lead to the development of feelings such as loneliness and anger, and cause short-term post-traumatic stress (Ahmed et al., 2020). In addition, the advance of

Screenshot

Bacillus coagulans, *Clostridium butyricum*, and others (Cheng et al., 2019; Gualtieri et al., 2020; Vaghef-Mehrabany et al., 2020).

Ingestion of adequate amounts of these bacteria can assist in the production of neuroactive substances, such as gamma-aminobutyric acid (GABA), norepinephrine, dopamine, acetylcholine, cholecystokinin, serotonin, substance P, glutamate, glucagon-like peptide-1, glucagon-like peptide-2, peptide YY (PYY), neuropeptide Y (NPY), and may regulate proteins such as brain-derived neurotrophic factor (BDNF), which are important in the regulation of functions and behaviors related to the central nervous system (CNS) and also in gut-brain communications, through immunological, humoral, neural and metabolic pathways (Cheng et al., 2019; Dinan et al., 2015, 2013; Lyte, 2013). Several studies have suggested that the administration of psychobiotics can be effective in treating depression (Hao et al., 2019; Tian et al., 2020; Wei et al., 2019), stress (Allen et al., 2016; Savignac et al., 2014), and anxiety (Liang et al., 2015; Messaoudi et al., 2011).

A clinical study conducted on 22 healthy volunteers showed that ingesting strains of *Bifidobacterium longum* 1714 (1×10^9 colony-form-

- *Lactobacillus gasseri CP2305* during 12 weeks it was effective in recovering from fatigue and in relieving anxiety and depressed mood in 49 male university students and improved mental status and sleep quality in young students exposed to chronic stress

33

PSYCHOBIOTICS

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 ☆

Laura Steenbergen [a,b,*], Roberta Sellaro [a,b], Saskia van Hemert [c], Jos A. Bosch [d], Lorenza S. Colzato [a,b]

[a] Leiden University, Institute for Psychological Research, Cognitive Psychology, Wassenaarseweg 52, 2333 AK Leiden, The Netherlands
[b] Leiden Institute for Brain and Cognition, P.O. Box 9600, 2300 RC Leiden, The Netherlands
[c] Winclove Probiotics, Halsweg 11, 1032 LB Amsterdam, The Netherlands

34

19. PROBIOTICS FOR IBS

- 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/bloating and stool urgency.

63 RCTs Studying IBS and probiotics

Most favorable (or at least no harm!)

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)

35

20. SCIENTIFIC REPORTS

OPEN

Gut microbiome alterations in Alzheimer's disease

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

Received: 21 June 2017
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.

nature

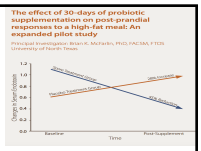
36

ALZHEIMER'S

- Data from 3 RCTs involving 161 individuals with Alzheimer's disease receiving *Lactobacillus* and *Bifidobacterium* strains showed no beneficial effect of probiotic supplementation on cognitive function with very low certainty of evidence.
- However, probiotic supplementation improved plasma triglycerides, vLDL, insulin resistance, and plasma malondialdehyde. No RCTs included synbiotic supplementation or assessed microbiota composition.
- Current evidence regarding the use of probiotics and synbiotics for individuals with dementia is insufficient to support their clinical application
  - *Jenifer F Krüger, et.al. Probiotics for dementia: a systematic review and meta-analysis of randomized controlled trials, Nutrition Reviews, Volume 79, Issue 2, February 2021, Pages 160–170*

37

OVERALL BENEFITS



- Spore-based probiotic supplementation was associated with:
  - 42% reduction in endotoxin
  - 24% reduction in triglyceride in the post-prandial period
  - Placebo subjects presented with a 36% increase in endotoxin
  - Significant post-prandial reductions in IL-12p70, and IL-1β. Compared to placebo post supplementation.
- McFarlin BK, et.al. Oral spore-based probiotic supplementation was associated with reduced incidence of post-prandial dietary endotoxin, triglycerides, and disease risk biomarkers. *World J Gastrointest Pathophysiol*. 2017;8(3):117-126.

More than 30 different diseases have been studied and have shown benefit w minimal harm!

38

INTESTINAL MICROFLORA: LOCATION & PREVALENCE WHERE DO WE FIND PROBIOTIC SPECIES?

- Rare in the esophagus
- Rare in the stomach
  - primarily gram (+)
  - 10^2 - 10^4
- 10^5 in the jejunum – primarily aerobes
- 10^{10} – 10^{12} in the colon
  - primarily anaerobes
  - 1000x more anaerobes than aerobes

39

PROBIOTIC STRAINS

Lactobacillus species

- ***L. acidophilus***
- ***L. plantarum***
- ***L. casei subspecies rhamnosus***
- ***L. brevis***
- ***L. delbreuckii subspecies bulgaricus***

***Bifidobacterium* species**

- ***B. adolescentis***
- ***B. bifidum***
- ***B. longum***
- ***B. infantis***
- ***B. breve***

- Lactobacillus is the number one selling probiotic strain in the U S.
- Of the types of bacteria within the microbiome, L. acidophilus only makes up a small fraction,
- In a healthy human gut microbiome, there aren't very high levels of L. acidophilus
- The main advantage of L. acidophilus to probiotic companies is that it is easy to culture, develop, and market commercially

40

- ***Streptococcus salivarius* ssp. *thermophilus***
- ***Lactococcus lactis* ssp. *lactis***
- ***Lactococcus lactis s* ssp. *cremoris***
- ***Enterococcus faecium***
- ***Leuconostoc mesenteroides* ssp. *dextranicum***
- ***Propionibacterium freudenreichii***
- ***Pediococcus acidilactici***
- ***Saccharomyces boulardii***

41

WHERE TO GET PROBIOTICS?

- FOOD
- YOGURTS
- FERMENTED MILK/KIEFER
- Capsules, tablets, powders, gummies, liquids etc

42

PROBIOTIC FOODS
FOODS THAT GO THROUGH A NORMAL FERMENTATION PROCESS

Fermentation- the process where food is exposed to bacteria

- Yogurt
  - Usually made from milk inoculated with *Streptococcus thermophilus* and either *Lactobacillus acidophilus* or *Lactobacillus bulgaricus.*
  - Available in all forms and flavors
- I advise patients to stick to the low sugar/no fruit versions for the most health benefits!

43

PROBIOTIC RICH FOODS!

- Frozen Yogurt
  - LaLoo's Goat's Milk Frozen Yogurt,

    S. Thermophilus, L. Bulgaricus, L. Acidophilus and *Bifidus.*
- *Yogurt Juice*
  - *Goodbelly, organic fruit juice-based probiotic beverage , contains L.Plantarum 299v, has effects on IBS*
- *Sauerkraut*
  - *My opinion- great as an adjunct for C.diff treatment and prevention*
- *Aged cheeses*
  - *Gouda, cottage cheese, some cheddar*

44

PROBIOTIC RICH FOODS!

- Kombucha
- Probiotic rich cereals

  Probiotic Digestive Wellness Cereal

- Yakult Dairy Drink
  - Probiotic, cultured dairy beverage
  - Sold in single-shot containers that contain around 8 billion live and active *Lactobacillus casei Shirota*

45

FOOD & YOGURT = GREAT CHOICE FOR PROBIOTICS!

DUE TO-

- Synergistic effect between components of foods and probiotic cultures.
- The natural buffering of stomach acid by food also enhances the stability of consumed probiotics.
- Dairy products containing probiotics provide a number of high nutrients:
  - Calcium
  - Protein
  - bioactive peptides
  - Sphingolipids
  - conjugated linoleic acids
  - Vitamin D
- Incorporating foods containing probiotics into daily food choices can become a lifestyle habit

46

WHAT ABOUT…PREBIOTICS

- A prebiotic is a nondigestible component which beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of colonic bacteria, thereby improving the health of the host
- An undigestable carbohydrate, i.e. dietary fiber, like inulin found gava fruit, chicory and artichoke
- Nutrients fermented by "good" bacteria such as *Bifidobacteria* and *Lactobacillus*.
- Examples- insulin, garlic, onions, chicory root, Asparagus, whole wheat, rye, barley, Apples, inulin sources
- Yellow veggies boosts immune system

47

CHARACTERISTICS OF PREBIOTICS

- Should not be hydrolyzed or absorbed in the upper part of G.I tract.
- Should be a selective substrate for one or a limited number of potentially bacterial commercial to the colon culture protagonist.
- Should be able to alter the colonic microflora towards a healthier composition or selectively stimulates the growth and or activity of intestinal bacteria associated with health and well being.
- Should help increase the absorption of certain minerals such as calcium and magnesium.
- Favorable effect on the immune system and provide improved resistance against infection.

48

PREBIOTICS HOW THEY WORK!

Short chain fatty acids (i.e. butyrate) produced by fermentation of prebiotics:

-Increase the height of villi and depth of the crypts creating a more absorptive mucosa

-Strengthen tight junctions and thus prevent intestinal leakage =improved barrier function

-Increase secretion of mucous and the thickness of the mucosal barrier

-Associated with reducing colon CA, enhancing calcium absorption

-Less constipation

- SCFAs Enter bloodstream and help regulate inflammation

-Prebiotics shift the composition of the microbiome to favor lactic acid bacteria (*Lactobacillus*) which lowers the pH and thus favors Firmicutes that produce butyrate and other SCFA

-Prebiotics are especially best targeted to infants in which the importance of Bifidobacteria has been more firmly studied.

49

MEASURE SCFAS

Short Chain Fatty Acids	Result	Unit	L	WRI	H	Reference Interval
% Acetate‡	71					50 – 72
% Propionate‡	16					11 – 25
% Butyrate‡	12					11 – 32
% Valerate‡	1.3					0.8 – 5.0
Butyrate‡	1.3	mg/mL				0.8 – 4.0
Total SCFA's‡	11	mg/mL				5.0 – 16.0
Intestinal Health Markers	**Result**	**Unit**	**L**	**WRI**	**H**	**Reference Interval**
pH	6.2					5.8 – 7.0
β-glucuronidase*	100	U/L				100 – 1200
Occult Blood	Negative					Negative

Chemistry Information:

50

CLINICAL TRIAL: PREBIOTICS ON MOOD

- Prebiotic strategy
  - Control or modify the GI tract microbiome by starving "bad" bacteria and nourishing "good" bacteria
  - Giving a nutrient favored by probiotics will expand their populations and increase their residency in the GIT

Those taking the prebiotic had a reduced tendency to pay attention to negative information, which is a key component of anxiety and depression.

- They also had lower levels of stress hormone cortisol, which has also been connected to anxiety and depression.

Schmidt, et al., 2014, Journal of psychopharmacology

51

EATING PREBIOTICS- LIKE FIBER

- Prebiotics feed the gut lining
- Consume prebiotic fibers:
  - Pectin, inulin, fructo-oligosaccharides, asparagus, garlic, onions, leeks, bananas
  - When gut microbiota ferment fiber, they release SCFA which are used for gut microbial fuel. When your gut lining isn't maintained by your gut bacteria, its barrier function is compromised.
- Plant based diets INCREASE the presence of the good bacteria that help to ferment the prebiotics in fiber (wow!)
- Ask patients about constipation!

Fiber is the great stool "equalizer"

52

IT'S MONDAY 0900

- Your first patient asks about taking a probiotic…

53

PICKING A GOOD PROBIOTIC

- What will the patient take/afford
- APPROPRIATE DOSE – remember there are 3 trillion organisms in the gut
- Viable/survives in the GI tract
- Acid Stable
- Bile stable
- Safe
- Proven benefit
- Human origin
- Ability to adhere to get mucosa.

Proven benefit
--
? Lactobacillus bulgaricus found in yogurt but no proven benefit

Choosing an appropriate probiotic product for your patient: An evidence-based practical guide

Jason C. Sniffen, Lynne V. McFarland, Charlesnika T. Evans, Ellie J. C. Goldstein

Published: December 26, 2018 • https://doi.org/10.1371/journal.pone.0209205

54

PROBIOTIC CONSUMPTION

- Minimum Consumption: 100g of a probiotic food with 10^7 cfu/ g.
- Most probiotics do not permanently adhere in the intestine, but exert their effects as they metabolize and grow during their passage through.
- Daily consumption of these bacteria is probably the best way to maintain their effectiveness

55

BEST PSYCHOBIOTICS

- Lactobacillus plantarum given to patients with IBS
  - significantly reduced their anxiety and improved their quality of life
- Bifidobacterium longum is present in the gut.
  - Show to help depression, reduces cortisol, address obsessions, compulsions, paranoia, anxiety.
- GABA: main inhibitory and relaxing neurotransmitter in the CNS
  - studies suggest that lactobacillus rhamnosus may reduce anxiety by changing the expression of GABA receptors

IMPORTANT –
Dose your probiotics in the BILLIONS! Why?

56

PROBIOTIC 'PRESCRIPTION'

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

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

Proprietary Blend
Lactobacillus acidophilus La-14®
Bifidobacterium longum BI-05™
Lactobacillus plantarum Lp-115®

409 mg (50 Billion CFU†)

Masters Formula
Not an endorsement

Xymogen

57

LOOK FOR MULTI-PROBIOTICS

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

1. ProBio GI, Des Bio
2. Acidophilus Pearls
   Lactobacillus acidophilus, Bifidobacterium longum
3. *Kyo-Dophilus*
   Lactobacillus acidophilus, Bifidobacterium bifidum, Bifidobacterium longum
4. *Symprove live activated probiotic*
   Lactobacillus plantarum, Lactobacillus acidophilus, Lactobacillus Casei, var. Rhamnosus, Enterococcus faecium, all in active state not freeze-dried

Supplement Facts
2 capsules contain:
Sodium 15mg
L. acidophilus (NCFM SD-5221) 16 Billion CFU*
Probiotic Blend 34 Billion CFU*
---Lactobacillus acidophilus DSM 21717
---Lactobacillus rhamnosus GGATCC 53103
---Bifidobacterium bifidum SD 5857
---Bifidobacterium lactis SD 5219
Other Ingredients: vegetable capsule (HPMC), hydroxypropyl methylcellulose, microcrystalline cellulose, pectin, sodium carbonate, silicon dioxide, stearic acid and corn maltodextrin.
*8 Billion CFU at expiration.
Contains MILK.

58

WHAT FORM?

- Enteric coated, high dose capsules (billions)
- Nutrition reviews 2018:
- Culture and culture-independent methods have established that many of these microbes present in fermented dairy and nondairy foods do reach the GI tract. Studies have shown that consumption of yogurt and other fermented foods may improve intestinal and extraintestinal health and might be useful in improving lactose malabsorption, treating infectious diarrhea, reducing the duration and incidence of respiratory infections, and enhancing immune and anti-inflammatory responses.

59

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

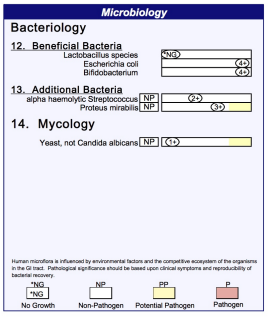
Consider taking probiotics containing Lactobacillus reuteri, Lactobacillus paracasei, Lactobacillus rhamnosus, and Bifidobacterium animalis.

60

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

61

Genova CDSA



62

PROBIOTICS- CAUTIONS

- 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.
- Severe pancreatitis (Lancet 2008)
- Lactobacillus bacteremia- rare!
- Sometimes interact with immunosuppressive drugs leading to life threating conditions.

63

PROBIOTICS ARE GRAS

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

64

STAY TUNED, CURRENT STUDIES

- Probiotics and COVID
- Probiotics and weight loss, w FMT
- Probiotics and autism, with/ without FMT
- Chronic pain
- Decreased frequency of dialysis
- Mitochondrial function 'antiaging'
- Inflammatory disease
- Vaccine enhancement

Tune into a future AAPA meeting for new probiotic uses!

65

T/F

1. In RCTs & meta-analysis, Probiotics have been shown to reduce the amount of antibiotic associated diarrhea TRUE
2. In RCTs & Meta-analysis, Prebiotics have been shown to reduce the amount of antibiotic associated diarrhea FALSE
3. All patients can benefit from probiotic use in a capsule form. FALSE
4. In patients with significant immune deficiency, probiotics may be harmful. TRUE
5. Cardiology PAs use probiotics for cholesterol and blood pressure lowering abilities. TRUE
6. The best probiotics are refrigerated to preserve potency. FALSE
7. Most probiotic prescribing is not supported by RCTs TRUE
8. The most expensive probiotics are the highest quality FALSE

66

IN SUMMARY,

- Probiotics are beneficial when used correctly
- Not all patients need probiotics
- Encourage patients to eat their probiotics
- Remind patients:
  - They need 30 gm of fiber a day
  - "You are what you eat" – eating healthy helps address the three leading causes of deaths—cardiovascular disease, cancer and type 2 diabetes — can be largely preventable, and including probiotics can help!
- LOOK FOR
  - Lactobacillus (firmicutes)
  - Bifidobacterium (actinobacteria) Doses should be in the BILLIONS!
- Not all probiotics are the same
- For antibiotic associated diarrhea, any strain will work, just pick the correct dose
- We desperately need more double blind & RCTs
- Combine with prebiotics!

67

SUPPORTING THE MICROBIOME

- Consume prebiotic fibers:
  - Pectin, inulin, fructo-oligosaccharides, asparagus, garlic, onions, leeks, bananas
- Eat fermented foods:
  - Kombucha, fresh sauerkraut, kimchi
- Take probiotics
  - Lactobacilli (multiple species)
  - Bifidobacteria (multiple species)

68

69

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.

70

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.
- O'keke 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.
- Tam NKM, Uyen NQ, Hong HA, et al. The Intestinal Life Cycle of Bacillus subtilis and Close Relatives. Journal of Bacteriology. 2006;188(7):2692-2700.
- "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):96-99.
- 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 Aging. 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.

71

REFERENCES-3

- Benno Y, Endo K, Mizutani T, et al. Comparison of fecal microflora of elderly persons in rural and urban areas of Japan. Applied and Environmental Microbiology. 1989;55(5):1100–1105.
- Schnorr SL, Candela M, Rampelli S, et al. Gut microbiome of the Hadza hunter-gatherers. Nature Communications. 2014 ;5: 3654.
- Vreeland RH, Rosenzweig WD, Powers DW. Isolation of a 250 million-year-old halotolerant bacterium from a primary salt crystal. Nature. 2000;407:897-900.
- Tremellen K, Syedi N, Tan S, Pearce K. Metabolic endotoxemia – a potential novel link between ovarian inflammation and impaired progesterone production. Gynecol Endocrinol. 2015;31(4):309-12.
- Boutagy NE, McMillan RP, Frisard MI, Hulver MW. Metabolic endotoxemia with obesity: Is it real and is it relevant? Biochimie. 2016;121:11-20.
- Karimi P, Farhangi MA, Sarmadi B, et al. The Therapeutic Potential of Resistant Starch in Modulation of Insulin Resistance, Endotoxemia, Oxidative Stress and Antioxidant Biomarkers in Women with Type 2 Diabetes: A Randomized Controlled Clinical Trial. Ann Nutr Metab. 2016;68(2):85-93.
- De Punder K, Pruimboom L. Stress induces endotoxemia and low-grade inflammation by increasing barrier permeability. Front Immunol. 2015;15(6):223.
- Gil-Cardoso K, Gines I, Pinent M, et al. A cafeteria diet triggers intestinal inflammation and oxidative stress in obese rats. Br J Nutr. 2017;117(2):218-229.
- Rocha DM, Caldas AP, Oliviera LL, et al. Saturated fatty acids trigger TLR4-mediated inflammatory response. Atherosclerosis. 2016;244:211-5.
- 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.
- Gong Y, Li H, Li Y. Effects of Bacillus subtilis on epithelial tight junctions of mice with inflammatory bowel disease. J Interferon Cytokine Res. 2016;36(2).
- Samanya M, Yamauchi K. Histological alterations of intestinal villi in chickens fed dried Bacillus subtilis var. natto. Comp Biochem Physiol A Mol Integr Physiol. 2002;133(1):95-104.
- Wong JM, de Souza R, Kendall CW, Emam A, Jenkins DJ. Colonic health: fermentation and short chain fatty acids. J Clin Gastroenterol. 2006 Mar;40(3):235-43.
- Vinolo M, Rodrigues H, Nachbar R, & Curi R. Regulation of inflammation by short chain fatty acids. Nutrients. 2011;3:858-876.

72

THANK YOU!

- Remember you are not alone & you are what you eat!
- I hope you come to share my excitement for safe, affordable and logical use of probiotics
- Stay tuned for future AAPA gut microbiome topics!
- Any questions or comments?
- Jerry Simons
- Gerald.simons@stonybrook.edu

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73