Probiotics:
Understanding the Microbiome and the Role of Probiotics in Long-term Health

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Objectives

- Learn the history of probiotics and the importance of their unique functions in a healthy diet.

- Understand the difference between microbiota and microbiome.

- Be able to identify sources of clinically relevant information on the microbiome.

- Understand probiotic supplementation options, including food sources and dietary supplements.
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History of Probiotics
Metchnikoff’s landmark observation that the “regular consumption of lactic acid bacteria in fermented dairy products, such as yogurt, was associated with enhanced health and longevity in Bulgarian peasant populations.”

He linked their improved health to the strain “Bulgarian Bacillus” and demonstrated how healthy bacteria in yogurt facilitated digestion and enhanced the immune system.

Published in 1907.

109 years later, you can order your copy on Amazon!
History of Probiotics

Pasteur noticed that common “bacilli” could suppress Anthrax growth

Alexander Fleming: antiseptics only killed harmful bacteria on the surface

Discovered penicillin in 1928 by accident

For many years, research went into antibiotics and not probiotics
Dietary Fiber Connection

TL Cleave:
• modern disease linked to refined CHOs > dietary fiber
• 1930s Naval Physician in WWII “Bran Man” (39)

Burkett:
• Africans ate 60-140 g of fiber/day  3-5X larger stools, 2X gut transit time
• “if you pass small stools, you have to have large hospitals”
• Published Don't Forget Fibre in 1979 (40)
• On the right track and then...
“Seven Countries Study”

Nation was distracted with Ancel Keys’ study on relationship with high fat diet and CVD

- Reported on only 7 of 22 countries
- Ignored countries with high fat, low CVD and low fat, high CVD findings
- This distraction has lasted decades and gave us more refined carbs (38)
It has taken many years to get back to the gut...

1980: Defined as “live microbial supplements which beneficially affect the host animal by improving its microbial balance.”

2001 WHO defines probiotics: “Live microorganisms which when administered in adequate amounts confer a health benefit on the host”
Increase in probiotic research

1,652 in 2015

www.probioticadvisor.com
Why are these live microorganisms vital to health?
Bacteria is ubiquitous

www.discovermagazine.com
What is Normal Gut Flora?

**Jejunum and Ileum**
(10^4-10^8 CFU/ml)
10,000 – 100 Million
pH 6-7.4

**Stomach and Duodenum**
(10^1-10^3 CFU/ml)
10 – 100
pH 1.5-3.5 Stomach
pH 6-6.6 Duodenum

**Colon**
(10^{10}-10^{12} CFU/ml)
10 Billion – 1 Trillion
pH 5.7 (cecum) – ~7

www.pinterest.com/nurseslabs
What they do for us

- Synthesizes some vitamins that we do not have the genes to make: B vitamins (biotin, folate, vit B5, vit B6, riboflavin, and thiamin), Vit K \(^{(34)}\)

- Breaks down indigestible CHO's: SCFAs
  1. Butyric acid
  2. Acetate
  3. Propionate
     - Protective effect on epithelium
     - Stimulate fluid absorption \(^{(35)}\)
     - Fuel cell proliferation/turnover
     - T-reg differentiation
     - Anti-inflammatory signaling enhances neuronal maturation and intestinal motility \(^{(28)}\)
What they do for us

- Pathogenic colonization resistance
  - Stimulate IgA production → Mucus
  - Promote anti-inflammatory cytokines
  - Down-regulate pro-inflammatory cytokines
  - Engage with dendrite cells “messengers”
  - Epithelial Cell integrity → prevent auto-immune cascade
Which gate would you prefer to protect your immune system?

A

B
What they do for us

- Nutrient extraction from diet\(^{(18)}\)

- Work with diet to promote bacterial diversity and health promoting metabolites
What they do for us

• Drug metabolism
  – Microbiome can affect efficacy \(^{(36)}\)

• Enteric Nervous System function
  – New field of study
  – How microbiome affects:
    • Peristalsis
    • Trans-mucosal fluid flux
    • Local blood flow
    • Release of intestinal hormones
    • Nutrient absorption
    • Immune system interaction
    • Studies with GABA (gut-brain axis) \(^{(27,29)}\)
      – Northwestern University study \(^{(9)}\)
      – GABA is produced by intestinal bacteria, helps with homeostasis & motility
        and GABA signaling linked to depression and anxiety \(^{(45,46)}\)
The Epithelial Barrier

- Commensal Bacteria layer
- Mucus Layer
- Epithelial Cell Layer
- Immune Cells of The Lamina Propria
- Smooth Muscle Layer
The mucus layer: physical barrier

- In healthy people, a bilayer mucus structure is promoted in the large intestine.
- Inner layer is thought to be sterile and attached to the epithelium.
- Outer layer is more fluid, containing microbes.

Purpose of mucus bilayer:
- High bacterial load of large intestine
- Reduced AMPs (anti-microbial peptides) production
- Increased colonic transit time for feces

- If we don’t consume the right amount of prebiotics, bacteria will start to eat the mucus layer for nutrition (22, 23, 32, 37)
Disease Pathogenesis

- **Dysbiosis**
  - Total Microbial Burdens
  - Inflammation

- **Composition of epithelial layer**
  - Altered toll-like receptor (TLR) Function
  - Bacterial translocation

- Secretion of antimicrobial peptides (AMPs)
- Mucus layer compromised
- Aerobic vs anaerobic environment
- pH of each section
- Intestinal motility rate modified
Our microbiome is essential to our health. So, how do we take care of it?
Your microbiome is your internal fingerprint

How were you born?

How were you fed?

Where did you live?

Did you have pets?

Was your home very clean?

Antibiotics as an infant/child?

Did your mom eat fermented foods or take a probiotic supplement? (44)
Take care of your microbiome

A well supported microbiome, looks like this:

A microbiome that is diseased or not well supported, may look more like this:
What affects your microbiome?

- Auto immune disease
- Chronic disease
- Medications, i.e. NSAIDs, Metformin
- Antibiotics
- Diet
- Activity
- Smoking
- Stress level
- Air pollution
- Environment
Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.
Hygiene Hypothesis

- Environment & Food more sanitized
- Anti-bacterial soaps
- Alcohol based sanitizers
- Less interaction with dirt
- Urban lifestyle
- C-section delivery ~30% of deliveries
- Formula feeding vs breastfeeding
- Antibiotics
- Not playing outside/video games
We know that good and bad bacteria are there, but what are they doing?
The Human Microbiome
The Human Microbiome

“Ecosystem” involving the host and microbiota, focusing on genetics

- Not that 2 strains are there, but how does each one affect another and the host → synergy

_Microbiota_: the 10-100 Trillion microbial cells living in and/or on the host

- Taxonomy

Ecosystem: _to do list_ vs. Microbiota: _the guest list_
Strain Synergy
Current Projects
Established in 2008

Generate resources so experts can figure out how alterations in the microbiome affect health, good and bad (7)
“An ever-growing number of studies have demonstrated that changes in the composition of our microbiomes correlate with numerous disease states, raising the possibility that manipulation of these communities could be used to treat disease.” www.hmpdacc.org
Metagenomics

- Microbiology techniques weren’t working

- Samples of microbial communities collected with a swab, stool or water sample
- Reveals microbial diversity
- Allows for DNA sequencing of this vast amount of genetic information
- Which ones may keep us healthy or turn on a disease process?
TED Talk: How our microbes make us who we are

http://www.ted.com/talks/rob_knight_how_our_microbes_make_us_who_we_are

Dr. Rob Knight
(Evolutionary Biologist)

In comes the American Gut Project...
www.americangut.org

- World’s largest crowd-funded citizen science project in existence
- Fill out questionnaire, send in stool sample kit, $99
- You get the genetic information for your microbiome
- They get to track trends for geography, diseases, etc
Benefits

SmartGut™ is a comprehensive screening test, with the most extensive panel of species and genera on the market.

Using next generation high-throughput DNA sequencing technology, our test identifies specific pathogens and other microbes in your gut that might be making you feel unwell.

We also measure your bacterial diversity and other useful metrics about your microbiome.

Symptoms and diagnoses

SmartGut is a screening test that can help you monitor your overall gut health regularly. It detects the microorganisms associated with several common gut symptoms, including:

- Abdominal pain/tenderness
- Constipation
- Crohn’s disease/Ulcerative Colitis
- Bloating
- Diarrhea
- Gas
- General Screening
- Irritable bowel syndrome (IBS)
Gut Kit $89
Sample one site: your gut!
From just your gut sample, you get a comprehensive breakdown of your microbiome, how it's functioning, and how it compares to others.
The best starter kit for curious beginners.

- One-time purchase: $89.00
- Subscribe & Save 20%: $71.20
Delivered every month

ADD TO CART

Gut Time Lapse $199
Sample three times: before, during and after a diet or lifestyle change.
Our most popular bundle goes a step further with multiple samples, to see how your microbiome changes over time.
It's a 25% discount off the normal Gut Kit, and you get three timepoints for comparison.

ADD TO CART

Five Site Kit $399
Sample all five sites: your gut, mouth, nose, genitals, and skin.
Get a complete picture of the inner workings of your entire body.

- One-time purchase: $399.00
- Subscribe & Save 20%: $319.20
Delivered every month

ADD TO CART
Gut Check: Exploring Your Microbiome

by University of Colorado Boulder & University of Colorado System

About this Course

Imagine if there were an organ in your body that weighed as much as your brain, that affected your health, your weight, and even your behavior. Wouldn't you want to know more about it? There is such an organ — the collection of microbes in and on your body, your human microbiome.

Subtitles available in English

Free!
Current areas being studied...

- Crohn’s Disease
- NEC
- STDs
- Acne
- PTSD
- DM
- Obesity
- MS
- Alzheimers
- RA

Specifically at Wash U (6)
FMT: Fecal Microbiota Transplantation

- Fecal matter is collected from a tested donor, mixed with a solution, strained, and placed in a patient:
  - NG tube
  - Fecal enema
  - Given during colonoscopy

- Currently a treatment for C-Diff, +90% effective

- Transplanting a whole community, not just introducing/adding a few new neighbors

- The transplanted community crowds out the pathogenic bacteria
Open Biome

We are a nonprofit stool bank, expanding safe access to fecal transplants and catalyzing research into the human microbiome.
Supplementation Options and Recommendations
How do we as RDs use this information clinically?
A 70 year old patient with watery diarrhea and severe abdominal pain from AAD. Her HCP recommends “Just go buy a probiotic it doesn’t matter which one.” She stops by the store to pick up a probiotic.
Probiotics
Probiotics

She is now standing in pain, hoping she does not have an accident in the probiotic section:

- Which strain?
- How many CFUs (Colony Forming Units)?
- Which ones work in AAD?
- Should I get a refrigerated one?
- Is a supplement ok?
- Should I just buy the cheapest one?
- What is a medical food?
- Do I need more than 1 strain?
Recommendations for Probiotic Use—2015 Update

Proceedings and Consensus Opinion

Martin H. Floch, MD,* W. Allan Walker, MD,†‡
on behalf of Mary Ellen Sanders, PhD,§ Max Nieuwdorp, MD, PhD,¶
Adam S. Kim, MD,∥ David A. Brenner, MD,** Amir A. Qamar, MD,††
Tamir A. Miloh, MD,‡‡§¶¶ Alfredo Guarino, MD,¶¶ Mario Guslandi, MD,##
Levinus A. Dieleman, MD, PhD,*** Yehuda Ringel, MD,‡‡‡
Eamonn M. M. Quigley, MD,‡‡‡§§§§ and Lawrence J. Brandt, MD¶¶¶

(J Clin Gastroenterol 2015;49:S69–S73)
History of Symposium

- **Problem:** there was growing literature on clinical trials but no increase in clinical recommendations

- 1st Yale symposium held in 2004, published recommendations in 2005

- Meet every 3-5 years

- 2015 Workshop held in March of 2015, published 12/15
Rankings

A
Strong, positive studies in the literature

B
Positive, controlled studies, but some negative studies that do not support primary outcome

C
Some positive studies, but not enough data for certainty
<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Effectiveness</th>
<th>Specific Strain of Organism and Strain References</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Infectious childhood—</td>
<td>A</td>
<td><em>Lactobacillus reuteri SD2112</em></td>
<td>27–30</td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention of infection</td>
<td>B</td>
<td><em>S. boulardii, LGG</em></td>
<td>27,28,30</td>
</tr>
<tr>
<td>Prevention of AAD</td>
<td>A</td>
<td>*S. boulardii, LGG, combination of L. casei DN114 G01, L. bulgaricus, sfn</td>
<td>31–33</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Streptococcus thermophilus</em></td>
<td></td>
</tr>
<tr>
<td>Prevention of recurrent</td>
<td>B/C</td>
<td><em>S. boulardii, LGG, FMT</em></td>
<td>34–37</td>
</tr>
<tr>
<td>CDAD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prevention of CDAD</td>
<td>B/C</td>
<td><em>LGG, S. boulardii</em></td>
<td>34,37</td>
</tr>
<tr>
<td>IBD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pouchitis</td>
<td>A</td>
<td><em>VSL#3</em></td>
<td>38–40</td>
</tr>
<tr>
<td>Preventing and</td>
<td>C</td>
<td><em>VSL#3</em></td>
<td>41</td>
</tr>
<tr>
<td>maintaining remission</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Induce remission</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ulcerative colitis</td>
<td>B</td>
<td><em>Escherichia coli Nisse, VSL#3</em></td>
<td>42–44</td>
</tr>
<tr>
<td>Inducing remission</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Maintenance</td>
<td>A</td>
<td><em>E. coli Nisse, VSL#3</em></td>
<td>43–45</td>
</tr>
<tr>
<td>Crohn’s</td>
<td>C</td>
<td><em>E. coli Nisse, S. boulardii, LGG</em></td>
<td>46–48</td>
</tr>
<tr>
<td>IBS</td>
<td>B</td>
<td>*Bifidobacterium infantis B5624, VSL#3</td>
<td>49–53*</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td><em>B. animalis</em></td>
<td>54</td>
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<tr>
<td></td>
<td></td>
<td><em>L. plantarum 299V</em></td>
<td>55</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>B</td>
<td>*L. acidophilus NCDO1748, B. bifidum NCDO1453</td>
<td>56,57</td>
</tr>
<tr>
<td>Recommendations from 2008†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune response</td>
<td>A</td>
<td><em>L. rhamnosus GG, L. acidophilus LAFT1, L. plantarum, B. lactis, L. johnsonii</em></td>
<td>58,59</td>
</tr>
<tr>
<td>Allergy</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Atopic eczema associated</td>
<td>A</td>
<td><em>VSL#3, L. acidophilus</em></td>
<td>59</td>
</tr>
<tr>
<td>with cow’s milk allergy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention</td>
<td>A</td>
<td><em>VSL#3, L. acidophilus</em></td>
<td>59</td>
</tr>
<tr>
<td>Radiation enteritis</td>
<td>C</td>
<td><em>VSL#3, L. acidophilus</em></td>
<td>60,61</td>
</tr>
<tr>
<td>Vaginosis and vaginitis</td>
<td>C</td>
<td><em>L. acidophilus, L. rhamnosus GR-1, L. reuteri RC14</em></td>
<td>62–64</td>
</tr>
<tr>
<td>Recommendations from 2015</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Liver disease</td>
<td>A</td>
<td><em>VSL#3</em></td>
<td>8–12</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonalcoholic fatty</td>
<td>C</td>
<td>*VSL#3, combinations of L. plantarum, L. delbrueckii, L. bulgaricus, L. acidophilus, L.</td>
<td>8,9,13,15,16</td>
</tr>
<tr>
<td>liver disease</td>
<td></td>
<td><em>rhamnosus, B. bifidum, S. thermophilus, B. longum</em></td>
<td></td>
</tr>
<tr>
<td>Nonalcoholic fatty</td>
<td>C</td>
<td><em>VSL#3, LGG</em></td>
<td>17</td>
</tr>
<tr>
<td>liver disease in children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>C</td>
<td>*VSL#3, LGG, L. acidophilus, L. bulgaricus, B. bifidum, B. longum with oligosaccharides</td>
<td>8–17</td>
</tr>
</tbody>
</table>

*Guandalini et al. was made available after the workshop meeting on April 8, 2011, but believed to be significant enough to qualify this probiotic to be in A category.
†Check 2008 references for further elaboration on strains used and their availability.
AAD indicates antibiotic-associated diarrhea; CDAD, *Clostridium difficile*-associated diarrhea; FMT, fecal microbiota transplant; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; LGG, *Lactobacillus GG*.
Now Picture this...

A Dad and his infant daughter see you at the pediatric office for infectious diarrhea. He has heard probiotics can help. What probiotics would you recommend?

1. S. Boulardii
2. L. Reuteri
3. LGG
Probiotic Recommendations

• Check out the research

• The cheapest one can be the most expensive because it may not help!

• You have trillions of bacteria, thousands of strains, verify potency

• Give it time! Can take up to 1 month to colonize and start working

• Harvard study showed that if the patient is not regularly consuming probiotic, colonization disappears at day 56 (30)

• If a patient reports probiotics didn’t work for them, maybe they didn’t try the right one for their clinical condition
Probiotics and Crohn’s Disease

- Location of the disease determines efficacy
  - Proximal small intestine challenging
    - More acidic than distal locations
    - More oxygenated than distal locations
  - Distal ileum or large intestine has the most potential
- CD patients report improvement in gas/bloating, but not helpful in disease progression
  - Fistulas
  - Fissures
- Refer to Symposium
- Most tolerant genera:
  - Lactobacillus, Streptococcus and Veillonella (21)
RDs and Data

- We separate ourselves by practicing evidence-based medicine

- Stay on top of research
  - Tailor alerts to your interest/specialty
  - I receive emailed alerts:
    - Microbiome Journal
    - New Scientist
    - Daily News from the Academy’s Knowledge Center
  - I follow:
    - Dr. Perlmutter, Chris Kresser, Dr. Axe, Dr. Hyman, Dr. Mercola

- Don’t jump to conclusions
  - Or abstracts only...
  - Who paid for it? (May have to research for conflict of interest)
  - Methods (especially for live microorganisms)
    - Handling, i.e. refrigeration
    - Freezing/thawing
Other reputable, unbiased resources
What if you do not have any diagnosis to contend with and you want to add probiotics to your daily routine?
To support your microbiome, add foods that are naturally fermented:

**Yogurt**
- Look for live and active cultures and more than one strain
- *Lactobacillus bulgaricus, Streptococcus thermophilus, Lactobacillus acidophilus*
- Brands may contain >7 strains
- [www.culturesforhealth.com](http://www.culturesforhealth.com)

**Kefir and Kvass**
- Kefir: tangy dairy drink packed with 10-20 strains/serving
- Kvass: Increased Vit B content, typically made from stale bread
Probiotics

- **Gouda is good-a for your digestion**
  - Some fermented, soft cheeses have probiotics that survive digestion
  - Parmesan and some cheddars

- **Buttermilk or acidophilus milk**
  - Milk consistency and typically 1-2 strains
Other Options

- **Sour pickles**
- **Tempeh**
- **Kombucha**
- **Unpasteurized Sauerkraut and Kimchi**
  - Kimchi is a spicy, Korean condiment
  - similar to sauerkraut
- **Miso**
- **Sourdough bread**
Now feed the probiotics...

**Prebiotics:** a non-digestible food ingredient that promotes the growth of beneficial microorganisms in the intestines.

For your microbiome:
Natural Prebiotic Sources

- Legumes, such as soybeans
- Inulin sources: Jerusalem artichoke, jicama, chicory
- Raw oats
- Unrefined wheat and barley
- **Raw** Garlic, Onion, Leek, under-ripe banana, asparagus
Big “MAC” Diet

MAC: Microbiota Accessible Carbohydrates

- Brown rice
- Cooked whole barley
- Beans
- Fruits
- Vegetables
- Limit packaged foods
- Limit refined flours
- Lentils
- Nuts
- Seeds
- Fish
- Dairy
- Small amounts of pasture-raised meat (20)

- Start slowly to decrease risk of bloating
- Assess every meal for MACs

The Good Gut
Taking Control of Your Weight, Your Mood, and Your Long-Term Health
Justin Sonnenburg and Erica Sonnenburg, PhDs
Foreword by Dr. Andrew Weil
So, instead of ...
A better defense

• Kefir over berries for breakfast
• Yogurt at lunch, with raw veggies
• Hand washing
• Outdoor activity
Resources

3. www.consumerreports.org
7. http://hmpdacc.org/overview/about.php
8. www.nature.com
11. www.probioticadvisor.com
12. http://www.ted.com/talks/rob_knight_how_our_microbes_make_us_who_we_are


Resources

40. http://jn.nutrition.org/content/124/9/1551.extract
41. www.openbiome.org
42. www.ubiome.com
Any Questions?

capizzij@hotmail.com
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Professional membership is $200/ year – students join for just $60