



Probiotics: An Overview of the Science and Utility in the Clinical Setting

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www.ashpadvantage.com/go/probiotics/webinar1

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The Evolving Role of Probiotics

Current Evidence and Strategies for Effective Use in Disease Management

Probiotics: An Overview of the Science and Utility in the Clinical Setting

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1.0 hr

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- Jon A. Vanderhoof, M.D.
 - i-Health, Inc.: consultant
 - Nu-tek BioScience: consultant
 - Reckitt Benckiser Group plc: consultant

Learning Objectives

At the conclusion of this educational activity, participants should be able to

- Review currently available evidence on the importance of the microbiome to health and well-being.
- Review the proposed mechanisms of probiotic action of commonly used products.
- Examine the importance of strain specificity and colony-forming units (CFUs) in achieving effectiveness with probiotics in the clinical setting.
- Evaluate the evidence for specific ailments for which probiotics might be successfully employed.

The Microbiome and Review of the Evidence on Probiotics

Normal Intestinal Microflora (Microbiota)

- Over 400 species, more bugs than cells
- Most acquired at birth
- Mostly from mother's birth canal
- May differ in infants delivered by cesarean section vs. vaginally

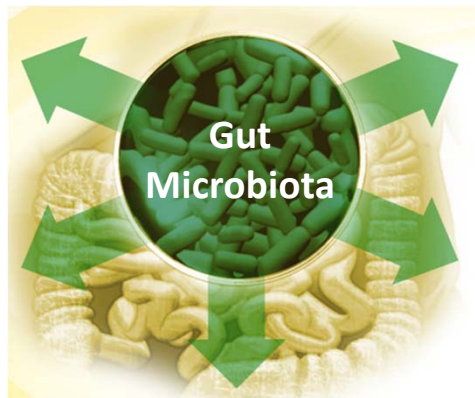
Functions of the Gut Microbiome

Barrier Protection

Epithelial barrier
Pathogen exclusion
Tight junctions
Bacteriocin

Digestive & Absorptive Functions

Intestinal transit
pH regulation
Diversity
Vitamins
Minerals
Glucose



Immune Modulation

Inflammation
Allergic response

Neuroendocrine Communication

Hormone production
Neurotransmitters
Gut-brain messaging

Nutrient Production

Short chain fatty acids (SCFAs)
Mucus
Vitamins (Bs, K2)
Enzymes

What is Dysbiosis?

- Term “dysbiosis” is not a standardized medical term
- Common definitions include
 - Microbial imbalance
 - Bacterial imbalance
 - Increased levels of harmful bacteria
 - Reduced levels of the beneficial bacteria

Microbiome Alterations in Allergic and Autoimmune Disease States

- Allergic infants in China exhibit specific microbial differences from nonallergic control infants
- People who develop type 1 diabetes have less bacterial diversity and much higher numbers of *Bacteroides* than patients without diabetes
- Patients with symptomatic celiac disease have different duodenal microbiota compared with asymptomatic patients in remission

Ling Z et al. *Appl Environ Microbiol.* 2014; 80:2546-54.

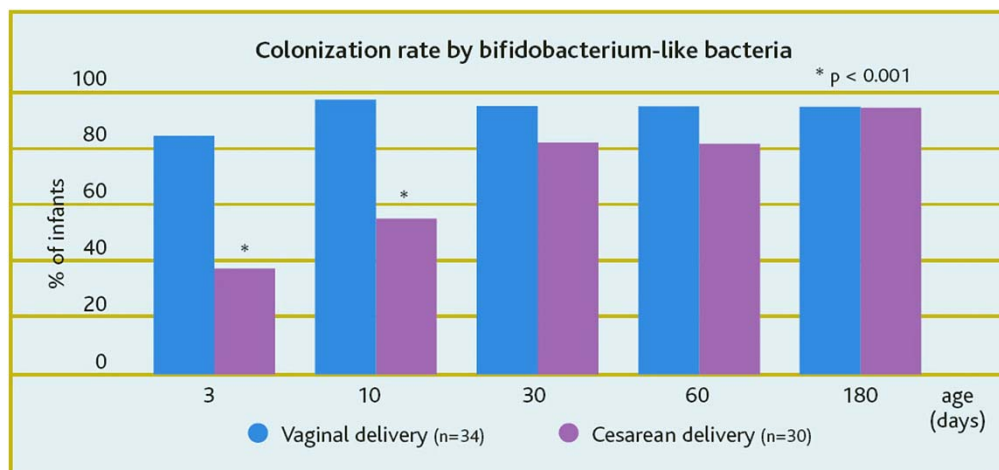
Brown CT et al. *PLoS One.* 2011; 6(10):e25792.

Wacklin P et al. *Am J Gastroenterol.* 2014; 109:1933-41.

Some Medical Conditions Associated with Dysbiosis

- Acute infectious diarrhea
- Antibiotic exposure
- Travelers' diarrhea
- Gastrointestinal (GI) allergy
- Crohn's disease
- Necrotizing enterocolitis
- Some cases of irritable bowel syndrome

Delay in Colonization with Bifidobacteria with C-section



Grönlund MM et al. *J Pediatr Gastroenterol Nutri.* 1999; 28:19-25.

What Are Probiotics? How Are They Regulated?

- Live microorganisms that confer a health benefit for the host when administered in adequate amounts
- Regulated as dietary supplements
 - They are not drugs and cannot be sold to treat or prevent specific diseases
 - Claims of health benefits are not reviewed or approved by FDA
 - Product quality and consistency are not subject to manufacturing requirements or guaranteed
- It is incumbent upon healthcare professionals to understand these limitations and be knowledgeable about the preparations available

Food and Agriculture Organization of the United Nations/World Health Organization. Guidelines for the evaluation of probiotics in food. Ontario, Canada. April 30, May 1, 2002.

What Do Probiotics Do?

- Modify the microbiota by
 - Secreting antibacterial substances
 - Competing with pathogens for adhesion to mucosal surfaces
 - Competing for nutrients necessary for pathogen survival
 - Producing bacteriocins
- Modulate the immune system
- Regulate the allergic immune cell response
- Reduce cell proliferation in cancer

NASPGHAN Nutrition Report Committee et al. *J Pediatr Gastroenterol Nutr.* 2006; 43:550-7.

On average, how many unique encounters do you personally have each month during which you are asked about or discuss the use of probiotics with patients, their caregivers, or other health professionals?



- a. None – I am not directly involved in patient care
- b. Less than 10 encounters/month
- c. 11-25 encounters/month
- d. 26-50 encounters/month
- e. More than 50 encounters/month

Important Concept

- Benefits of probiotics are strain-specific
- These must be proven for each strain in randomized controlled studies
- Not all strains with proven benefit are appropriate for all uses
- Think of probiotics like antibiotics: pick the strain with proven benefit for the specific disorder you want to prevent or treat

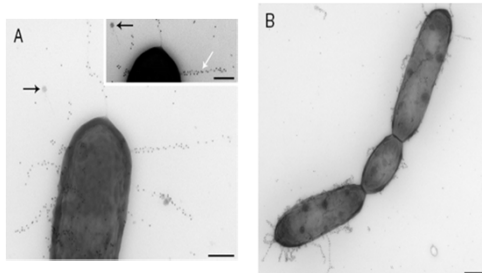
Canis lupus familiaris



Lactobacillus GG (LGG)

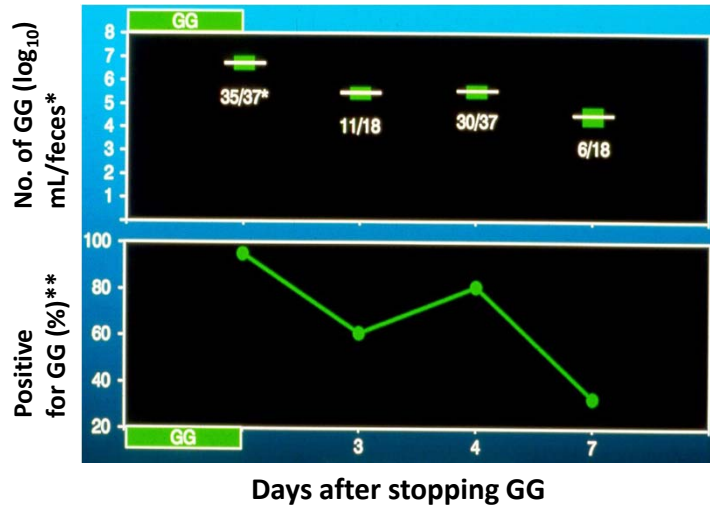
Lactobacillus rhamnosus GG (ATCC 53103)

- Single circular chromosome
3.01 Mbp
- 2,944 genes
- 0 plasmids
- 331 strain-specific proteins
(7% secreted or cell surface
exposed)



Kankainen M et al. *Proc Natl Acad Sci U.S.A.* 2009; 106:17193-8. Used with permission of author.

Persistence of Lactobacillus GG after Discontinuing Feeding



*Mean ± SE

**% = No. of positives/no. of subjects x 100

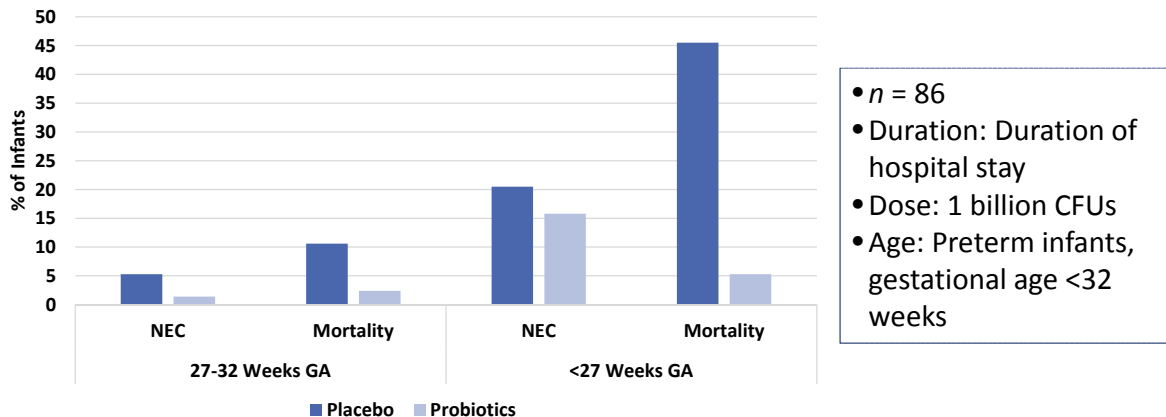
Goldin BR et al. *Dig Dis Sci.* 1992; 37:121-8.

Necrotizing Enterocolitis (NEC)

- *Lactobacillus acidophilus* vs. *Bifidobacterium infantis*
- 367 preterm infants
- Death: 7 vs. 20, $p = 0.009$
- Death or NEC: 9 vs. 24, $p = 0.009$

Lin HC et al. *Pediatrics.* 2005; 115:1-4.

Lactobacillus GG May Reduce the Risk of NEC



Uberos et al. *Br J Nutr.* 2017; 117:994-1000.

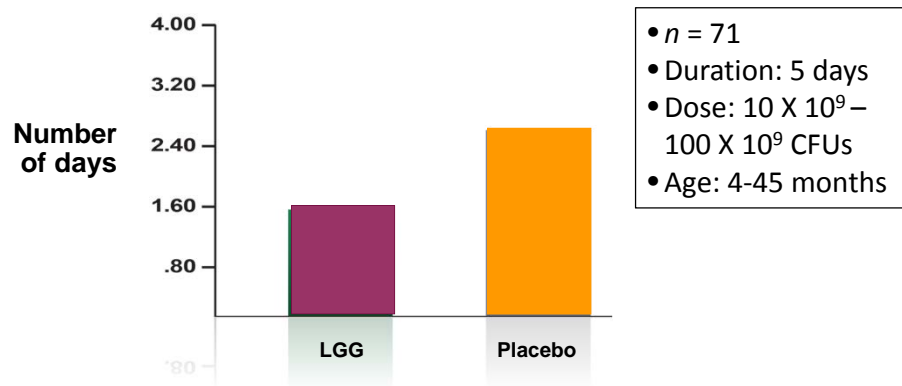
Adult Irritable Bowel Syndrome (IBS)

- *L. salivarius* UCC4331 vs. *B. infantis* 35624
- 77 adult IBS patients randomized
- *B. infantis* reduced pain, bloating, and difficulty with defecation vs. *L. salivarius* and placebo
- PBMC interleukin (IL)-10/IL-12 ratio increased with *B. infantis*
- IBS may be an inflammatory disease that responds to treatment with *B. infantis*

PBMC = peripheral blood mononuclear cell

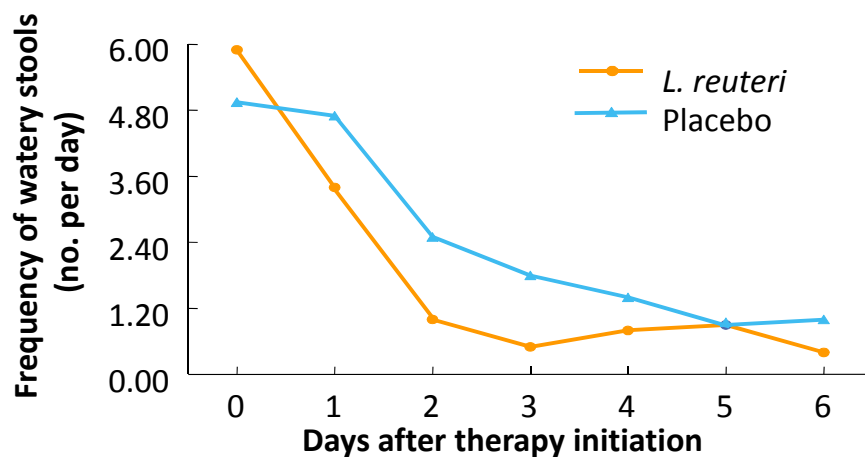
O'Mahony L et al. *Gastroenterology.* 2005; 128:541-51.

Lactobacillus GG Shortens Acute Infectious Diarrhea in Young Children



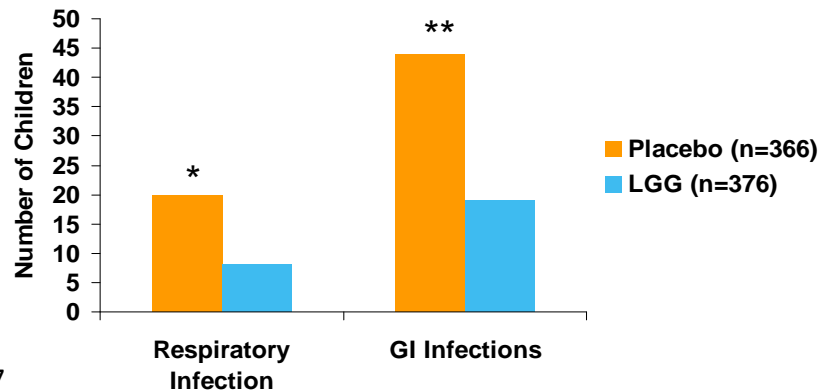
Isolauri E et al. *Pediatrics*. 1991; 88:90-7.

Lactobacillus reuteri DSM 17938 for Acute Diarrhea in Children



Shornikova A-V et al. *J Pediatr Gastroenterol Nutr*. 1997; 24:399-404.

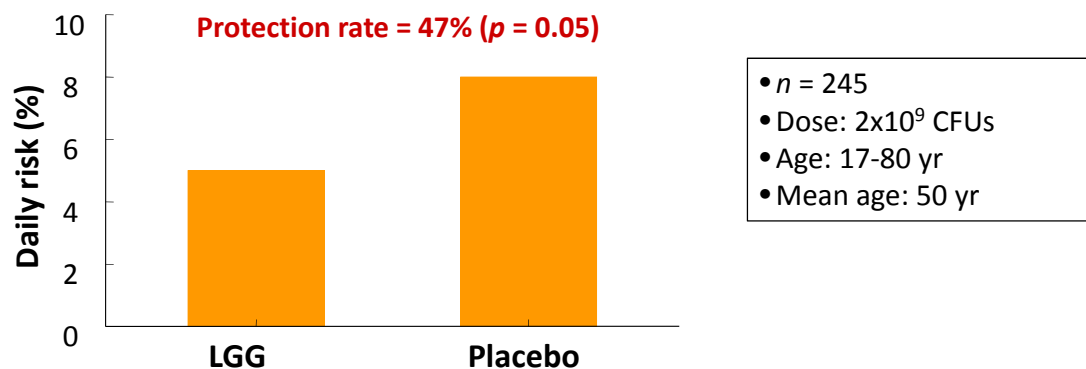
Nosocomial Respiratory Tract and GI Infections in Children Receiving LGG



* $p = 0.017$
 ** $p < 0.001$

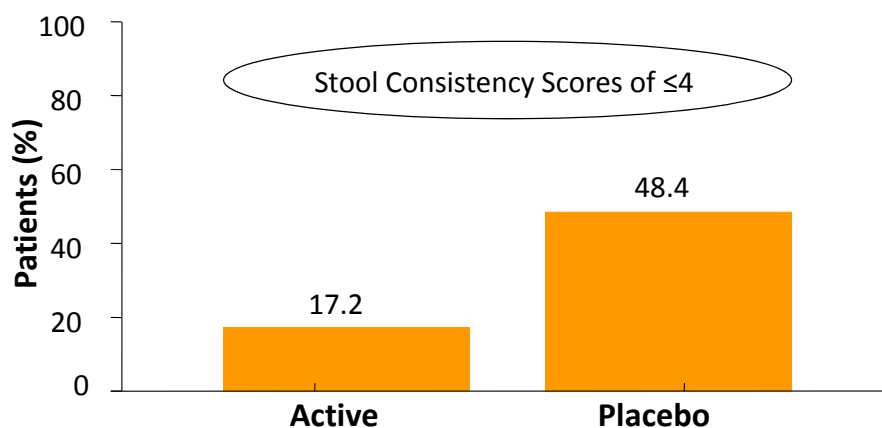
Abdović S et al. *ESPGHAN*. 2009; 10:OP3-02.

Lactobacillus GG for Travelers' Diarrhea



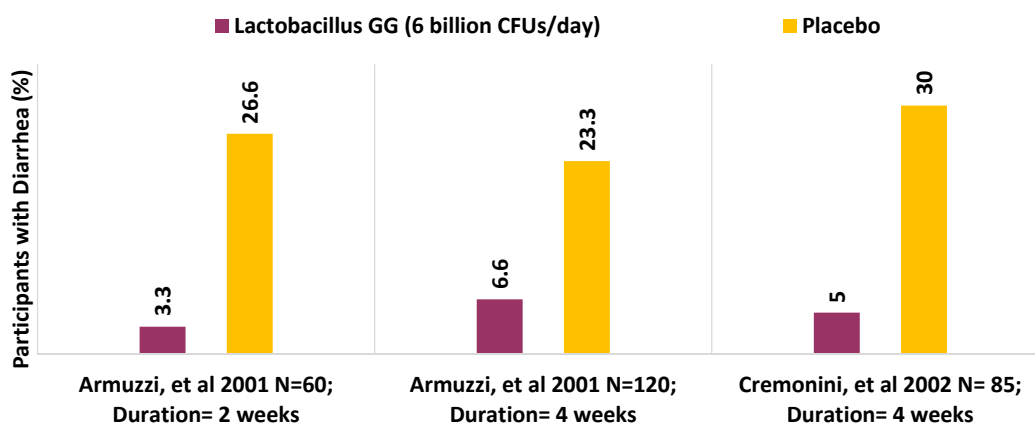
Hilton E et al. *J Travel Med*. 1997; 4:41-3.

Lactobacillus GG in Children on Broad-Spectrum Antibiotics: Incidence of Diarrhea (Day 9)



Vanderhoof JA et al. *J Pediatr.* 1999; 135:564-8.

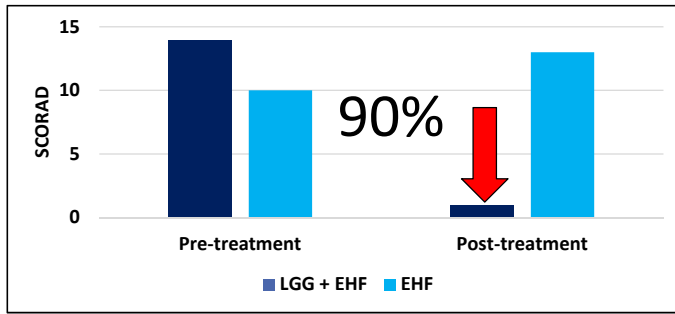
Lactobacillus GG Reduces the Incidence of Diarrhea During Antibiotic Therapy



Armuzzi A et al. *Aliment Pharmacol Ther.* 2001; 15:163-9.

Armuzzi A et al. *Digestion.* 2001; 63:1-7. Cremonini F et al. *Am J Gastroenterol.* 2002; 97:2744-9.

Lactobacillus GG Reduces the Severity of Eczema in Infants



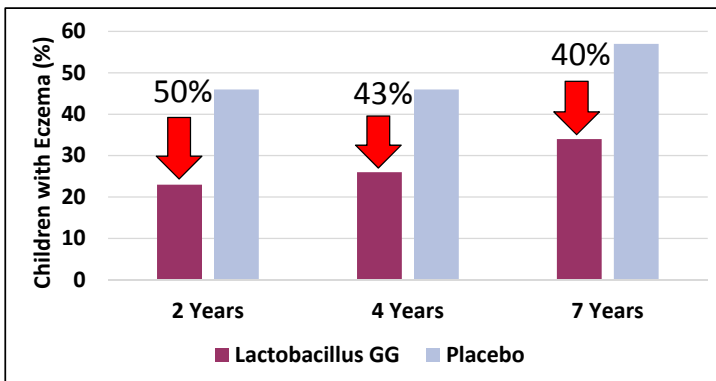
- $n = 27$
- Duration: 2 months
- Dose: 3×10^9 CFUs
- Mean age: 4.6 months

SCORAD (Scoring atopic dermatitis) is the severity score used for atopic dermatitis

EHF = extensively hydrolyzed whey formula

Isolauri et al. *Clin Exp Allergy*. 2000; 30:1604-10.

Lactobacillus GG Reduces the Risk of Eczema in High Risk Children



- $n = 132$
- Duration: 4 months prenatal, 6 months postnatal
- Dose: 10×10^9 CFUs

Kalliomaki M et al. *Lancet*. 2001; 357:1076-9.

Kalliomaki M et al. *Lancet*. 2003; 361:1869-71.

Kalliomaki M et al. *J Allergy Clin Immunol*. 2007; 119:1019-21.

Occult Blood Stool after 4 Weeks of Dietary Treatment

	EHCF + LGG	EHCF
Negative	12	5
Positive	0	9
Total	12	14

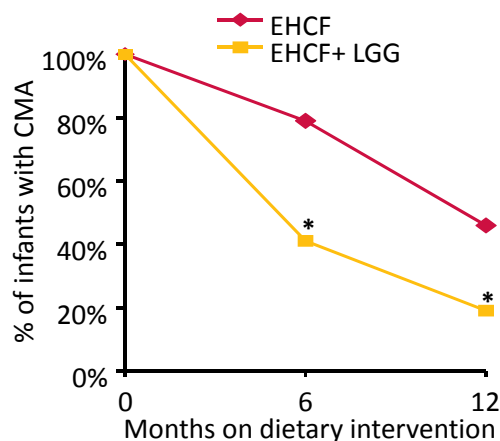
$\chi^2 = 11.798$, $p = 0.001$

EHCF = extensively hydrolyzed casein formula

Baldassarre ME et al. *J Pediatr.* 2010; 156:397-401.

Acquisition of Tolerance

- 80 infants with suspected cow's milk allergy (CMA)
- Randomized to receive EHCF + LGG or control (i.e., EHCF alone)
- After remission of symptoms, CMA confirmed by oral challenge in 55 patients (study population)
- Rechallenged at 6 and 12 months
- At both times, significantly more infants had acquired tolerance in the LGG group vs. control



* $p < 0.05$; data on file

Canani B et al. *J Allergy Clin Immunol.* 2012; 129:580-2.

Microbiome and the Immune System

- Balance between inflammation and tolerance
- Crosstalk between the microbiota and immune cells is necessary
- Certain probiotics are capable of interacting directly with the mucosal immune system, resulting in stimulation of T regulatory cells, T helper Th1 cells, or Th2 cells
- The resulting cytokine production may enhance response to infection or dampen the immune response in autoimmune or allergic disease
- These responses are highly specific to individual probiotic organisms and are not generalizable

Lactobacillus GG Abundance Is Associated with Profound Shifts in Infant Gut Microbiome

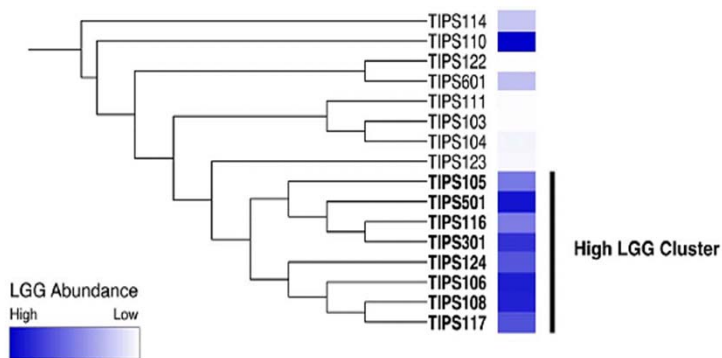


Figure 2. Hierarchical cluster analysis of infant stool samples. Hierarchical cluster analysis reveals that LGG abundance is associated with specific bacterial community structures.
doi:10.1371/journal.pone.0008745.g002

Cox MJ et al. *PLoS One*. 2010; 5:e8745. doi: 10.1371/journal.pone.0008745.

Randomized, Double-blind Trial of Lactobacillus GG vs. Placebo in Crohn's Disease

- 75 children aged 5–21 years with Crohn's disease in remission
- Randomized to LGG or placebo and followed for up to 2 years
- Median time to relapse was 9.8 months in LGG group, 11 months in placebo group
- 31% of patients in LGG group relapsed vs. 17% in placebo group
- Differences were not statistically significant and no benefit of probiotics was apparent

Bousvaros A et al. *Inflamm Bowel Dis.* 2005; 11:833-9.

Key Takeaways

- Early in life, certain microbial populations in our GI tract likely program us to be more susceptible to allergy, autoimmunity, or neither one
- Changes in the microbiome over time may be responsible for at least some of the epidemiologic shifts we have seen in these diseases
- Many GI and even non-GI disorders are associated with altered GI microbial colonization
- Some specific strains of certain probiotics might positively impact the clinical course in some of these disorders in the short term with continuous administration, but may not significantly alter the microbiome
- One should avoid broad statements suggesting probiotics in general are beneficial in such circumstances and refer to specific strains, specific disorders, and double-blind placebo-controlled clinical trials supportive of specific probiotic use

Strategies for Selecting Probiotic Products

Related Affiliation

- Member of Scientific Advisory Working Group of the Alliance for Education on Probiotics, also known as AEProbio

Strain Specificity

- Probiotics are like drugs
 - Each probiotic strain has different effect and mechanism of action, not always interchangeable
 - Some probiotic products may contain multiple strains
- Match the right strain with the desired effect

Colony-Forming Units (CFUs)

- 1 CFU = 1 bacterium capable of dividing and forming colonies
- Generally expressed as billions/dosage unit
- Studies done at various dosages
 - Number of CFUs needed may vary depending on what was shown to be effective in clinical studies

Storage Conditions and Expiration Date

- Quality products express CFUs as number expected at the expiration date
- Pay attention to manufacturer's directions for storage since some require refrigeration
- Probiotics on sale may not be a good value

Which of the following is your greatest concern in recommending the use of specific probiotic products?



- a. Lack of FDA review and approval of products
- b. Cost
- c. Limited availability of authoritative product information
- d. None of these
- e. Not applicable - I am not directly involved in patient care

Useful Database Sources

- AEPbio
 - www.usprobioticguide.com
- Consumer Lab
 - www.consumerlab.com
- Natural Medicines
 - <https://naturalmedicines.therapeuticresearch.com>

Selection Criteria for Probiotic Databases

- Use a review board of experts who agree on the conclusions presented
- Rate the level of evidence for the uses of specific products
- Provide links to the primary literature
- Are updated regularly

AEProbio

- Supported by Alliance for Education on Probiotics (AEProbio)
 - 14 industry Alliance members in U.S. and Canada (2018)
 - Supports the Probiotic Chart Initiative



Clinical Guide to Probiotic Products Available in USA
Indications, Dosage Forms and Clinical Evidence to Date - 2018 Edition

- Inclusion criteria
 - Commercially available in U.S.
 - Generally Recognized as Safe status by FDA
 - Favorable published clinical evidence for the strain(s) present
 - If contains multiple strains, evidence must be for the combination, not extrapolated from evidence for separate probiotic strains

www.usprobioticguide.com (accessed 2018 Apr 30).

AEProbio

- Uses chart format, organized by brand name
 - Product name, probiotic strain(s), dosage form, CFUs/dose, uses with level of evidence
 - Includes links to references
- Level of evidence: I, II, III
- 2018 edition
 - 38 probiotic products for adult health, 4 for women's health, and 27 for pediatric health
 - 12 functional foods

www.usprobioticguide.com (accessed 2018 Apr 30).

Consumer Lab



- Privately held company that provides independent test results and information related to dietary supplements, including probiotics
 - Requires a subscription
 - Not affiliated with manufacturers but revenue sources include certification fees and authorized use of CL seal of approval
- Products tested are purchased through regular retail and online channels, not directly from manufacturer

www.consumerlab.com (accessed 2018 Apr 30).

Consumer Lab

- Possible uses (organized by species for probiotics)
 - Uses evidence quality rating system
 - Effective, partially effective, not effective, no definitive result
- Product review results (organized by product brand name)
 - Probiotic dose testing
 - Contains listed amount and ≥ 1 billion CFUs daily
 - Contamination testing
 - Free of lactose, pathogenic bacteria, unwanted molds, gluten
 - Disintegration testing
 - If disintegrated properly (or NA)
- Also provides narrative with background information about products



www.consumerlab.com (accessed 2018 Apr 30).

Natural Medicines | natural medicines™

- Comprehensive database of all ingredients in natural products, including probiotics
- Developed by Therapeutic Research Center (TRC), publisher of *Pharmacist's Letter* and *Prescriber's Letter*
- Subscription required
 - Provides online CME and CPE for selected monographs
- Shares info with Medline Plus in Spanish and English

<https://naturalmedicines.therapeuticresearch.com> (accessed 2018 May 7).

Natural Medicines

- Monograph format organized by specific probiotic species, such as *Lactobacillus*, *Saccharomyces*
 - Includes all uses for that species (with references)
- Rates evidence for effectiveness, safety, severity of interactions
 - Includes interactions with herbs, other dietary supplements, drugs, foods, laboratory tests, diseases, and conditions
- Includes links to references
- Provides patient education handouts for download (English, Spanish, French)

<https://naturalmedicines.therapeuticresearch.com> (accessed 2018 May 7).

U.S. Pharmacopeial Convention (USP) Actions Related to Probiotics

- November 2015 convened Probiotic Roundtable
 - Led USP to publish monographs (4 Lactobacillus and 3 Bifidobacterium strains) in USP 40-National Formulary 35 (USP-NF) and propose general Chapter <64> Probiotic Tests
- October 2017 convened Probiotics Expert Panel
 - Will provide recommendations to Non-Botanical Dietary Supplement Expert Committee on standards for development of probiotics

<https://www.usp.org/sites/default/files/usp/document/get-involved/stakeholder-forums/3c-updates-usp-standards-probiotics-2017-06-07.pdf> (accessed 2018 Apr 30).

USP Dietary Supplement Verification Program

- Voluntary program
- Testing and auditing criteria
- Website with list of supplements that received USP Verified designation
- No probiotics currently listed



<http://www.usp.org/verification-services/dietary-supplements-verification-program> (accessed 2018 Apr 30).

Certification Seals

- Verified probiotic products or manufacturing sites

- www.consumerlab.com

- 41 products



- www.nsf.org/Certified/Dietary/

- 3 manufacturing sites



(Sites accessed 2018 May 3).

MedWatch



- FDA Safety Information and Adverse Event Reporting Program
- Collects and reports adverse reactions from probiotics, natural supplements, and drugs
- Can use search feature to determine if a specific product has reports filed against it

www.fda.gov/Safety/MedWatch/default.htm (accessed 2018 Apr 30).

Precautions and Adverse Effects

- Generally considered safe
 - Gas and bloating most common adverse effect
- Allergic reaction or anaphylaxis to inert ingredients
 - Gluten, milk proteins, lactose
- Secondary infection from pathogenic bacterial contaminants
- Secondary infection in frail populations
 - *Saccharomyces* fungemia and *Lactobacillus* bacteremia
- Mesenteric necrosis when used to treat acute pancreatitis

Doron S et al. *Clin Infect Dis*. 2015; 60(Suppl 2):S129-34.

Polito NB et al. *Am J Health-Syst Pharm*. 2018-75:595-6.

Besselink MG et al. *Lancet*. 2008; 371:651-9.

Key Takeaways

- Probiotic efficacy requires live microorganisms at the site of action
- Use available resources to select products carefully
 - Evaluate level of evidence for intended use
 - Select product with specific strain and number of CFUs that matches intended use