

Gastroenterology – Probiotics, IBS, SIBO, FODMAPs, etc.

WJ Lawton



I have no financial disclosures
or conflicts of interest

Overview

- Probiotics
 - Human Microbiome
 - Value/relevance in medical care
- New Diagnoses
 - Irritable Bowel Syndrome:
 - FODMAP diet
 - Breath Testing
- Questions

Understanding our Biome

- Human Microbiome Project
 - National Institutes of Health 2007
- ~ 50 bacterial phyla described:
 - Only 4 phyla constitute the majority of mammalian microbiota.
 - Bacteroidetes
 - Firmicutes
 - Actinobacteria
 - Proteobacteria
 - 2/4 predominate our intestines
 - >4000 bacterial species reside our intestines
 - intestinal bacteria weigh ~ 1 kg
 - 40-100 trillion bacteria

Stomach and duodenum

- Harbor very low numbers of microorganisms: $< 10^3$ cells per gram of contents
- Mainly lactobacilli and streptococci
- Acid, bile, and pancreatic secretions suppress most ingested microbes
- Phasic propulsive motor activity impedes stable colonization of the lumen (also true for the small intestine)

Jejunum and ileum

- Numbers progressively increase from 10^4 in the jejunum to 10^7 cells per gram of contents in the distal ileum

Large intestine

- Heavily populated by anaerobes: up to 10^{12} cells per gram of luminal contents
-

- Microbial diversity between individuals is quite remarkable: each individual harbors his or her own distinctive pattern of bacterial composition, determined partly by the host genotype, by initial colonization at birth via vertical transmission, and by dietary habits.

Intestinal Microbiota

■ Gastrointestinal:

- Cholelithiasis
- Colon cancer
- Hepatic encephalopathy
- Idiopathic constipation
- IBS
- IBD
- Familial Mediterranean fever
- Gastric carcinoma
- Lymphoma
- Recurrent C.diff infection

■ Non-gastrointestinal:

- Arthritis
- Asthma
- Autoimmune disorders
- Chronic fatigue syndrome
- Diabetes mellitus
- Eczema
- Fatty liver
- Fibromyalgia
- Hay fever
- Hypercholesterolemia
- Idiopathic thrombocytopenic purpura
- Ischemic heart disease
- Metabolic syndrome
- Mood disorders
- Multiple sclerosis
- Obesity
- Parkinson's disease

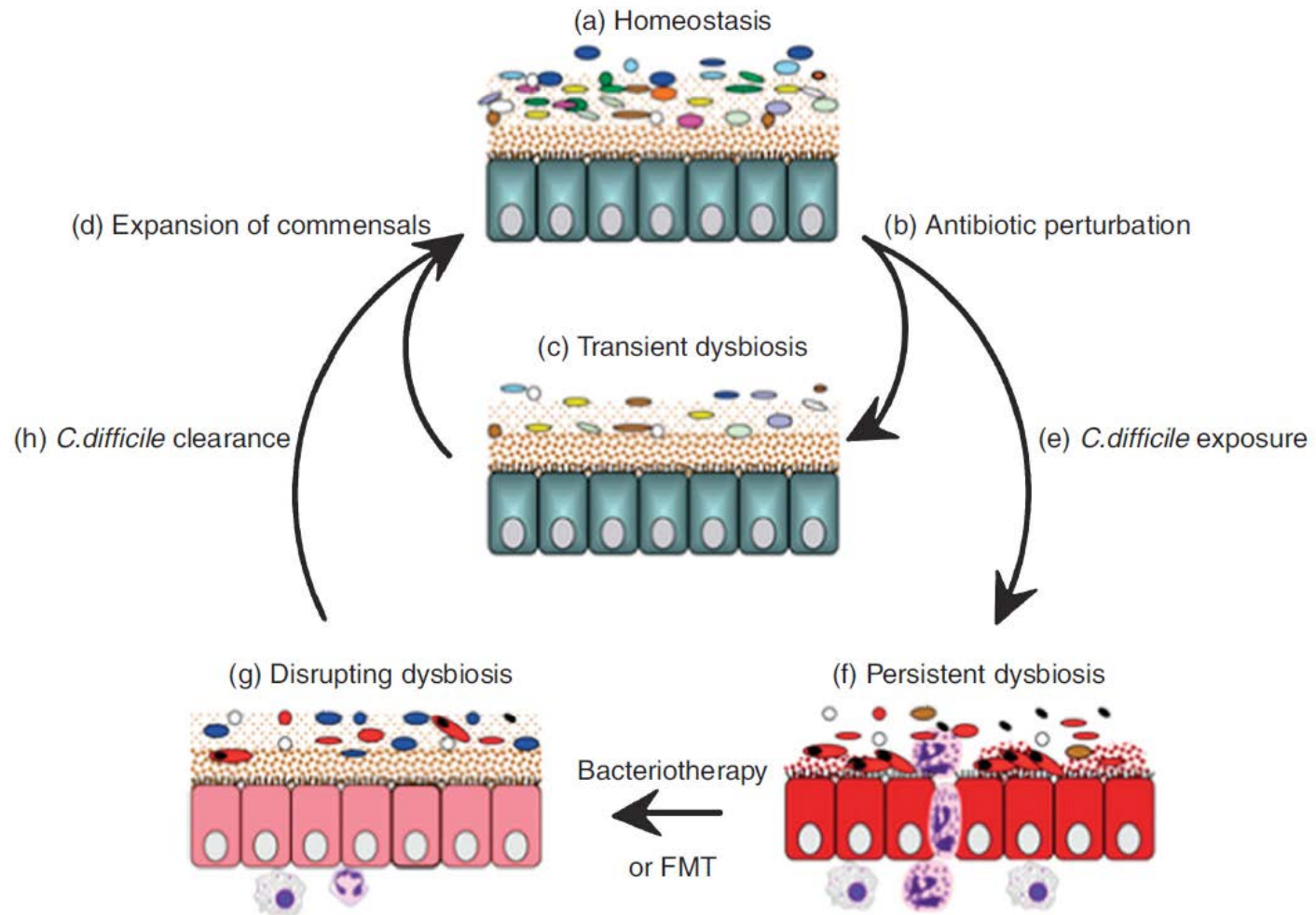
Summary:

The “balance” of bacteria in our microbiome is more important than we thought.....Many studies have shown that populations of colonizing microbes differ between healthy individuals and others with disease or unhealthy conditions. However, researchers are still not able to define the composition of a healthy human microbiota.

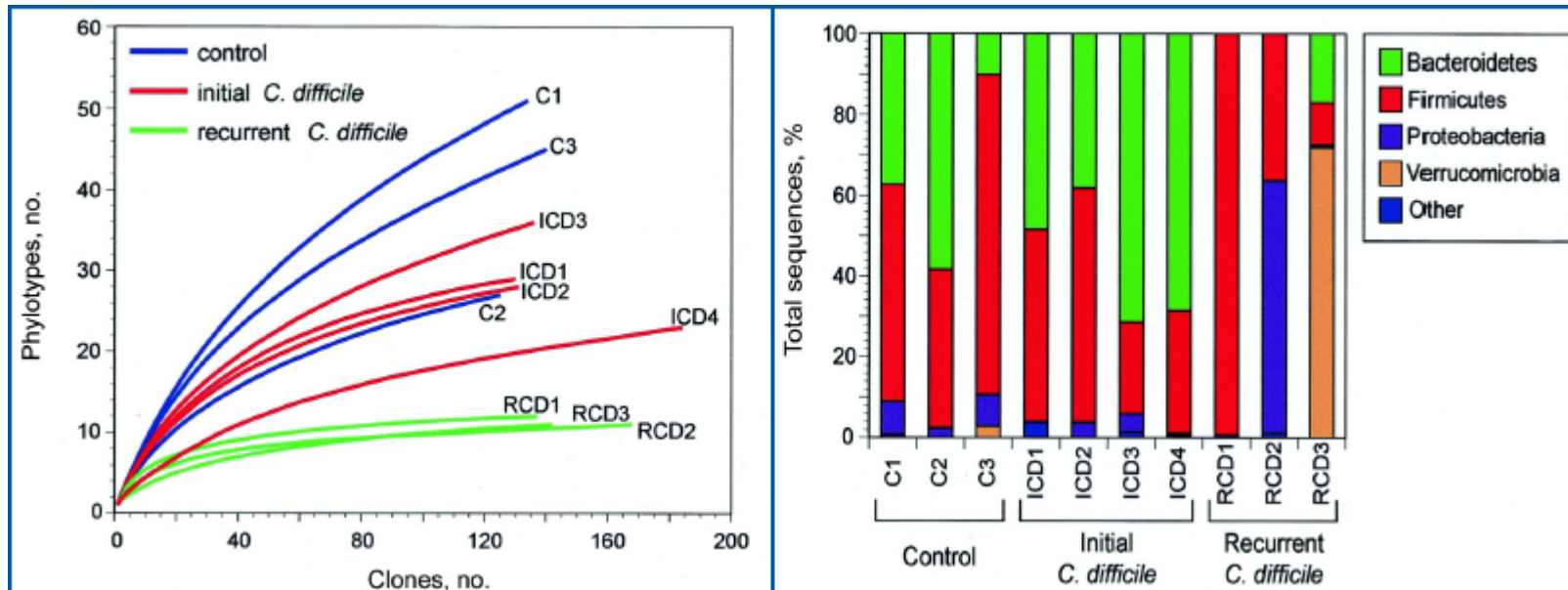
Balance Disruption

- Microbial Balances:
 - Gut microbiome is a balance/symbiosis
 - Recent decades → Western lifestyle, medicines (antibiotics) have causes a disruption in our biome.
 - Intestinal microbiota is related to food we eat, controls appetite regulation, energy utilization, digestion and absorption of nutrients, and drug metabolism.
 - Changes quickly with dietary and environmental exposures
 - Antibiotics
- Can we restore the appropriate bacterial balance?
 - Example = C.diff

Disrupted Gut “Balance”



Decreased Diversity in RCDI



- Patients with RCDI have decreased phylogenetic diversity
- Bacteroidetes and firmicutes are reduced in patients with RCDI – not reduced in just one episode of CDI.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

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VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D.,
Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D.,
Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D.,
Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

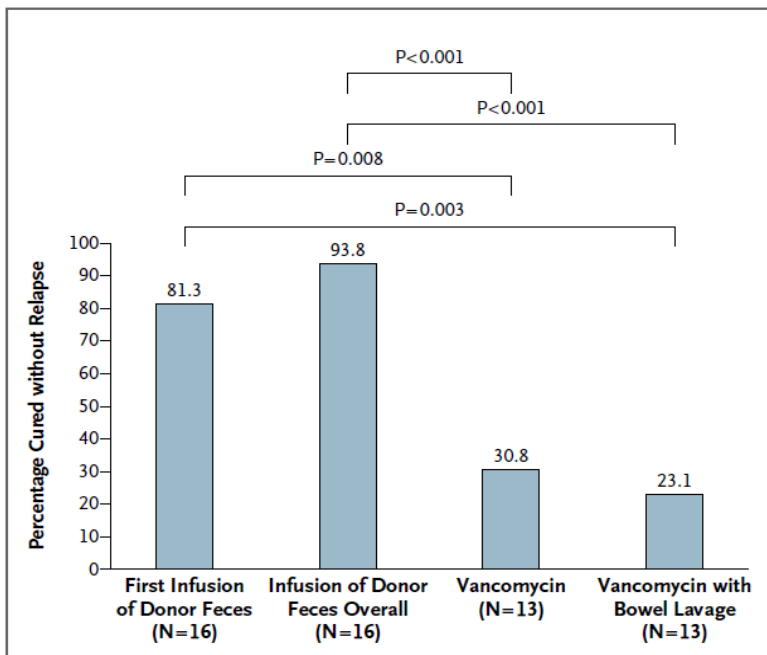


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

- Randomized control study
 - infusion of donor feces via nasoduodenal tube vs. vancomycin.
 - 81% vs. 31% respective success rate.
 - 2/3 treatment failures in the FMT arm resolved with a second infusion from a different donor, bringing the overall success rate to 93.75% (7)
 - Study was terminated early.

ACG Governors/ASGE Best Practices Course

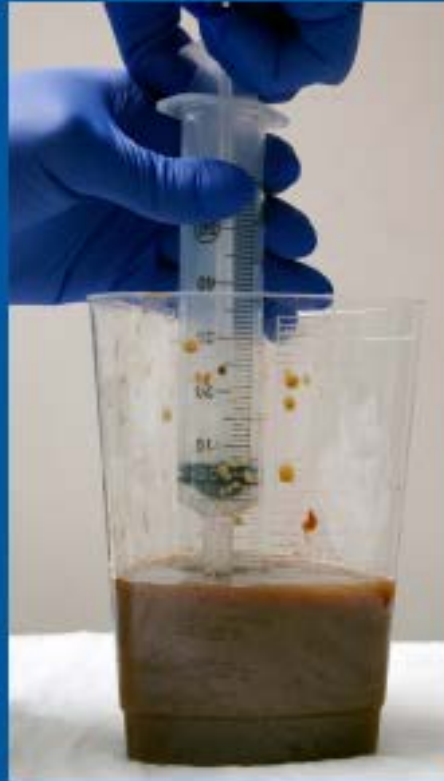
January 24-26, 2014 Las Vegas, Nevada



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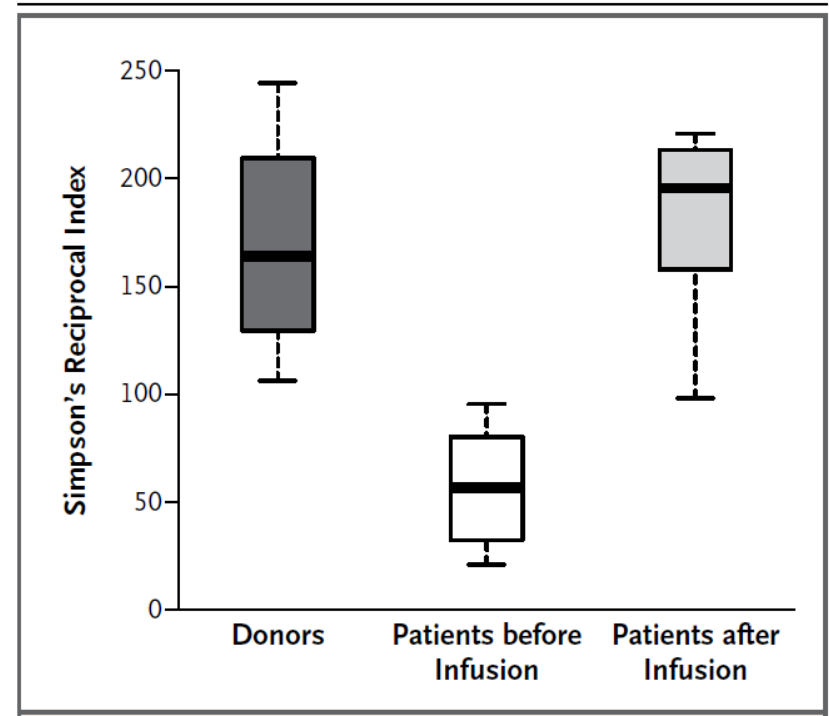
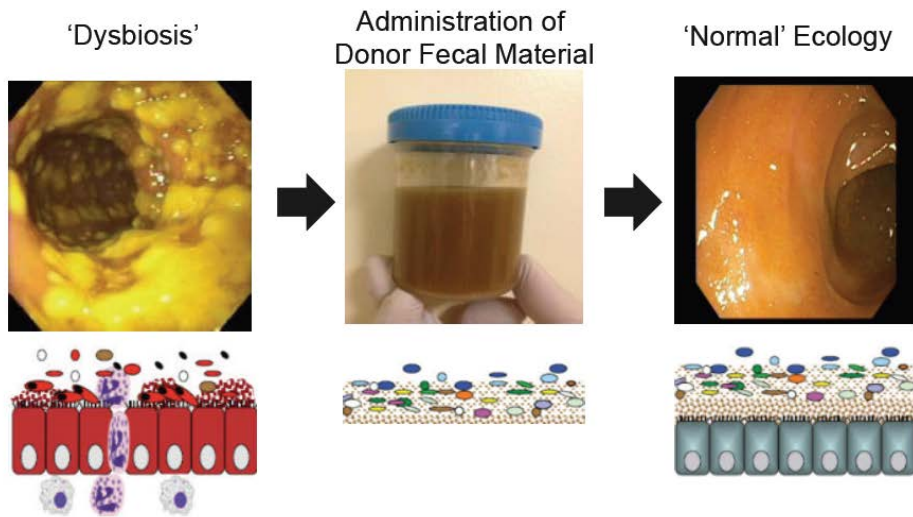
January 24-26, 2014 Las Vegas, Nevada







Restore the Balance



Can a balance be restored with probiotics?

Desperate Patients

- Can probiotics restore the balance?





Probiotics

- Probiotics

- Live microorganisms that confer a health benefit on the host when administered in adequate amounts
 - act by prohibiting pathogen attachment, enhancing the immune response and by assisting in re-establishing the microflora.

- Prebiotic

- Dietary substances that nurture specific changes in the composition and/or activity of the GI microbiota (favoring beneficial bacteria), thus conferring benefit upon host health

- Synbiotics

- Products that contain both probiotics and prebiotics

Strains

- *Lactobacillus* and *Bifidobacterium* species are the most commonly used probiotics.
 - Most probiotics were initially cultured from humans and resemble known commensal gut bacteria.

Genus	Species	Subspecies	Strain designation	International strain depository designation	Strain nickname	Product name
<i>Lactobacillus</i>	<i>rhamnosus</i>	None	GG	ATTC 53103	LGG	Culturelle
<i>Bifidobacterium</i>	<i>animalis</i>	<i>lactis</i>	DN-173 010	CNCM I-2494	<i>Bifidus regularis</i>	Activia yogurt
<i>Bifidobacterium</i>	<i>longum</i>	<i>longum</i>	35624	NCIMB 41003	Bifantis	Align

What has the research shown?

Probiotics

Immunologic benefits

- Activate local macrophages to increase antigen presentation to B lymphocytes and increase secretory immunoglobulin A (IgA) production both locally and systemically
- Modulate cytokine profiles
- Induce tolerance to food antigens

Nonimmunologic benefits

- Digest food and compete for nutrients with pathogens
- Alter local pH to create an unfavorable local environment for pathogens
- Produce bacteriocins to inhibit pathogens
- Scavenge superoxide radicals
- Stimulate epithelial mucin production
- Enhance intestinal barrier function
- Compete for adhesion with pathogens
- Modify pathogen-derived toxins

When do I use Probiotics?

- Probiotic Therapy for GI Conditions
 - Acute Infectious Diarrhea
 - Children only
 - Antibiotic Associated Diarrhea
 - Adults and Children
 - C.Difficile-Associated Diarrhea
 - Maybe, but not usually
 - IBS
 - Variable
 - IBD
 - Pouchitis only

Infectious Diarrhea

■ Pediatrics:

- Most common cause = Rotavirus

- Preventing Diarrhea = No

- With the currently available rotavirus vaccine in consideration, the American Academy of Pediatrics states that probiotics for *preventing* acute infectious diarrhea are not universally endorsed.

- Treating Diarrhea = Probably

- *Lactobacillus rhamnosus* GG (LGG) is the most effective probiotic reported
 - reducing both severity and duration of diarrhea by **approximately 1 day**.
- American Academy of Pediatrics supports the recommendation of LGG early in the course of acute infectious diarrhea to reduce symptom duration.

Infectious Diarrhea

- Culturelle

- Species:

- LGG

- Effectiveness:

- Grade = A



- DanActive

- Species:

- L. casei

- Effectiveness:

- Grade = A



Infectious Diarrhea

■ Adults (2016 ACG Guidelines)

- In 2010, Cochrane systematic review was published on the topic of probiotics and treatment of intestinal infection
 - Between 1966 -2010, 63 studies including 8,014 subjects met the eligibility criteria.
- Based on the current evidence, there are **not** enough studies, which would support the recommended use of any particular probiotic product for treatment in acute adult diarrhea infection.

Antibiotic Associated Diarrhea

■ Children

- 2011 Cochrane Review evaluating more than 3400 patients from 16 studies concluded that the overall evidence suggests a protective effect of probiotics in preventing AAD.
- American Academy of Pediatrics supports the recommendation of probiotics for prevention of, but not treatment of, AAD.

■ Adults

- A meta-analysis evaluating studies on various probiotics and antibiotic regimens published between 1977 and 2005 found that both LGG and *S. boulardii* offered a reduction in risk of AAD.

In the prevention of antibiotic-associated diarrhea, there is strong evidence of efficacy in adults or children who are receiving antibiotic therapy.

AAD Prevention

■ Culturelle

Species:

■ LGG

Effectiveness:

■ Grade = A



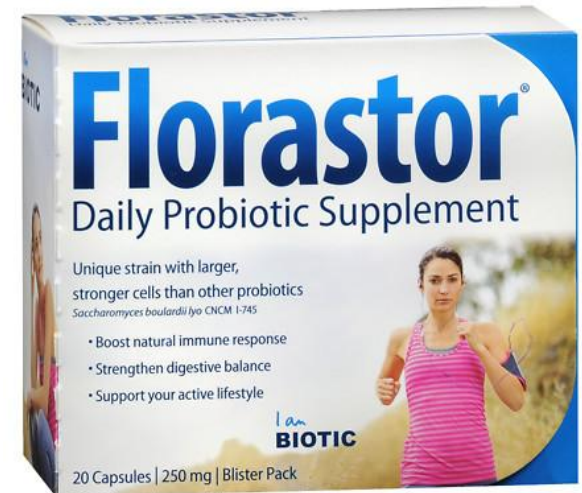
■ Florastor

Species:

■ *Saccharomyces boulardii*

Effectiveness:

■ AAD → Grade = A



C Difficile–*Associated Diarrhea*

■ 2013 ACG Guidelines:

- There are no strong data to support the use of probiotics for RCDI treatment, and only weak evidence of therapeutic efficacy for *S. boulardii*.
- There is no evidence for the use of probiotics in the treatment of initial or severe disease.
- *S. Boulardii*? The most recent systematic review and meta-analysis concluded that although there is strong evidence from numerous large RCTs for efficacy in prevention of antibiotic-associated diarrhea, the evidence for efficacy in the treatment of *C. difficile* as an adjunct to antibiotics is weak and more RCTs are needed.

I no longer routinely use probiotics in treatment of C. Difficile.

IBS

- Although controversy exists, bacteria likely contribute to at least some symptoms of IBS.
- Pathophysiology of IBS remains unknown, but several lines of evidence link symptomatic expression of this disorder with the intestinal microbiota.
- IBS patients may have subtle differences in their luminal and mucosal-associated intestinal microbiota compared with controls.

IBS: Recommendations from ACG

- There are at least some positive controlled studies showing that probiotic supplementation reduces IBS symptoms in some patients.
- The evidence of benefit is not sufficiently strong to support the general recommendation of probiotics for IBS;
 - benefit appears greatest for *bifidobacteria* species (rather than single species *lactobacillus* probiotics).
- With probiotics, patients might experience a global improvement in symptomatology rather than specific improvement in bowel function.
- Because treatment options for IBS remain limited in both number and efficacy, a therapeutic trial of probiotics is reasonable for patients interested in this approach.

IBS

■ Activia

□ Species:

- B.lactis L.bulgaricus, L. lactis, Streptococcus thermophilus

□ Effectiveness:

- Grade = C



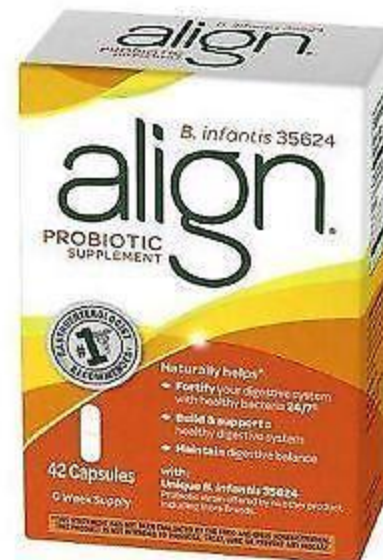
■ Align

□ Species:

- B.infantis

□ Effectiveness:

- Grade = B



Summary of Probiotics in IBD

	Crohn's	UC	Pouchitis
Probiotics	Weak	Weak	Strong

- In general, I do not use probiotics for either Crohn's disease or UC as primary therapy.
 - Exception: Pouchitis

Pouchitis

■ VSL #3

□ Species:

- Combination probiotic product (*Streptococcus thermophilus*, *B breve*, *B longum*, *B infantis*, *L acidophilus*, *L plantarum*, *L paracasei*, *L delbreuckii/bulgaricu*)

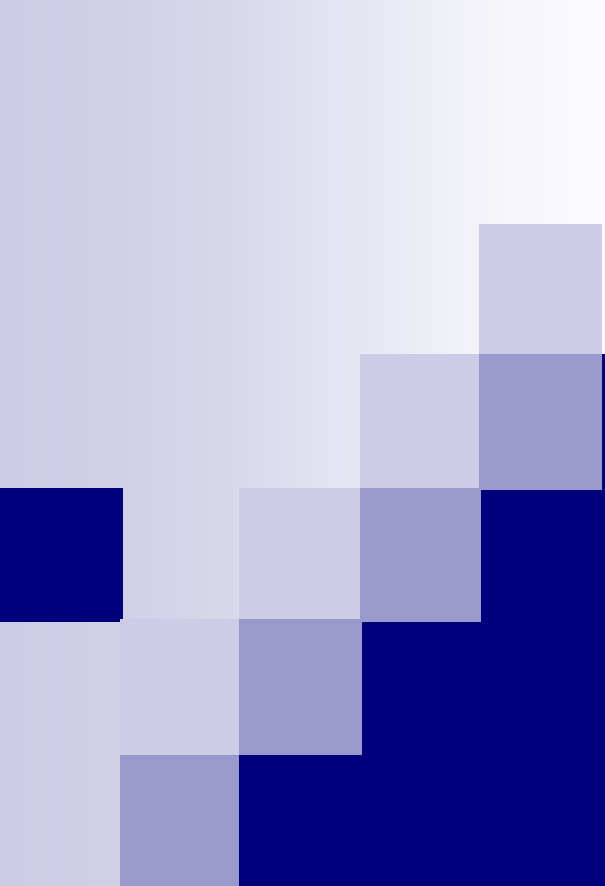
□ Effectiveness:

- Pouchitis → Grade = A
- IBS → Grade = B/C



General Considerations

- Capacity of probiotics to modify disease symptoms is likely to be modest and varies among probiotic strains—not all probiotics are right for all diseases.
- Probiotics do not colonize the human intestine. Use needs to be indefinite for continued effects.
- Probiotics are considered dietary supplements.
 - Not covered by medical insurance
 - Production is not regulated by the FDA
 - product quality, purity, and viability reported
- When NOT to use probiotics
 - Acute pancreatitis, central vein lines, immunodeficiency



FODMAPS, Fructose, SIBO

We have to talk about IBS

IBS

- IBS is chronic continuous or remittent GI illness characterized by frequent unexplained symptoms that include pain, bloat, and bowel disturbances that include diarrhea, constipation, or both.
- Common:
 - Everyone has symptoms of IBS at some point in their life
 - Most commonly diagnosed GI disorder.
 - Comprises 25-50% of all outpatients seen by gastroenterologists.
 - Women > Men ; Young > Old
 - Substantial \$\$\$ burden. Multiple billions spent each year.

Diagnostic Issues

- IBS is an *illness* – a state of mental and visceral disharmony – rather than a specific medical disease.
 - Difficulty in confirming the diagnosis may lead to further worry and doubt, resulting in numerous visits to doctors and repeated, unpleasant tests.
 - Unnecessary operations complicate the condition with scar pain, adhesions, and further alteration of bowel habits.



Pathophysiology

- Altered GI Motor Activity
 - Abnormal contractions of the colon
 - “spastic bowel”
- Altered Visceral Sensation/Psychological
 - Brain vs. Gut Brain
 - People with IBS who seek medical help are more likely to suffer from anxiety and stress.
- Gut inflammation
 - IBS following infections of the GI tract
 - Gut “microbiome”
- Food intolerances/SIBO
 - Food sensitivity or allergy

Treatment for IBS

- Pharmacological treatments generally aimed at improving the predominant symptoms
 - Constipation, pain, or diarrhea
- Psychological
 - CBT, Hypnotherapy, Biofeedback
- Change microbiome
 - FMT
- Diet
 - Remove food that is causing the problem

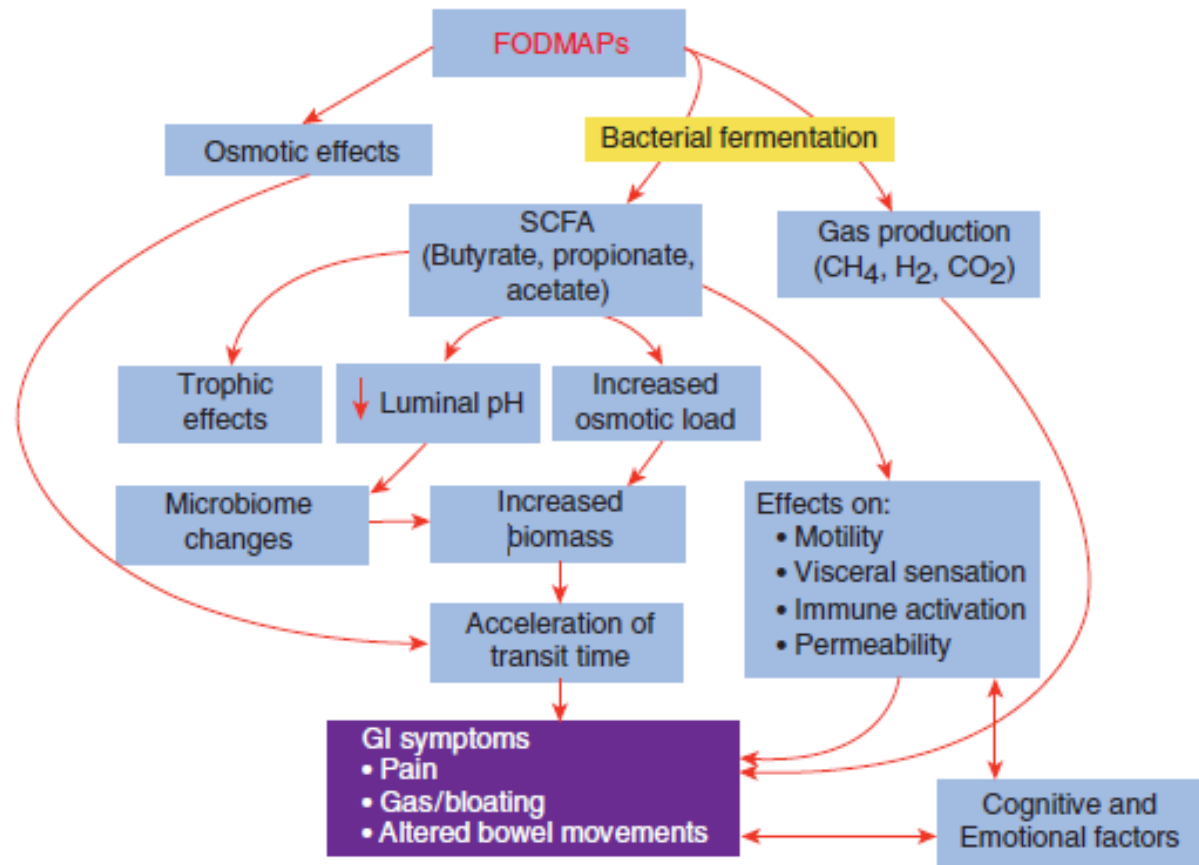


FODMAPs

What are FODMAPs

- Variable chain carbohydrates:
 - poorly or nondigested by the human small intestine
 - Reach the colon where they are fermented by the resident microbiome producing short-chain fatty acids and a number of gases including hydrogen and methane.
- Individual FODMAPs common physiologic effects.
 - Increasing water retention small intestine (osmotic)
 - Rapid fermentation → gas and short chain fatty acids.
 - Luminal distension → induce sensations of pain and bloating → abnormal motility in patients with IBS

FODMAPs and Symptoms



Adapted from Spencer M, et al. Cur Tx Opt GI. 2014;12:424-440

FODMAPs

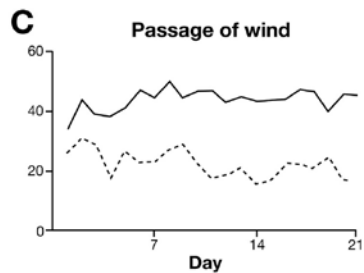
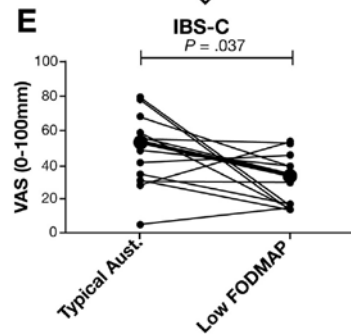
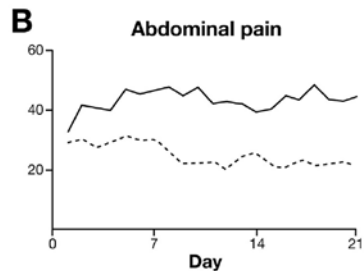
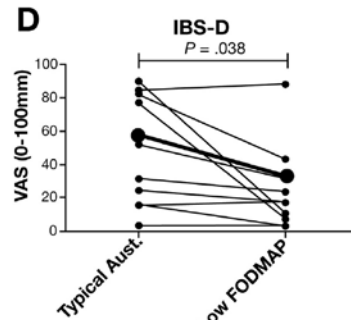
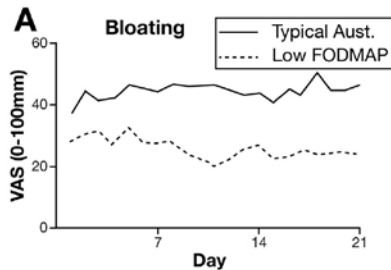
- F = Fermentable
- O = Oligosaccharides (non-absorbable)
 - Fructans
 - Inulin and fructo-oligosaccharides (FOS)
 - Galacto-oligosaccharides (GOS)
- D= Disaccharides
 - Lactose
- M = Monosacchrides
 - Fructose (problematic when free fructose > glucose)
 - Slowly absorbed. Some patients better than others
- P = Polyols
 - Sorbitol, mannitol (sugar alcohols)
 - osmotically active

CLINICAL—ALIMENTARY TRACT

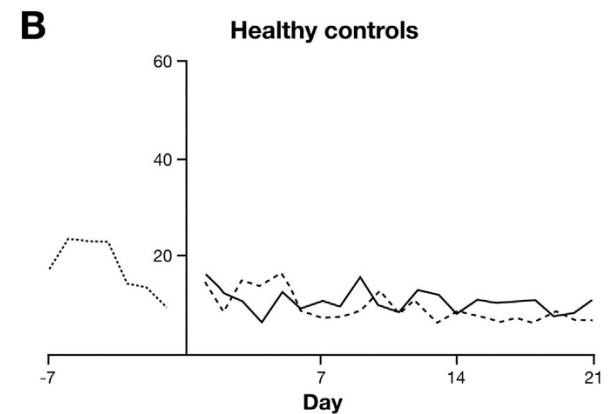
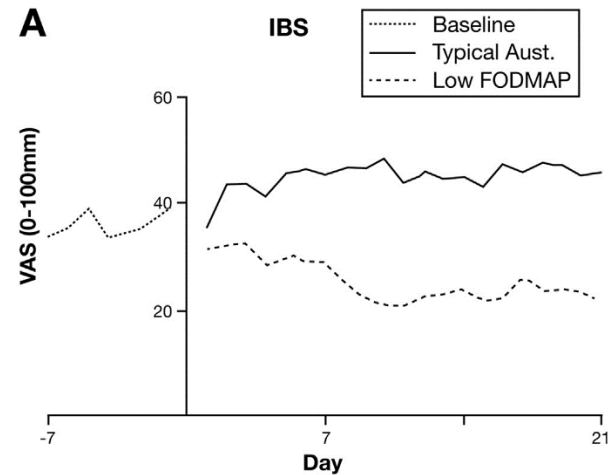
A Diet Low in FODMAPs Reduces Symptoms of Irritable Bowel Syndrome

Emma P. Halmos,^{1,2} Victoria A. Power,¹ Susan J. Shepherd,¹ Peter R. Gibson,^{1,2} and Jane G. Muir^{1,2}

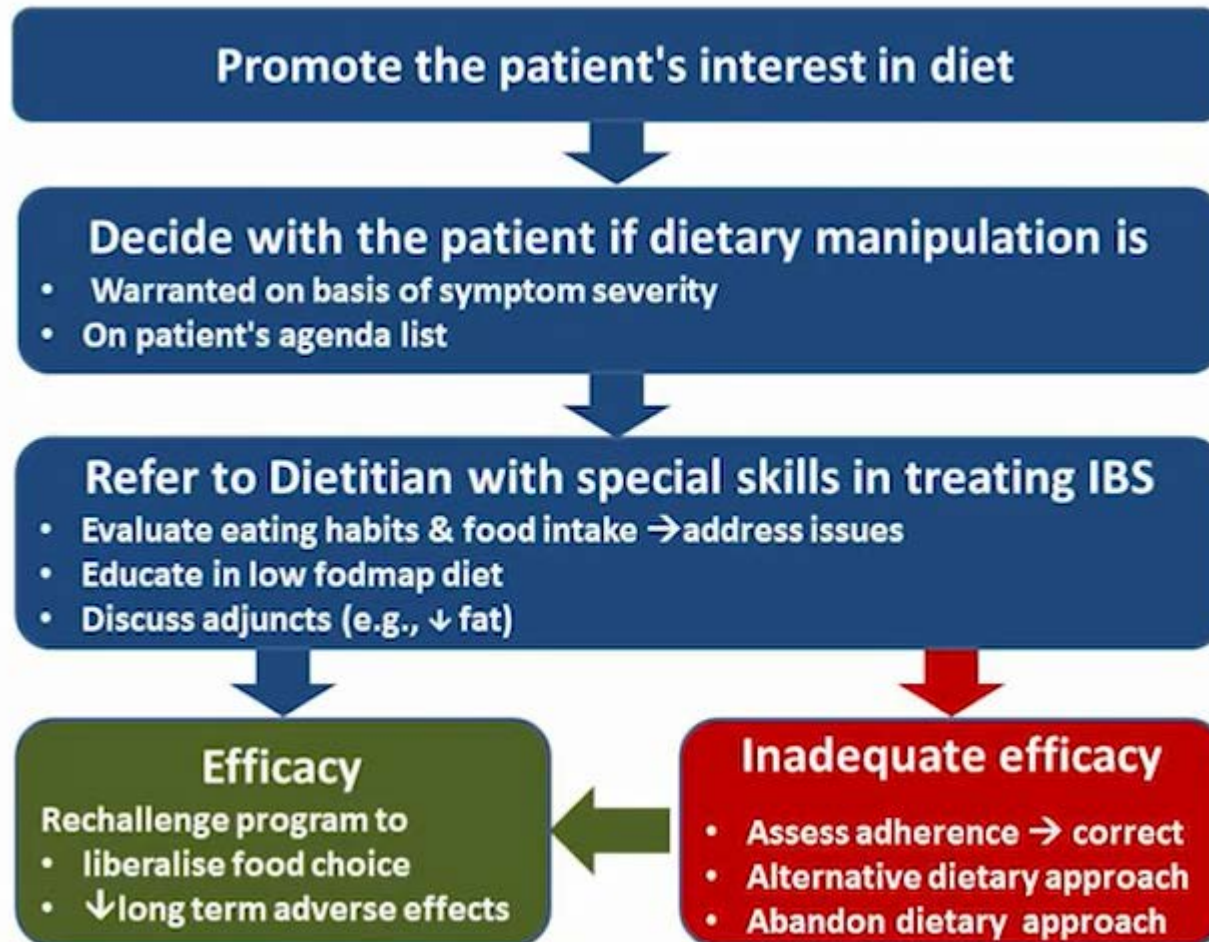
¹Department of Medicine, Eastern Health Clinical School, Monash University, Box Hill, Victoria, Australia; ²Department of Gastroenterology, Central Clinical School, Monash University, Melbourne, Victoria, Australia



Low FODMAP diet halves GI symptoms in IBS pts vs. typical Australian diet.



How I use FODMAPS

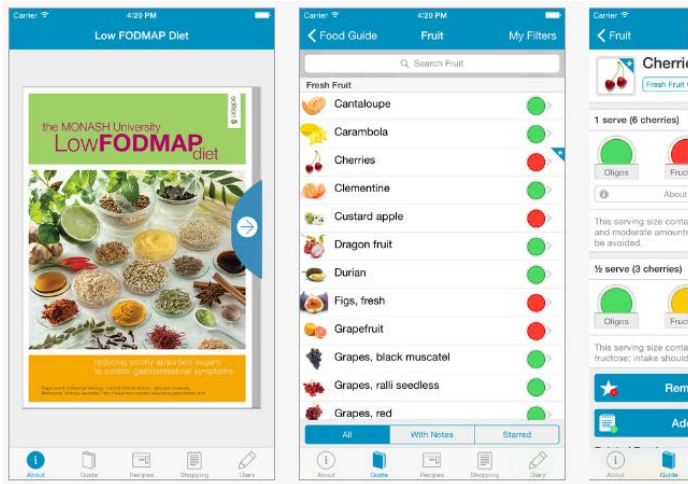




Practical Points

- Teaching ideally provided by trained dietician.
- 2-4 week trial is usually sufficient to gauge clinical response.
- Bloating and abdominal pain are most likely respond.
- Diarrhea does better than constipation.

Resources



Bridget Easley, Power Nutrition

Nutritionist in Lincoln, Nebraska

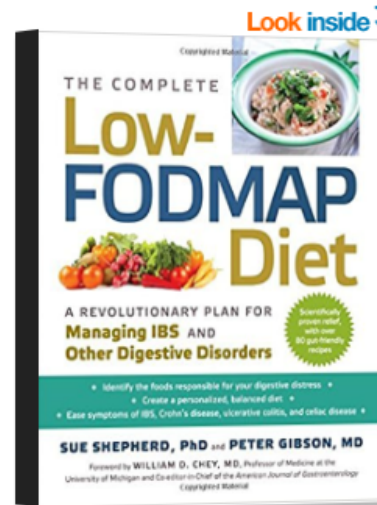


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The Complete Low-FODMAP Diet:

– August 13, 2013

by Sue Shepherd PhD (Author), Peter Gibson MD (Author),

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A diet plan proven to relieve symptoms of irritable bowel disorders—presented by the world's leading expert

“A must-have survival guide” —Gerard E. Mullin, M.D. Director of Integrative GI Nutrition Services at the J



Breath Testing

Breath Testing

- Breath test (BT) is performed to aid in the diagnosis of many common GI conditions including small intestinal bacterial overgrowth (SIBO), irritable bowel syndrome (IBS)-like symptoms, and carbohydrate maldigestion.
 - Most common: SIBO, Fructose, Lactose
 - The bloated patient

Breath Testing

- BT relies on measurement of gases produced in the intestine which diffuse into the systemic circulation and are expired through the lungs.
- H₂ and CH₄ are exclusively produced via microbial fermentation in the gut, which is the principle behind clinical breath testing.
- Gut microbes readily digest carbohydrates, resulting in production of these gases, which then diffuse into the abdominal venous circulation and are transported to the lungs, where they can be detected in the exhaled breath

SIBO

- More recognized
- Symptoms: chronic diarrhea, bloating, abdominal distention, and the irritable bowel syndrome.
- Traditional dx based on jejunal aspirates
- SIBO more recently was defined by measurable changes in exhaled gases produced by the bacterial metabolism of orally ingested carbohydrates or bile salts.

Table 1. Conditions Associated With SIBO

Developmental and acquired anatomic abnormalities

- Small-bowel diverticulosis
- Small-bowel strictures
- Small-bowel fistula
- Small-bowel Crohn's disease

Surgical alterations of the GI tract

- Gastric fundoplication
- Gastric resection
- Gastric bypass
- Small-bowel resection
- Ileocecal valve resection

GI motility disorders

- Gastroparesis
- Small-bowel pseudo-obstruction
- Colonic inertia

Other GI disorders

- Celiac disease
- Chronic pancreatitis
- Achlorhydria
- Cirrhosis

Systemic disorders

- Diabetes mellitus
- Scleroderma
- Amyloidosis
- Hypothyroidism
- Immune deficiency syndrome
- Chronic renal disease

Miscellaneous conditions

- Advanced age
- Chronic narcotic use
- Chronic PPI use?



Breath Testing for SIBO

- Provides a more readily available, safe, inexpensive, and noninvasive alternative to jejunal aspiration culture for the diagnosis of SIBO.
- By measuring exhaled gases produced by bacterial fermentation of various orally ingested substrates, the bacterial load within the small bowel can be assessed indirectly.

Treatment of SIBO

- Rifaximin
 - 550 mg TID x 10 day
- Amoxicillin-clavulanate
 - 875 mg BID x 10 days
- Combination:
 - Metronidazole 500 mg TID; **plus** Cephalexin 500 mg TID x 10 days
 - Metronidazole 500 mg TID; **plus** Trimethoprim-sulfamethoxazole 1 double-strength BID x 10 day

Fructose Intolerance

- In the US, high fructose corn syrup sweeteners were not commercially available until 1960s.
 - now comprise more than 20% of total daily carbohydrate intake
 - Surpassed sucrose as the leading sweetener in the United States food industry (especially in soft drinks)
- In fructose intolerant subjects, unabsorbed fructose is fermented by the colonic bacteria causing IBS-like symptoms.

Fructose

■ Treatment

- Refer to dietitian

- Low fructose vs. No fructose

- Continue symptom treatment

- Diarrhea, bloating, gas, etc

- Assess for pain

- bloating



Thank You

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