Dysbiosis: Prebiotics, Probiotics & Synbiotics in Sickness and in Health

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Advanced Practice Module: Restoring Gastrointestinal Equilibrium
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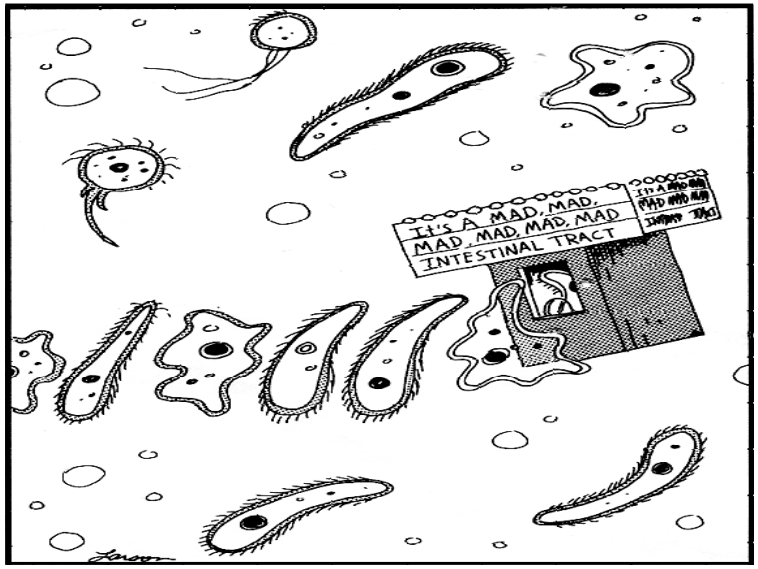
Learning Objectives

- **Develop treatment protocols for dysbiosis that incorporate the '5R' approach to improve outcomes in patients with GI dysfunction**
- **Be able to appropriately prescribe foods, botanicals, nutraceuticals and pharmaceuticals to improve outcomes in patients with GI dysbiosis**



Dysbiosis is not so much about the microbe as it is about the effect of that microbe on a susceptible host; i.e., it is about the *relationship* between host and microbe.

Dysbiosis

- We are not looking for classic "infection"
- Determine which underlying disruptions may be exacerbating inflammation and the patient's symptomatology
- Dysbiosis in one patient may present with dermatitis; the same microbial imbalance in another patient can present as peripheral neuropathy or inflammatory arthritis
- Often what we find when working with autoimmune/inflammatory patients is that they are having a *pathogenic inflammatory response* to a *nonpathogenic* microbe

Key Functional Roles of the Gut:

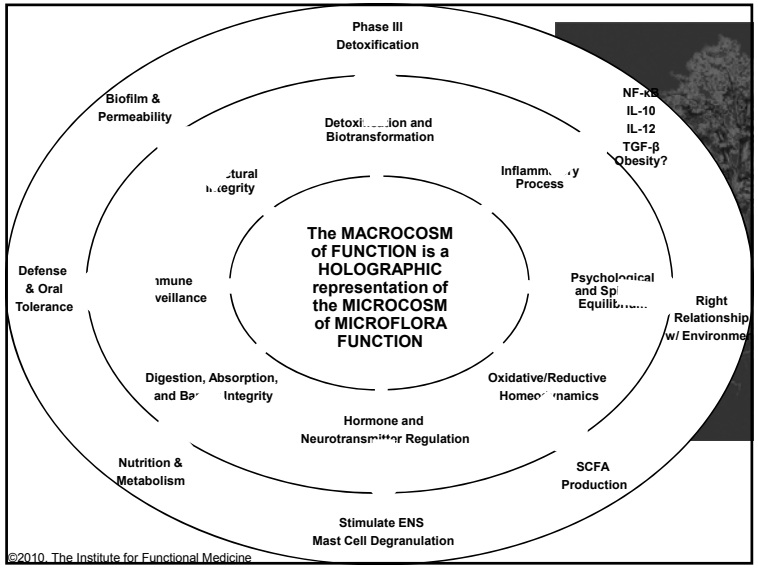
Digestion/Absorption

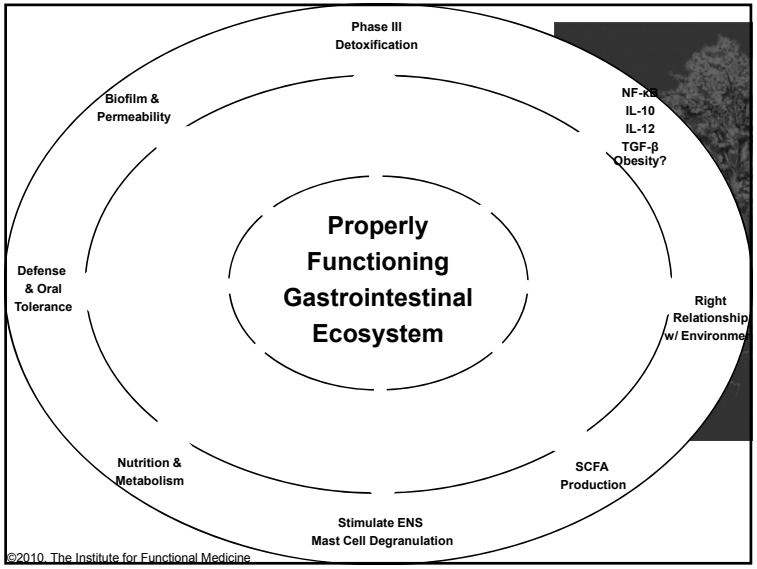
Intestinal Permeability

Gut Microbiota/Dysbiosis

Inflammation/Immune

Nervous System





"Re-balancing" Dysbiosis

- Diet
  - Prebiotics
  - Fermented Foods (e.g., "Body Ecology Diet")
  - Specific carbohydrates
  - Soluble fiber
- Probiotics
  - Dosage?
  - Strains?
  - Safety?
- Synbiotics = Pre- + Pro-biotics

Prebiotics: Food as Medicine

Three Necessary Criteria:

1. Must be non-digestible by host enzymes
2. Must be fermented in the GI tract by anaerobic endogenous bacteria in colon
3. Must be selective in the stimulation of intestinal flora/metabolic activity




Prebiotics

Foods that support the growth of gut microflora:

- Bran, psyllium, resistant starch (high amylose), breast milk, oligofructose (FOS), inulin, germinated barley foodstuff (GBF), synthetic oligosaccharides, & lactulose
- FOS are found in onions, garlic, rye, chicory, blueberries, and bananas
  - give texture and a slightly sweet taste
  - dietary intake averages 2–8 g/day
- Inulins are derived from chicory and artichoke

Benefits of Oligosaccharides

- Promote the growth of bifidobacteria and lactobacilli
- Lower colon pH
- Discourage growth of clostridia
- Prevent constipation and diarrhea
- Have low glycemic index
- Water soluble and of low viscosity
- Do not bind minerals

FOS & Bifidobacteria

At least 4 g/day of FOS are needed to increase counts of bifidobacteria, with a dose-response effect noted

Bifidobacteria:

- **actively ferment oligosaccharides to form SCFAs**
- **help to produce B vitamins and some amino acids**
- **restore flora after antibiotics**
- **inhibit the growth of pathogenic bacteria**

Sartor R.B. Curr Opin Gastroenterol. 2003, 19:358–365.

Inulin

- **Naturally occurs in fruits and vegetables**
- **Longer chain length than FOS**
- **Provides a fat-mimicking texture when added to food**
- **Now available in a supplement**

Clinical Use of Prebiotic Inulin

- **Constipation - 40g/d inulin for 19 days increased bifidobacteria and produced soft stools** (Kleessen B, et al. AJCN. 1997 May;65(5):1397-402.)
- **IBS - two studies: no significant effect**
- **IBD - two Japan reports in open label decreased symptoms**
- **Controversial lipid-lowering effect**
- **Main positive reports are increase in bifidobacteria in infants by use of FOS**

Sartor R.B. Curr Opin Gastroenterol. 2003, 19:358–365.

Hepatic Encephalopathy

- **Lactulose as a prebiotic alters the enteric flora and successfully reduces encephalopathy**
- ***Lactobacillus acidophilus* has also been used and associated with a decrease in urease and amino-acid-oxidase activity**

Sharma BC, et al. Gastroenterology. 2009 Jun 6. [Epub ahead of print]
Macbeth W, et al. Lancet, 1965;1:399-403.

Prebiotic Substances Available Commercially

- In USA:
  - FOS
  - Guar
  - Lactulose
  - Inulin
- In Japan and Europe, many of the other oligosaccharides are available
- Nutraceuticals, such as acemannan, a beta-linked acetylated polymannan, are also available

Prebiotic Foods

- Jerusalem artichokes
- Onions
- Chicory
- Garlic
- Leeks
- Bananas
- Fruit
- Soybeans
- Burdock root
- Asparagus
- Sugar maple
- Chinese chives
- Peas
- Legumes
- Eggplant
- Honey
- Green Tea
- Yogurt, cottage cheese, kefir

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"Re-balancing" Dysbiosis

- Diet
  - Fermented Foods (e.g., "Body Ecology Diet")
  - Specific carbohydrates
  - Soluble fiber
  - Prebiotics
- Probiotics
  - Dosage?
  - Strains?
  - Safety?
- Synbiotics = Pre- + Pro-biotics

Diets for Dysbiosis

Fermented foods (e.g., Body Ecology Diet) – Restore and maintain "inner ecology" through:

- **Cultured foods**
- **Decreasing sugars and carbohydrates**

Specific carbohydrate diet

- **Undigested carbohydrates feed "downstream" bacteria → further dysbiosis; see www.scdiet.org**

Soluble fiber (e.g., modified citrus pectin)

- **Paleolithic man consumed > 100 g fiber/day**
- **Increases beneficial short-chain fatty acids (SCFAs)**

Dietary Fiber

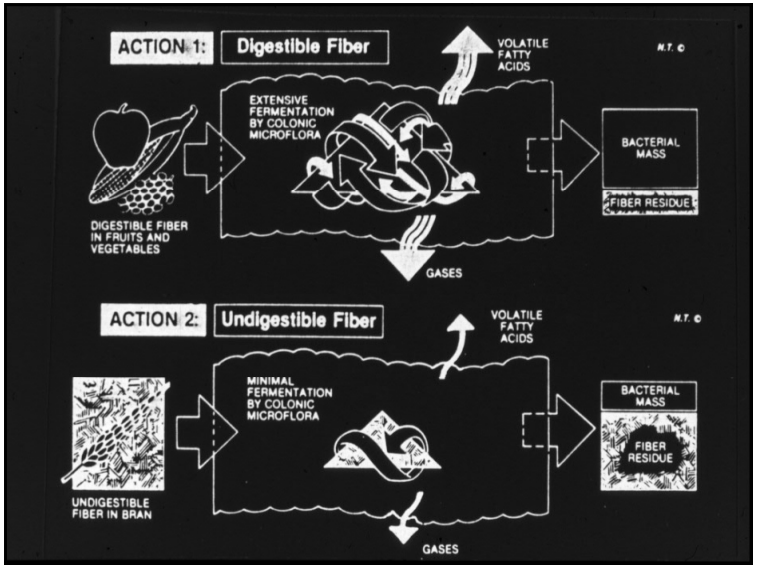
- **Fiber is broken into *soluble* and *insoluble* components (cf. resistant starch identified by other chemical method)**
  - ***Soluble* components are pectin substances, gums, and mucilages that are completely fermented by the bacterial flora**
  - ***Insoluble* components are cellulose, waxes, and lignins primarily in plant cell walls that are only slightly fermented**

***Wheat* is 90% insoluble and 10% soluble**
***Oats* are 50% insoluble and 50% soluble**
***Psyllium* is 10% insoluble and 90% soluble**

Dietary Fiber

Physiologic Properties

1. **Slows transit in small bowel**
2. **Increases stool bulk**
3. **Holds on to water**
4. **Forms gels**
5. **Binds minerals and organic substances**
6. **Stimulates bacterial growth**
7. **Metabolized to SCFA**



SCFA Production in Colon

Starch	Bacterial	Butyric
+	⇨	Acetic
Non-starch Polysaccharides	Enzymes	Propionic

Dietary Fiber Intake

Recommended intake 25–35 g/day

Actual intake ranges from 8–50 g/day

- **Cereal content varies, but bran is usually insoluble cell wall (e.g., Raisin Bran = 8 g, Fiber One and All Bran = 12–14 g)**
- **Fruits and vegetables vary, and portions contain 2–5 g fiber (apple 2.8, beans 5, berries 5, potatoes 1.8). Fruits are mostly soluble, and vegetables are ~ ½ soluble and ½ insoluble fiber**
- **Meats, fowl, fish, eggs, and pure dairy contain no fiber**

Prebiotics: Practical Issues

- **Treatment time – indefinite**
- **FOS/fructo-oligosaccharides, 1000-5000 mg, QD-TID**
- **Inulin, 1000-5000 mg, QD-TID**
- **Fiber (high soluble)**
  - **Larch (arabinogalactans), 500-5000 mg, QD-TID**
  - **Modified citrus pectin, 3-5 g, BID-TID**

Probiotics: Definitions

World Health Organization:

- **"Live microorganisms which when administered in adequate amounts confer a health benefit on the host"**
- **A bacterial strain that:**
  - **Survives the stomach acid and bile**
  - **Adheres to intestinal lining**
  - **Grows and establishes temporary residence in the intestines**
  - **Imparts health benefits**

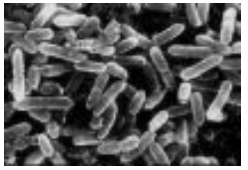
R Fuller. Probiotics: The Scientific Basis. London: Chapman and Halls; 1992.

Probiotic Overview

- What are probiotics and how do they work?
- Current proposed uses and a look at some of the evidence
- Issues in prescribing their use

Probiotics

- *Lactobacillus* sp.
  - *reuteri*
  - *casei*
  - *rhamnosus*
  - *acidophilus*
- *Streptococcus* sp.
- *Bifidobacterium* sp.
  - *infantis*
  - *lactis*
  - *longum*
  - *breve*
  - *bifidum*
- *S. boulardii* (nonhuman)

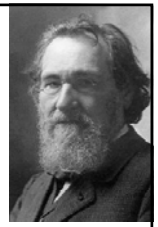


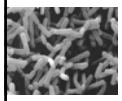
Probiotics

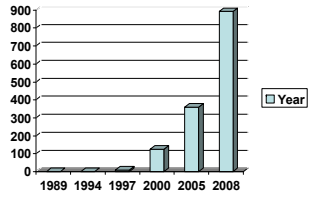
"Live micro-organisms, when ingested in adequate amounts, confer a beneficial effect"

Metchnikoff (1874-1961)

- 1908 Nobel Prize recipient
- Increase longevity – Bulgarian farmers
- Hypothesized beneficial effect from the bacteria used in yogurt
- *Lactobacillus bulgaris* was named after Bulgaria, where it was first used

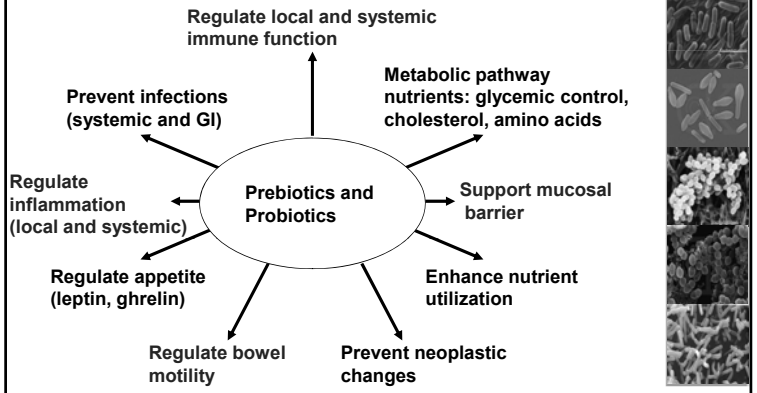


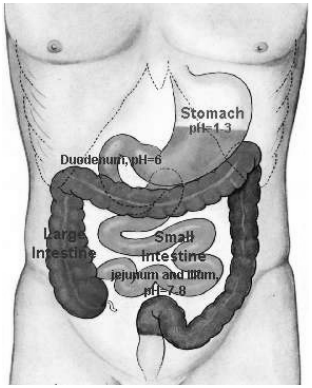




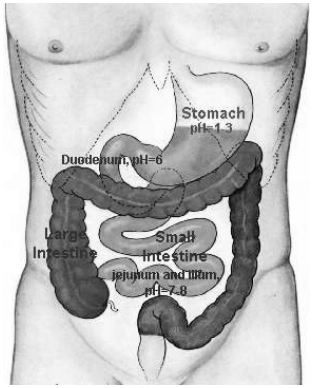
Rapidly expanding literature on the role of probiotics and GI disease

Probiotics and Prebiotics: Exploring the Mutually Beneficial Effects of Bacteria and their Substrates in the Human Host



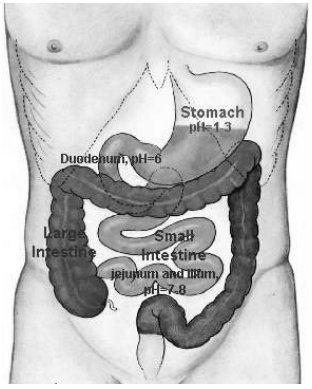


- At birth, digestive tract of humans is sterile
- Colonized by microbes within the first few days of life
- At first, predominantly bifidobacteria (breast-fed infants)

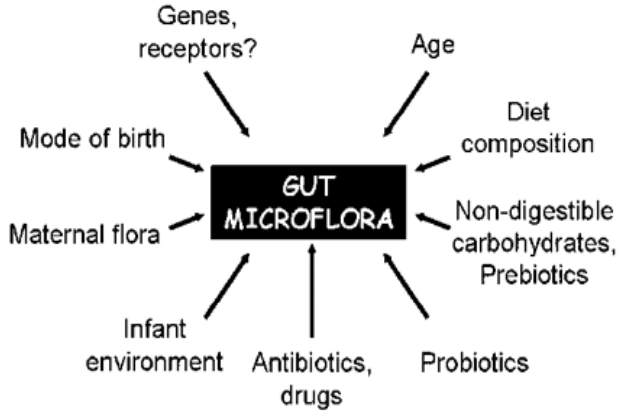


Colonization begins with birth and breast-feeding and continues through life, leading to:

- 100 trillion bacteria
- 70% of human immune system localized in digestive tract
- Accounts for half of the volume of contents in the colon



- With the introduction of other foods, a diverse microbial population develops in the GI tract
- By now, of all the cells in a human body, the overwhelming majority are nonhuman
- In children and adults, "successful" treatment with probiotics leads to ONLY temporary colonization



Postnatal Development of Mucosal Immunity

<u>Antigen Exposure and Nutrition</u> – suboptimal stimulation of the sIgA-dependent mucosal barrier function → increased frequency of:

- **allergies**
- **asthma**
- **inflammatory mucosal disorders**
- **INCREASED RISK OF SYSTEMIC INFLAMMATION**

Infants with a family history of atopic allergy who received a *Lactobacillus* probiotic had a 50% ↓ in atopy @ 2 years old and again @ 4-year-old follow-up.

Brandtzaeg P. Ann NY Acad Sci. 2002;964:14-45.

Postnatal Development of Mucosal Immunity

<u>Mucosal Homeostasis vs. Allergy</u>

Intestinal Th1 cell activity is minimal:

- **due to decreased microbial stimulation**
- **requires the presence of commensal bacteria to drive Th1 dominance**

Breast milk contains immunoregulatory factors that stimulate lactic-acid-producing bacteria. This also promotes a Th1 cytokine balance and oral tolerance.

Brandtzaeg P. Ann NY Acad Sci. 2002;964:14-45.

Let Them Eat . . . Dirt?

- **Children who are "too clean" are more likely to develop asthma & atopy**
- **Mycobacteria in dirt stimulate cell-mediated (Th1) immunity whereas vaccinations stimulate humoral immunity (Th2)**
- **A modern, sanitized, vaccinated child is likely to overdevelop Th2 immunity and underdevelop Th1 immunity, rendering him or her susceptible to asthma and atopy**

Hamilton G. New Scientist, July 18, 1998:26-31.
Rook GAW, Stanford JL. Immunology Today. 1998;19:113-116.

LEADING ARTICLE

Microbes, immunoregulation, and the gut

G A W Rook, L R Brunet

Contact with "old friends" is greatly diminished in rich countries but increased on farms, in cowsheds, and through contact with pets.

Rook GA, Brunet LR. Gut. 2005;54:317-320.

Postnatal Development of Mucosal Immunity

- Healthy gut flora play a crucial role in maturation of the immune system
- Constant stimuli are required
- Timing is everything:
  - ✓ Prolonged reintroduction of flora does <u>not</u> promote oral tolerance
  - ✓ Delayed reintroduction of flora leads to a decrease in circulating IgA- and IgM-secreting cells

Kalliomaki M, et al. Lancet. 2001;357:1076-1079.

Vol 444|21/28 December 2006 nature

Nature. December 2006.

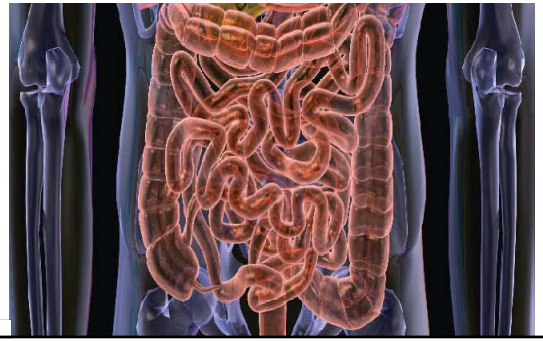
NEWS & VIEWS

PHYSIOLOGY

Obesity and gut flora

Matej Bajzer and Randy J. Seeley

The intestinal bacteria in obese humans and mice differ from those in lean individuals. Are these bacteria involved in how we regulate body weight, and are they a factor in the obesity epidemic?



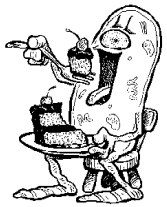
Probiotics: Proposed Mechanisms

- Adherence and subsequent stimulation of gut immune system
  - Upregulation of mucin gene
  - Enhance secretory IgA
  - Maintain normal macrophage function
- Competition for essential nutrients
- Production of antimicrobial factors
- Provide favorable environment for growth of other beneficial bacteria
- Production of SCFAs with anti-inflammatory properties

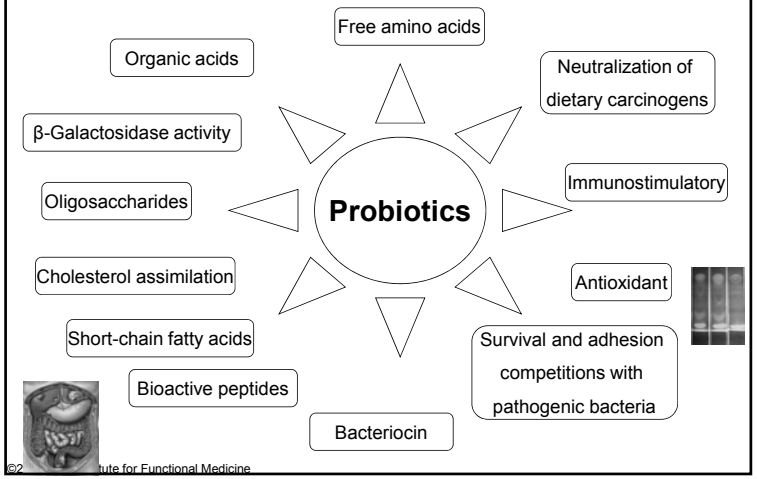
Microflora Functions in the Gut

- Metabolic Activities:
  - Microflora ferments non-digestible dietary residue releasing SCFAs, vitamin K, and some glucose
- Trophic Activities:
  - SCFAs produced by microflora control epithelial cell proliferation and differentiation in the colon (protect against the development of neoplasia)
- Protective Activities:
  - The barrier effect: resident bacteria provide resistance to colonization by exogenous, potentially pathogenic microbes

What we eat influences the population and metabolic activity of our microflora



Probiotics: Possible Mechanisms of Action



Mechanisms of Action of Gut Bacteria

Inhibit Pathogenic Bacteria	Improve Epithelial Function	↑ Immunoregulation
↓ Luminal pH	↑ SCFA (butyrate)	↑ IL-10, TGFβ
Bacteriocidal proteins	↑ Healing	↓ TNF, IL-12
Colonization resistance	↑ Mucus	↓ T cell proliferation
↓ Epithelial binding	↓ Apoptosis	↑ Apoptosis TH1 cells
↓ Epithelial invasion	↑ Barrier integrity	↑ sIgA
↑ β defensins	↑ HSP 25, 72	↓ NFκB

Sartor RB. J Clin Gastro. 2007;41:S37-S43.

Probiotics: Proposed Uses

- Infectious diarrhea
- Antibiotic-associated diarrhea
- IBD, IBS, and pouchitis
- Necrotizing enterocolitis
- Bacterial vaginosis
- Recurrent UTIs
- Atopic diseases
- Immune system enhancement
- *H. pylori* infections
- Dental caries
- Radiation-induced diarrhea
- Cardiovascular risk reduction
- Constipation
- Rheumatoid arthritis

Probiotics: Proposed Uses

Ratings: A: strong B: good C: fair

Rating the Evidence	Floch, et al (2006)	Natural Standard (2006)
Infectious diarrhea	A	B
Antibiotic-associated diarrhea	A	C
Diarrhea prevention	B	B
IBS	C	B
Atopic dermatitis/allergy	B?	B/C

Floch, et al. J Clin Gastro. 2006;40(3).
www.naturalstandard.com

Probiotics: Proposed Uses

Ratings: A: strong B: good C: fair

Rating the Evidence	Floch, et al (2006)	Natural Standard (2006)
Ulcerative colitis	C	B
Crohn's disease	C	
H. pylori infection	C	A
NEC		C
Bacterial vaginosis	C	C
UTIs		C

Floch, et al. J Clin Gastro. 2006;40(3).
www.naturalstandard.com

Probiotics: Prescribing

- Which organism to use?
- Which product?
- For what conditions?
- What dose?
- For how long?
- Any side effects to be aware of?
- How much does it cost?

Probiotics: Prescribing

- *Lactobacillus GG* best studied to date
- Combination products not well studied, but may work as well
- 10 billion organisms/d
- Keep in fridge
- Give in cool food/drink
- 2% risk bloating/gas

Probiotics: Prescribing

ConsumerLab.com tested 25 probiotic products

- **19 for general population, 3 for children, 3 yogurts**
- **8 claimed a specific number of organisms per *serving***
- **13 claimed only a number of organisms *at time of manufacture***
- **8/25 contained less than 1% of the claimed number of live bacteria or of the expected minimum of 1 billion**
- **7 of the 8 that gave expected numbers per serving met those counts**
- **None contaminated with bacteria, mold, or fungus**
- **All enteric-coated capsules passed testing**

Lactobacilli and Bifidobacteria: Why They Are Safe

- **Many exposures in pediatrics**
- **Fermented foods**
- **Probiotics**
- **The host's own microflora**
  - **Oral cavity**
  - **Ileum and colon**
  - **Vagina**

Lactobacilli and Bifidobacteria: Why They Are Safe

- **Cases of infection extremely rare**
- **Account for 0.05% to 0.4% of infective endocarditis and bacteremia**
- **Less than 1 case per million people**
- **Review of 143 human clinical trials from 1961-1988**
  - **Over 7500 subjects**
  - **No reported adverse events**

Lactobacilli and Bifidobacteria: Why They Are Safe

- **Increasing probiotic consumption has not led to increased opportunistic infections**
  - **National Public Health Institute-Finland 1995-1999**
    - **Increasing cases of bacteremia (all types)**
    - **Increasing use of probiotics**
    - **Constant level of *Lactobacillus* bacteremia**

Probiotics: Safe, However ...

- Several reports of fungemia associated with use of yeast-based probiotics (*S. boulardii)*
- Difficult to determine pathogenicity
  - Virulence factors for pathogens (adherence, colonization) are common in probiotic bacteria
  - When bacteremia occurs, often polymicrobial and in critically ill host

Invasive *Lactobacillus* Infection

Occasional reports of invasive infections

- Bacteremia (rare)
- Endocarditis: 16 reported cases (1992-2001)
  - 5 cases with yogurt or probiotic
  - Only 1 confirmed to be identical to probiotic
- Liver abscess (74-year-old woman)
  - Daily consumption of probiotic drink
  - Indistinguishable from probiotic strain

Probiotics: Practical Issues

- Purified strains of bacteria
- Selected for ability to:
  - Survive acid/bile in upper GI tract
  - Colonize
  - Adhere
- Must have shelf viability
- Should have quality control

Probiotics: Practical Issues

- Not FDA regulated
  - Quality control is poor
  - 80% of preparations tested had 1% or less of the bacterial concentration on the label
- Numerous preparations on the market
  - Which strains work best?
  - Do different strains work better for different diseases?
  - Do combinations work better than single strains?

Probiotics: Practical Issues

- Typically $1 to $3 per day
  - VSL#3®: $56 for 20-day supply
  - Culturelle® (LGG): $55 for 30-day supply
  - Custom Probiotics CP-1: $40 for 30-day supply
- May need several months of therapy to see an effect
- Likely stop working after discontinued
- Concentration (dose) highly variable

Probiotics: Practical Issues

Treatment time – indefinite

- Lactobacillus (various species): 10–100 billion live organisms daily or higher
- *S. boulardii*: 500 mg–3 g daily
- Bifidobacteria (various species): 10–100 billion live organisms daily (combinations now using as high as 3.6 trillion a day)

Consumer Labs

- Contained Listed Amount of Probiotic Organisms
- Provided At Least 1 Billion Bacteria Per *Daily Serving*
- Free of Microbial Contamination
- **5 out of 19 failed this test.**

Product Review: *Probiotic Supplements (Including Lactobacillus acidophilus, Bifidobacterium, and Others)* — Initial Posting: 12/12/06 Updated: 5/25/07

Consumer Labs

- Withstanding stomach acid
  Some products have an enteric coating, because certain probiotic bacteria need protection in order to survive exposure to stomach acid. In general, most *Lactobacillus, Bifidobacterium,* and *Streptococcus* species do not need enteric coating as they can survive passage through the stomach.

Product Review: *Probiotic Supplements (Including Lactobacillus acidophilus, Bifidobacterium, and Others)* — Initial Posting: 12/12/06 Updated: 5/25/07

Probiotics in Yogurt

National Yogurt Association's definition of yogurt: Probiotics or live cultures added to yogurt *must* include *Lactobacillus bulgaricus* and *Streptococcus thermophilus*.

- **Dannon Danimals 1-3 billion (*L. acidophilus GG*)**
- **Dannon Activia 1-3 billion (*B. regularis*)**
- **Stonyfield Farms *L. acidophilus*, *Bifidus*, *L. casei* and *L. reuteri*.**
- **Dannon over 3000 strains of probiotics**
- **Dannon Immune *Lactobacillus casei***
- **Brown Cow. *B. Bifidus***
- **24 hour homemade: up to 100 billion**

Lifeways Kefir

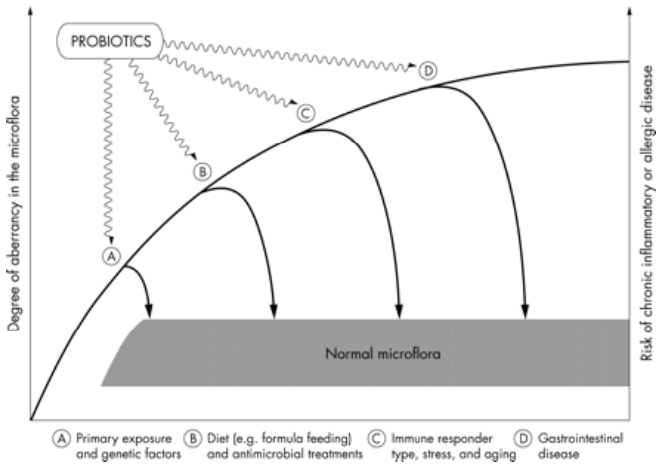
- ***Lactobacillius Lactis***
- ***Lactobacillus Rhamnosus***
- ***Streptococcus Diacetylactis***
- ***Lactobacillus Plantarum***
- ***Lactobacillius Casei***
- ***Saccharomyces Florentinus***
- ***Leuconostoc Cremoris***
- ***Bifidobacterium Longum***
- ***Bifidobacterium Breve***
- ***Lactobacillus Acidophilus***

Helios Kefir

- ***Lactobacillus kefyr***
- ***Lactococcus lacti***
- ***Lactococcus cremoris***
- ***Lactococcus diacetylactis***
- ***Leuconostoc cremoris***
- ***Candida kefyr***
- ***Saccharomyces unisporous***

Probiotics: Questions???

- **Dosages → vary from 3.6 trillion organisms, 450 billion, 20 billion, and 1 billion**
- **Take once a day vs. two or more times/day?**
- **Mixtures or not? Which strains?**
- **Human strains vs. synthetic strains?**
- **With or without FOS? i.e. Synbiotics**
- **Refrigerate or not?**
- **Live or dead?**
- **Casein-free?**
- **Bacteria or yeast?**
- **Oral or injectable?**
- **Fecal bacteriotherapy!**



Treating Dysbiosis

Stool culture Microbiology	Potentially Pathogenic Bacteria: NORMAL	Potentially Pathogenic Bacteria: ABNORMAL
Beneficial Bacteria: NORMAL	No need to treat	Treat with anti-microbial herbs
Beneficial Bacteria: ABNORMAL	Treat with ProBiotics 25-50 billion cfu qD	Treat with Probiotics 25-50 billion cfu qD + antibiotics

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***If patient is ILL – add probiotics @ ~50 billion cfu qD & advance to antibiotics more quickly.**

Key Functional Roles of the Gut:

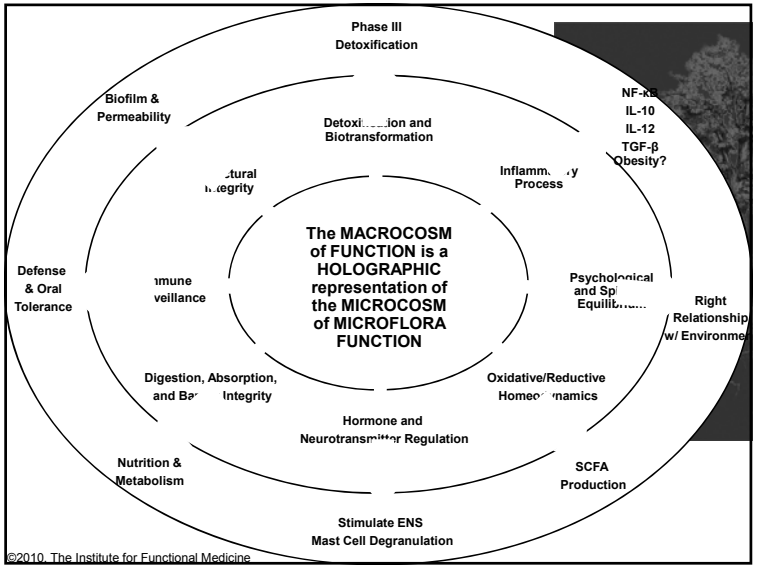
Digestion/Absorption

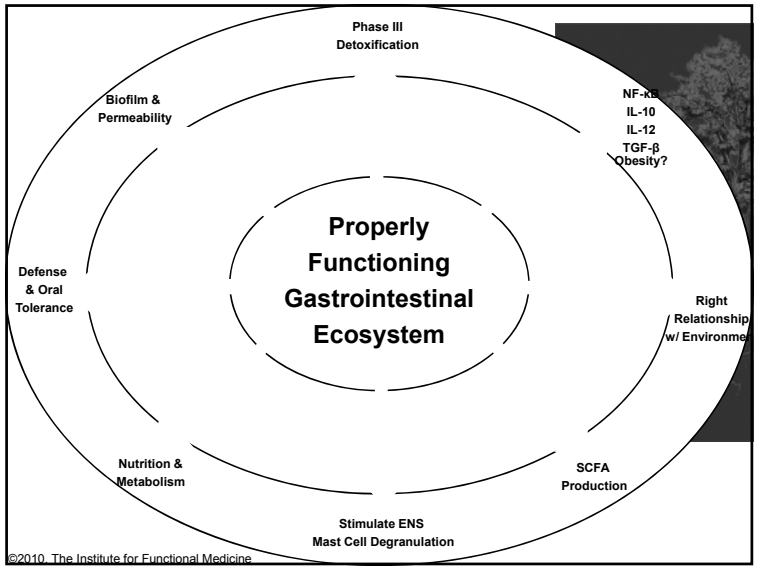
Intestinal Permeability

Gut Microbiota/Dysbiosis

Inflammation/Immune

Nervous System





Treatment Approach to the Patient with *Acute* Complaints

Infectious Diarrhea (Review)

- **Salmonella and shigella**
- **Shiga toxin *Escherichia coli*: enterohemorrhagic *E. coli*, including subtype H-0157**
- ***Campylobacter jejuni:* the most frequent cause of bacterial diarrhea, including traveler's diarrhea**

Infectious Diarrhea: *C. difficile*

Anaerobic, spore-forming, gram + bacteria associated with diarrhea and colitis after antibiotic use

- **More common than previously thought**
- **Presentation not always "sick" patient**
- **Chronic and recurrent infections common**
- **Need to test for toxins A and B**
- **NEW LETHAL STRAIN NOW PRESENT!**

Difficult Treatment: *C. difficile*

- **Oral vancomycin – Stops production of the toxin, but does not eradicate the bacteria! Thus, treatment is always symptomatic, awaiting the activation of the immune system to "finish the job"**
- ***Saccharomyces boulardii* – Effective for overgrowth of all clostridial species**

Difficult Treatment: *C. difficile*

S. boulardii, a* strain of *S. cerevisiae

- **Increases immunoglobulin synthesis and secretion of sIgA**
- **Inactivates *E. coli* toxins and decreases TNF-α levels in tissue**
- **Yeast cells directly excrete sucrase and other enzymes, as well as stimulating the brush border membrane (BBM) enzymes**

Difficult Treatment: *C. difficile*

***S. Boulardii* increases brush border enzyme activity:**

- **excretes enzymes that degrade allergens**
- **degrades and decreases enterotoxin-binding**
- **degrades molecules used by microbes to attach to the gut epithelium**
- **modulates gut epithelial immune activity**

Difficult Treatment: *C. difficile*

S. boulardii

- **Dosage = 250 mg BID x 2–4 weeks, often concomitantly with vancomycin or metronidazole**

Fecal bacteriotherapy – 95% effective!

- **Fecal enemas from healthy relatives and family members. Feces from noninfected donors are made into a suspension and administered as enemas to the patient with multiple relapses. The normal bacteria from the donor's stool displaces the *C. difficile* bacteria**

Botanical Medicines with Antibacterial Activity

- *Allium* (garlic)
- *Astragalus*
- *Berberis* spp, Oregon grape, barberry
- Clove
- Coptis root
- Curcumin
- *Echinacea*
- *Glycyrrhiza* (licorice)
- Grapefruit seed extract
- *Hydrastis* (goldenseal)
- Oregano oil
- *Salvia* (sage)
- *Thyme*
- *Usnea* (old man's beard)
- *Arctostaphylos uva-ursi* (bearberry)

Antibacterial Treatments

- Standard antibiotics Rx = 7–10 days
  - Ciprofloxacin/norfloxin
  - Co-trimoxazole oral
- Herbal treatment time = 4–12 weeks
  - Garlic (*Allium sativum*), standardized to 5000 mcg allicin potential, TID
  - Goldenseal (*Hydrastis canadensis*), standardized to contain berberine, 200-400 mg, TID
  - Artemisia/chinese wormwood (*Artemisia annua*), 1-3 g, TID

Small Bowel Bacterial Overgrowth

A frequently overlooked contributor in common disorders:

- IBS
  - 78% of patients tested positive; 48% of successfully-treated patients no longer met Rome criteria for IBS
- Fibromyalgia and CFS
  - 78% and 77% of subjects, respectively, have small bowel bacterial overgrowth (SBBO); both disorders overlap with IBS

Pimentel M, et al. Am J Gastroenterol. 2000;95:3503-3506.
Pimentel M, Chow EJ, Hallegua D, et al: J Musculoskelet Pain 9:107-113, 2001
Aaron LA, Burke MM, Buchwald D: Arch Intern Med 160:221-227

Small Intestinal Bacterial Overgrowth
A Framework for Understanding Irritable Bowel Syndrome

Henry C. Lin, MD

IRRITABLE BOWEL SYNDROME (IBS) is a common diagnosis that affects 11% to 14% of the population.[1,2] Currently, IBS is a diagnosis made on the basis of meeting clinical criteria.[3] This symptom-based approach has been used because no consistent biological marker or unifying framework has been available to explain the different symptoms and findings of IBS. The varying symptoms in IBS have led to efforts looking at differences rather than similarities between patients.[4]

Another way we have emphasized the difference rather than the similarity is in the grouping of one set of symptoms of these patients as IBS and another set of symptoms as belonging to some other diagnosis. The clinical criteria for IBS do not include the extraintestinal symptoms that are common in these patients such as fatigue or myalgia. Instead, these complaints are viewed as symptoms of other diagnoses that coexist with IBS such as chronic fatigue syndrome and fibromyalgia.[5] This separation may be an artifact of medical specialization.[6] As such, a unifying framework for understanding IBS that could account for both the gastrointestinal as well as the extraintestinal symptoms of these patients would warrant serious consideration.

EVIDENCE ACQUISITION

Ovid MEDLINE was searched through May 2004 for articles using combinations of the terms bloating, gas, IBS, postinfectious IBS, small intestinal bacterial overgrowth (SIBO), microbial metabolism, bacteria, visceral hypersensitivity, immune response, autonomic dysfunction, central nervous system, intestinal motility, fibromyalgia, chronic fatigue syndrome, interstitial cystitis, lactulose and glucose breath test, and sickness behavior. Additional sources were identified by scanning through the bibliographies of articles and books. Publications reviewed ranged from randomized controlled trials to case control studies. Although randomized controlled trials were considered to be the strongest evidence, such studies were few, so the evidence was considered to be most compelling when there was consistency among the results of multiple different studies. Quality of data was assessed by publication in a peer-reviewed journal. A few critical recent abstracts were also considered.

EVIDENCE SYNTHESIS

Postprandial Bloating as a Unifying Symptom of IBS

Regardless of whether an IBS patient is troubled predominantly by constipa-

Context Irritable bowel syndrome (IBS), which affects 11% to 14% of the population, is a puzzling condition with multiple models of pathophysiology including altered motility, visceral hypersensitivity, abnormal brain-gut interaction, autonomic dysfunction, and immune activation. Although no nosological framework accounts for all the symptoms and observations in IBS, a unifying explanation may exist since 92% of these patients share the symptom of bloating regardless of their predominant complaint.

Evidence Acquisition Ovid MEDLINE was searched through May 2004 for relevant English-language articles beginning with those related to bloating, gas, and IBS. Bibliographies of pertinent articles and books were also scanned for additional substantive citations.

Evidence Synthesis The possibility that small intestinal bacterial overgrowth (SIBO) may explain bloating in IBS is supported by greater total hydrogen excretion after lactulose ingestion, a correlation between the pattern of bowel movement and the type of excreted gas, a prevalence of abnormal lactulose breath test in 84% of IBS patients, and a 75% improvement of IBS symptoms after eradication of SIBO. Altered gastrointestinal motility and sensation, changed activity of the central nervous system, and increased sympathetic drive and immune activation may be understood as consequences of the host response to SIBO.

Conclusions The gastrointestinal and immune effects of SIBO provide a possible unifying framework for understanding frequent observations in IBS, including postprandial bloating and distension, altered motility, visceral hypersensitivity, abnormal brain-gut interaction, autonomic dysfunction, and immune activation.

JAMA. 2004;292:852-858

Author Affiliation: Division of Gastrointestinal and Liver Diseases, Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles.

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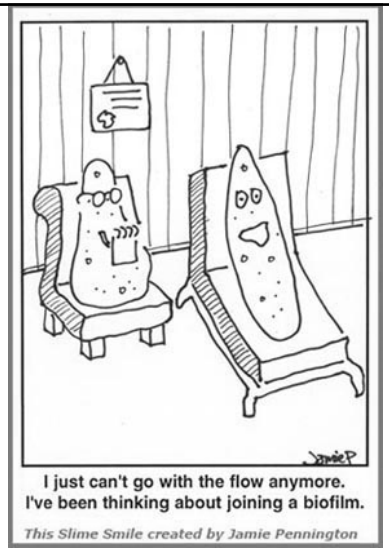
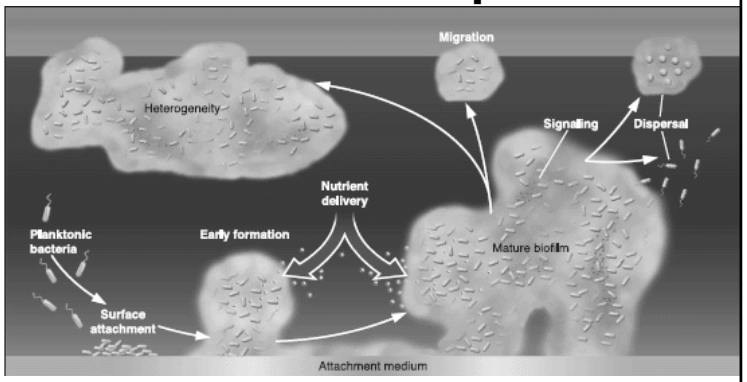
Corresponding Author: Henry C. Lin, MD, Division of Gastrointestinal and Liver Diseases, Department of Medicine, Keck School of Medicine, University of Southern California, 2011 Zonal Ave, HMR 707, Los Angeles, CA 90033 (henry.c.lin@usc.edu).

Section Editor: Michael S. Lauer, MD. Contributing Editor: We encourage authors to submit papers for consideration as a Clinical Review. Please contact Michael S. Lauer, MD, at lauerm@ccf.org.



Biofilms: Formation & Dispersion



Leid J. Microbe. Feb. 2009

The Effect of a Nonabsorbed Oral Antibiotic (Rifaximin) on the Symptoms of the Irritable Bowel Syndrome

A Randomized Trial

Mark Pimentel, MD; Sandy Park, BA; James Mirocha, MS; Sunanda V. Kane, MD; and Yuthana Kong, MPH

Background: Alterations in gut flora may be important in the pathophysiology of the irritable bowel syndrome (IBS).

Objective: To determine whether the nonabsorbed antibiotic rifaximin is more effective than placebo in reducing symptoms in adults with IBS.

Design: Double-blind, randomized, placebo-controlled study.

Setting: 2 tertiary care medical centers.

Participants: 87 patients who met Rome II criteria for IBS and were enrolled from December 2003 to March 2005.

Interventions: Participants who met enrollment criteria were randomly assigned to receive 400 mg of rifaximin 3 times daily for 10 days (n = 43) or placebo (n = 44). Eighty participants completed rifaximin therapy or placebo, and follow-up data were available for at least 34 participants per study group at any time point thereafter.

Measurements: A questionnaire was administered before treatment and 7 days after treatment. The primary outcome was global improvement in IBS. Patients were then asked to keep a weekly symptom diary for 10 weeks.

Results: Over the 10 weeks of follow-up, rifaximin resulted in greater improvement in IBS symptoms ($P = 0.035$). In addition, rifaximin recipients had a lower bloating score after treatment.

Limitations: The major limitations of the study were its modest sample size and short duration and that most patients were from 1 center.

Conclusions: Rifaximin improves IBS symptoms for up to 10 weeks after the discontinuation of therapy.

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Ann Intern Med. 2006;145:557-563.
For author affiliations, see end of text.
ClinicalTrials.gov Identifier: NCT00209950.

The irritable bowel syndrome (IBS) is one of the most common chronic medical conditions (1–6), yet its cause is unknown. Among other contributors, alterations in gut flora have been identified as potentially important. Results of recent studies indicate that up to 84% of patients with IBS have an abnormal lactulose breath test result, suggesting small-intestinal bacterial overgrowth (7, 8). On the basis of this concept, the antibiotic neomycin can statistically significantly improve the symptoms of IBS (7, 8). In addition, the effect of neomycin correlates with the elimination of bacterial overgrowth, as indicated by the normalization of the lactulose breath test result (7, 8).

Although neomycin seems to improve symptoms, it effectively eliminates bacterial overgrowth in only about 25% of patients with IBS (8). Furthermore, side effects limit the use of neomycin. Low efficacy also applies to other antibiotics (for example, doxycycline and amoxicillin–clavulanate) that have been previously investigated for treating bacterial overgrowth (9). An ideal antibiotic for IBS is, arguably, one with negligible systemic absorption, minimal side effects, and high efficacy for bacterial overgrowth.

Rifaximin is a gut-selective antibiotic with negligible systemic absorption (<0.4%) and broad-spectrum activity in vitro against gram-positive and gram-negative aerobes and anaerobes (10). On the basis of this broad spectrum, eradication rates with rifaximin in bacterial overgrowth are as high as 70% (11). Furthermore, rifaximin has a similar tolerability profile to that of placebo and has known activity against *Clostridium difficile* (12). These properties make it a good candidate for treating a condition that is as common as IBS.

Our study aimed to determine whether the nonabsorbed antibiotic rifaximin is more effective than placebo in reducing symptoms in adults with IBS.

Methods

Setting and Participants

Our study was conducted at the Cedars-Sinai Medical Center, Los Angeles, California, and the University of Chicago, Chicago, Illinois. We recruited patients with IBS through advertising in local media (radio and news publications). We did not recruit patients from the IBS clinics of the Cedars-Sinai Gastrointestinal Motility Program to avoid enrollment of tertiary care patients. The institutional review board of both centers approved the study, and all patients provided written informed consent.

Treatment for SBBO

- Flora in SBBO typically comprises both coliforms and strict anaerobes
- Non-absorbed antibiotics may minimize side effects:
  - 7-day course of rifaximin (400 mg TID) normalized breath H_2 in 70% of patients
  - TCN normalized breath H_2 in 27% of patients
- Probiotics to minimize side effects

Di Stefano M, et al. Aliment Pharmacol Ther. 2000;14(5):551-6.

Treatment for SBBO

- **Natural approach:**
  - **Broad-spectrum botanicals**
  - **Enteric-coated peppermint oil to reduce symptoms?**
  - ***Lactobacillus acidophilus* and *L. casei***
- **Address underlying causes! Stasis, slow transit time, low stomach acid (betaine HCl, stop PPIs), maldigestion, lactose intolerance**
- **Temporarily restrict carbohydrates, especially disaccharides such as lactose**

Common Parasites

A recent study revealed 23.5% of clinical samples tested positive for at least one parasite (3,223/13,857):

- ***Blastocystis hominis* (12.5%)**
- ***Dientamoeba fragilis* (3.8%)**
- ***Entamoeba* spp. (3.4%)**
- ***Endolimax nana* (2.2%)**
- ***Giardia lamblia* (0.7%)**

Am. J. Trop. Med. Hyg., 70(4), 2004, pp. 383–385

IRRITABLE BOWEL SYNDROME: IN SEARCH OF AN ETIOLOGY: ROLE OF *BLASTOCYSTIS HOMINIS*

JAVED YAKOOB, WASIM JAFRI, NADIM JAFRI, RUSTAM KHAN, MUHAMMAD ISLAM, M. ASIM BEG,* AND VIQAR ZAMAN*

Section of Gastroenterology, Departments of Medicine and Pathology, Aga Khan University Hospital, Karachi, Pakistan

Abstract. This study was designed to examine stool specimens of irritable bowel syndrome (IBS) patients for *Blastocystis hominis*, a common intestinal parasite. One hundred fifty patients were enrolled, 95 IBS cases and 55 controls. These patients provided a medical history, and underwent physical and laboratory evaluations that included stool microscopy and culture for *B. hominis* and colonoscopy. The 95 cases (51 males and 44 females) had a mean ± SD age of 37.8 ± 13.2 years. Stool microscopy was positive for *B. hominis* in 32% (30 of 95) of the cases and 7% (4 of 55) of the controls ($P = 0.001$). Stool culture was positive in 46% (44 of 95) of the cases and 7% (4 of 55) of the controls ($P < 0.001$). Stool culture for *B. hominis* in IBS was more sensitive than microscopy ($P < 0.001$). *Blastocystis hominis* was frequently demonstrated in the stool samples of IBS patients; however, its significance in IBS still needs to be investigated. Stool culture has a higher positive yield for *B. hominis* than stool microscopy.

- ***Blastocystis hominis*:**
  - **Four times more frequent in IBS patients**
  - **Symptoms resolve in 80% of IBS patients when *B. hominis* treated.**

Pharmaceutical Treatment for Parasites

"Medical Letter" lists pharmaceutical protocols (metronidazole and other "-azoles")

- **Metronidazole**
- **Tinidazole**
- **Nitazoxanide**
- **Lodoquinol**
- **Paromomycin**

Natural Treatment for Parasites

Herbal therapies:

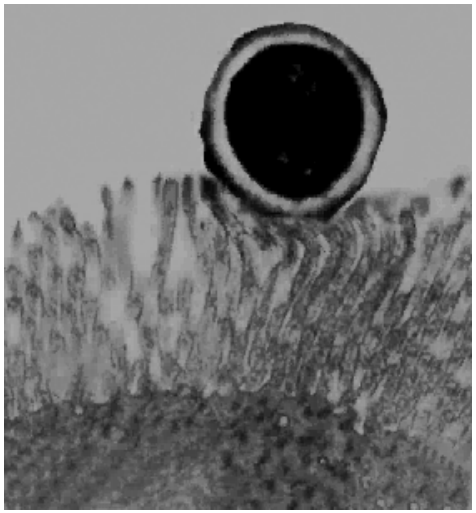
- ***Juglans nigra* (black walnut hulls)**
- ***Artemisia absinthium/annua* (wormwood)**
- ***Quassia amara* (bitterwood)**
- ***Allium sativum* (garlic)**
- ***Hydrastis canadensis* (goldenseal)**
- **Oil of oregano**
- **Olive leaf extract**

Natural Treatment for Parasites

Herbal therapies:

- **Oregano (*Origanum vulgare*) oil caps, 200 mg TID x 2 weeks**
- **Thyme (*Thymus vulgaris*), standardized to thymol, 100–200 mg TID**
- **Goldenseal (*Hydrastis canadensis*), standardized to contain berberine, 200–400 mg TID**
- **Artemisia/Chinese wormwood (*Artemisia annua*), 1–3 g TID**

"Of course, I'll need to run some tests. But offhand, I'd say it's some sort of fungal infection."



Dietary Treatment of *Candida albicans*

- Eliminate all sugar:
  - fruit juice
  - white flour
  - refined grains
- Eat a higher-protein, lower-carbohydrate, high-fiber diet
- Avoid fermented foods including alcohol

Botanical Medicines with Antifungal Activity

- *Allium* (garlic)
- *Astragalus*
- Barberry, Oregon Grape
- Citrus Seed Extract
- Grapefruit Seed Extract
- *Hydrastis* (Goldenseal)
- Olive Leaf
- *Tabebuia* (pau d'arco)
- Plant Tannins

Volatile Oils (enteric coated)

- Anise
- Oregano
- Rosemary
- Sage
- Thyme

Antifungal Treatment

- Prescription antifungal agents:
  - Nystatin, 500,000 IU, 1–2 tabs TID
  - Fluconazole, 100 mg qD–BID
  - Oral amphotericin – experimental
- Herbal agents:
  - Oregano (*Origanum vulgare*) oil caps, 200 mg, TID
  - Thyme (*Thymus vulgaris*), standardized to thymol, 100–200 mg TID
  - Garlic (*Allium sativum*), standardized to 5000 mcg allicin potential, TID
  - Goldenseal (*Hydrastis canadensis*), standardized to contain berberine, 200–400 mg TID

Treatment time: 4–12 weeks

Irritable Bowel Syndrome

- 44-year-old woman, IBS x 35 years
- Postinfection GE at 12 years old
- Severe postprandial bloating
- Constipation, diarrhea
- Uncontrollable "sh-t attacks"
- Exacerbated by dairy, refined carbohydrates, rich foods
- Hx frequent antibiotics
- Rectal itching and monilial vaginitis

Other History

- Premenstrual migraines, PMS, dysmenorrhea, and irregular cycles
- Fatigue, acne, and food cravings
- Weight 145 lbs, BMI 25

Laboratory Evaluation

- TSH 2.5, FT4 1.1, FT3 317
- TPO 74 and ATG 186 (elevated)
- Celiac panel negative
- 25-OH vitamin D 26 (nl 50–100)
- Ferritin 25
- IgG food antibody: dairy, eggs, wheat, yeast, chicken
- Nutritional testing: low Zn, n-3 FA
- Organic acids: indican and arabinitol elevated

Initial Assessment

- Digestive Imbalances
  - SBBO
  - Yeast overgrowth
  - IgG food sensitivities
  - Maldigestion
- Hormonal Imbalances
  - PMS, dysmenorrhea, migraines
  - Hashimoto's Thyroiditis
- Nutritional Imbalances
  - Zinc deficiency
  - Vitamin D deficiency
  - Omega-3 fatty acid deficiency

Treatment

- Correct Digestive Imbalances
  - IgG food elimination diet
  - Rifaximin, 400 mg bid x 7 d and fluconazole, 100 qd x 30 d
  - Anti-inflammatory rice protein shake
  - Prebiotics (fiber)
  - Digestive enzymes
  - Probiotics
- Support Nutrition
  - Omega-3 fatty acids
  - Multivitamin and Cal/Mg
  - Zinc citrate
  - Vitamin D3 5,000 U

Treatment

- Balance Hormones
  - Diet – crucifers, soy, flax
  - Magnesium, vitamin B6, taurine, evening primrose oil
  - Chinese herbal PMS formula
  - Armour® thyroid 30 mg (half grain)

Outcome

- Complete resolution of GI symptoms after 35 years, including bloating, constipation, diarrhea, and rectal itching (and vaginitis)
- Weight loss 20 lbs (size 12 to 6)
- PMS resolved
- No premenstrual migraines
- Chronic neck and back pain gone
- LDL from 121 to 101, HDL from 57 to 64; small LDL particles from 1081 to 749
- TSH 1.2, FT4 1.0, and FT3 317
- 25-OH vitamin D from 26 to 65

Key Functional Roles of the Gut:

Digestion/Absorption

Intestinal Permeability

Gut Microbiota/Dysbiosis

Inflammation/Immune

Nervous System

Learning Objectives

- Develop treatment protocols for dysbiosis that incorporate the '5R' approach to improve outcomes in patients with GI dysfunction
- Be able to appropriately prescribe foods, botanicals, nutraceuticals, and pharmaceuticals to improve outcomes in patients with GI dysbiosis

Dysbiosis is not so much about the microbe as it is about the effect of that microbe on a susceptible host; i.e., it is about the *relationship* between host and microbe.