

Functional Medicine: It all starts in the gut!

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Objectives

1. Describe the impact of altered gut microbiota and gut inflammation on GI disorders and overall health
2. Recognize environmental factors that influence gut microbiota
3. Describe Small Intestinal Bacterial/Fungal Overgrowth (SIBO/SIFO)
4. Select pharmaceutical and non-pharmaceutical supplements options to address healing the gut and re-establishing healthy gut flora
5. Compare and contrast dietary modifications for patients with GI disorders
6. Discuss integrative treatment options for prevalent GI disorders.

Basic Principles of Functional Medicine

Functional Medicine

Why doesn't our current model work?



7 Core Principles of FM

- ▶ Acknowledging the biochemical individuality of each human being, based on concepts of genetic and environmental uniqueness
- ▶ Incorporating a patient-centered rather than a disease-centered approach to treatment
- ▶ Seeking a dynamic balance among the internal and external factors in a patient's body, mind, and spirit
- ▶ Addressing the web-like interconnections of internal physiological factors
- ▶ Identifying health as a positive vitality—not merely the absence of disease—and emphasizing those factors that encourage a vigorous physiology
- ▶ Promoting organ reserve as a means of enhancing the health span, not just the life span, of each patient
- ▶ Functional Medicine is a science-using profession

Core Imbalances Produce Multiple Types of Clinical Dz

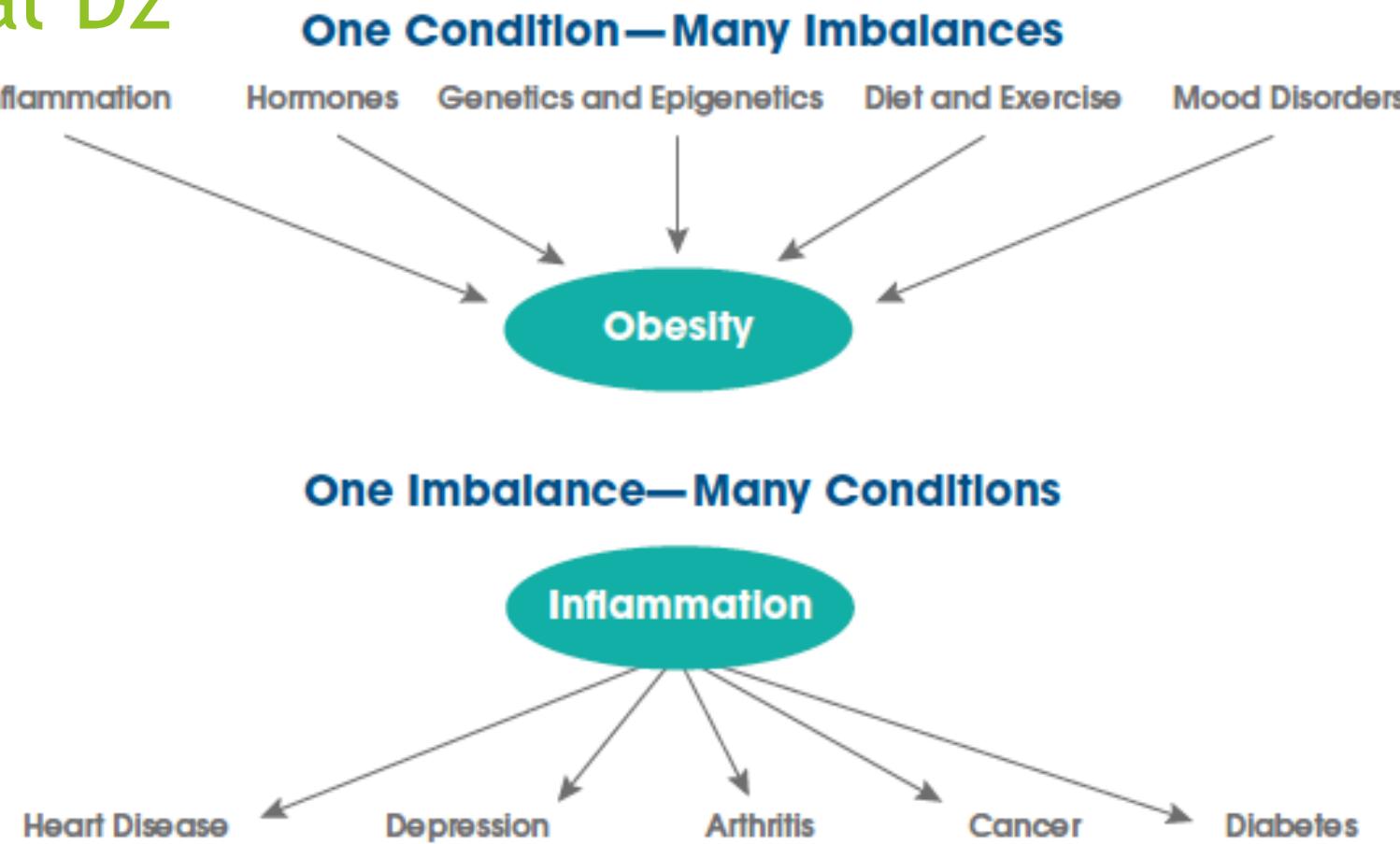
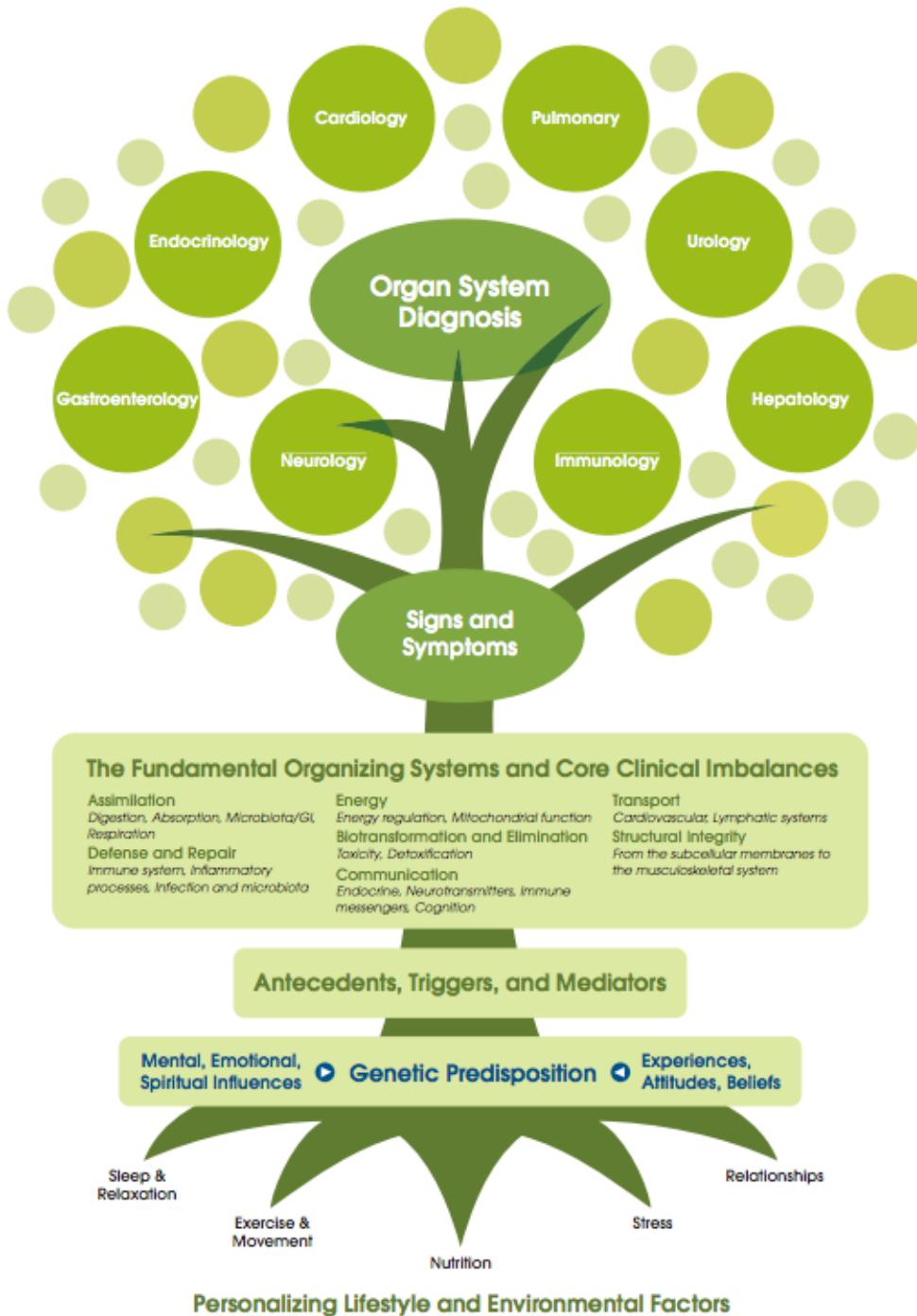


Figure 2. Core Clinical Imbalances—Multiple Influences

The practice of functional medicine involves 4 essential components...

1. Eliciting the patient's complete story during the Functional Medicine intake
2. Identifying and addressing the challenges of the patient's modifiable lifestyle factors and environmental exposures
3. Organizing the patient's clinical imbalances by underlying causes of disease in a **systems biology matrix framework** and using the timeline and GOTOIT system to develop a comprehensive assessment and plan
4. Establishing an **effective therapeutic partnership** between practitioner and patient

The FM Tree



FUNCTIONAL MEDICINE TIMELINE

Mediators/Perpetuators

Antecedents

Triggers or Triggering Events

Preconception

Prenatal

Birth

Current Concerns

Signs, Symptoms or Diseases Reported

Name: _____

Date: _____

CC: _____

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FUNCTIONAL MEDICINE MATRIX

Retelling the Patient's Story

Antecedents

(Predisposing Factors—
Genetic/Environmental)

Triggering Events (Activators)

Mediators/Perpetuators (Contributors)

Physiology and Function: Organizing the Patient's Clinical Imbalances

Assimilation

(e.g., Digestion,
Absorption, Microbiota/GI,
Respiration)

Structural Integrity

(e.g., from Subcellular
Membranes to
Musculoskeletal
Structure)

Communication

(e.g., Endocrine
Neurotransmitters, Immune
messengers)

Defense & Repair

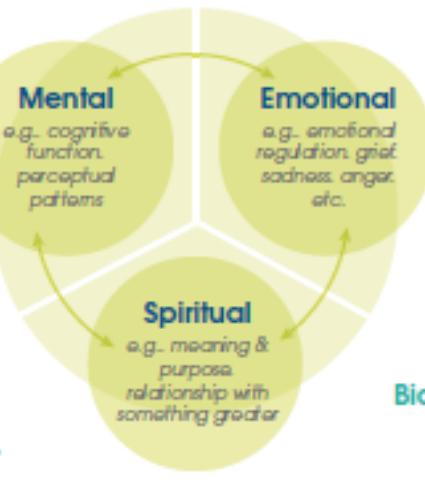
(e.g., Immune,
Inflammation,
Infection/Microbiota)

Energy

(e.g., Energy
Regulation,
Mitochondrial
Function)

Biotransformation & Elimination

(e.g., Toxicity,
Detoxification)



Modifiable Personal Lifestyle Factors

Sleep & Relaxation

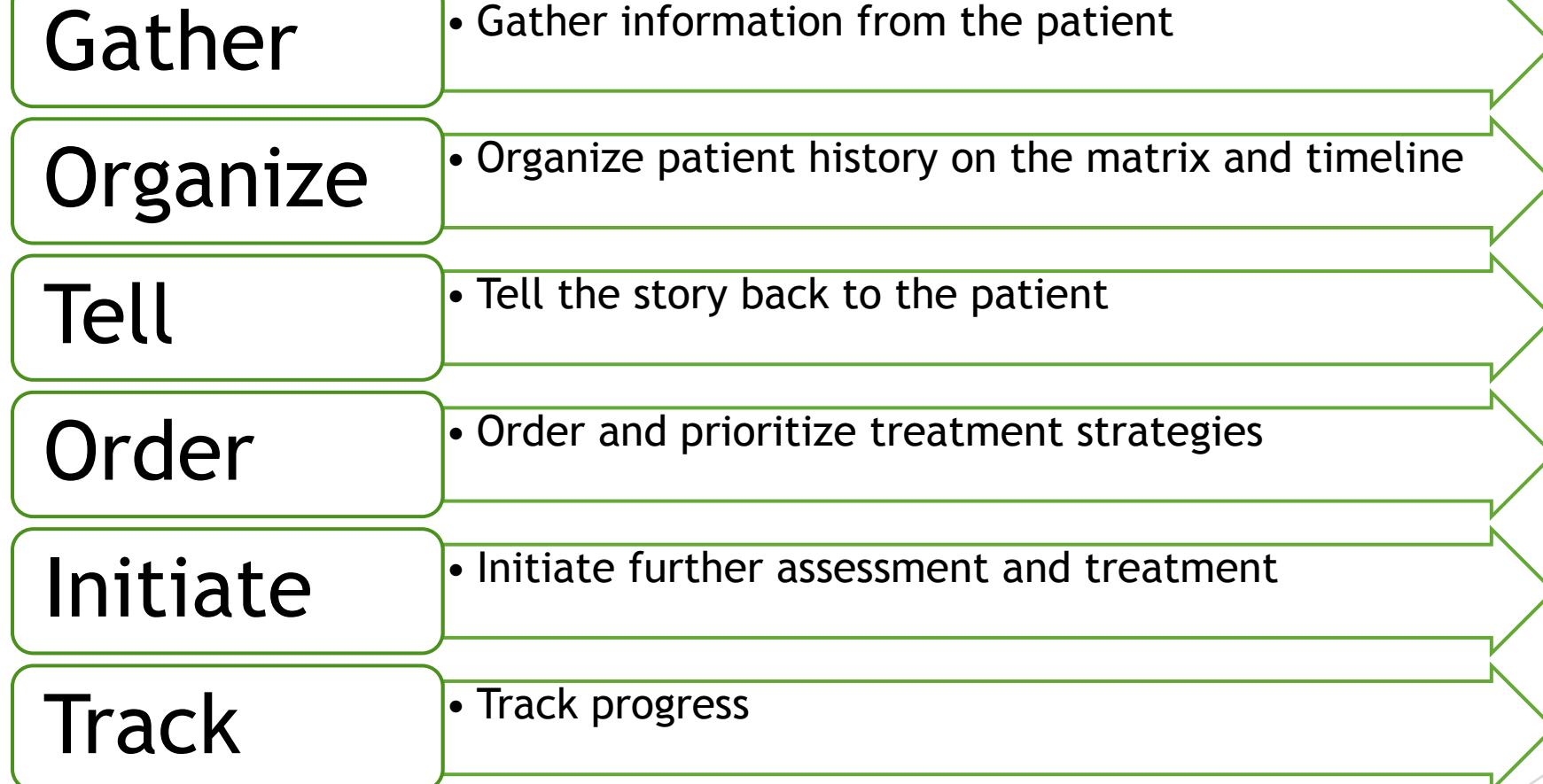
Exercise & Movement

Nutrition

Stress

Relationships

GO TO IT



Functional Medicine & the Gut!

"All Disease Begins In The Gut." -Hippocrates

Understanding the Root Cause

- ▶ GI system is complex
- ▶ Significant Interrelationships between
 - ▶ **D**igestion/Absorption
 - ▶ **I**ntestinal Permeability
 - ▶ **G**astrointestinal Flora
 - ▶ **I**mune Regulation & Inflammation
 - ▶ **N**ervous System

Basic Functions of the GI System

- ▶ Digestion
 - ▶ Enzymes (pancreas & Small intestine microvilli), HCL, bile salts, transport proteins
- ▶ Immune Function
 - ▶ Gut Associated Lymphoid Tissue (GALT)
 - ▶ B cells, T Cells, and phagocytes
 - ▶ As much as 70% of the total body reserves of lymphoid tissue
 - ▶ Developing oral tolerance is an important mechanism of immune regulation
 - ▶ Antigens that survive the digestive process are examined by the GALT tissue
 - ▶ Generally non-beneficial will be processed and inhibit the development of allergy by increasing IgA and cytokines at the mucosal and luminal level
 - ▶ Secretory IgA binds to and neutralizes microbes and other antigens before they cross the mucosal barrier
 - ▶ Chronic intestinal infection or inflammation can lead to more immunogenic responses to common antigens
- ▶ Phase I and Phase II start in intestinal mucosa
- ▶ Communication to endocrine and immune systems

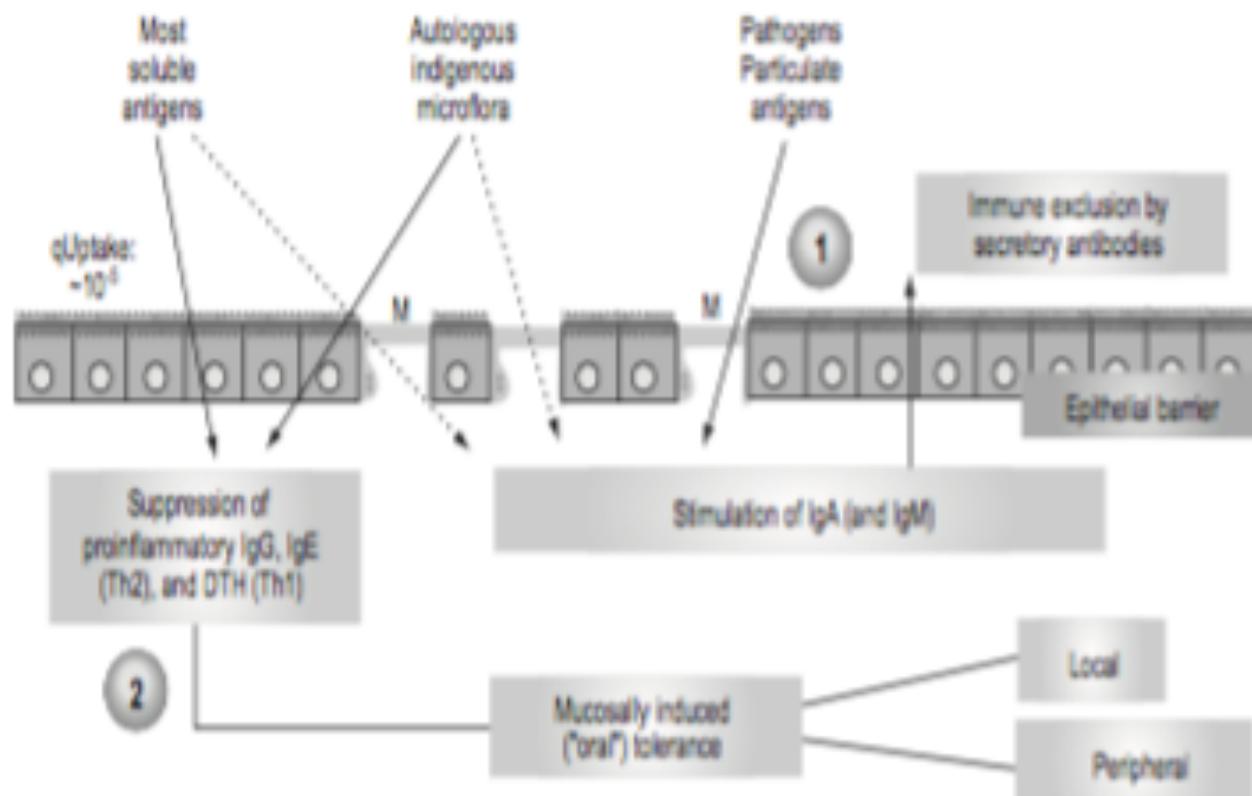


Figure 28.1 Developing oral tolerance

Source: Ann N Y Acad Sci. 2002 May;964:13-45. Figure 1. © 2002 New York Academy of Sciences, USA. Used with permission.

Role of Gastric Acid

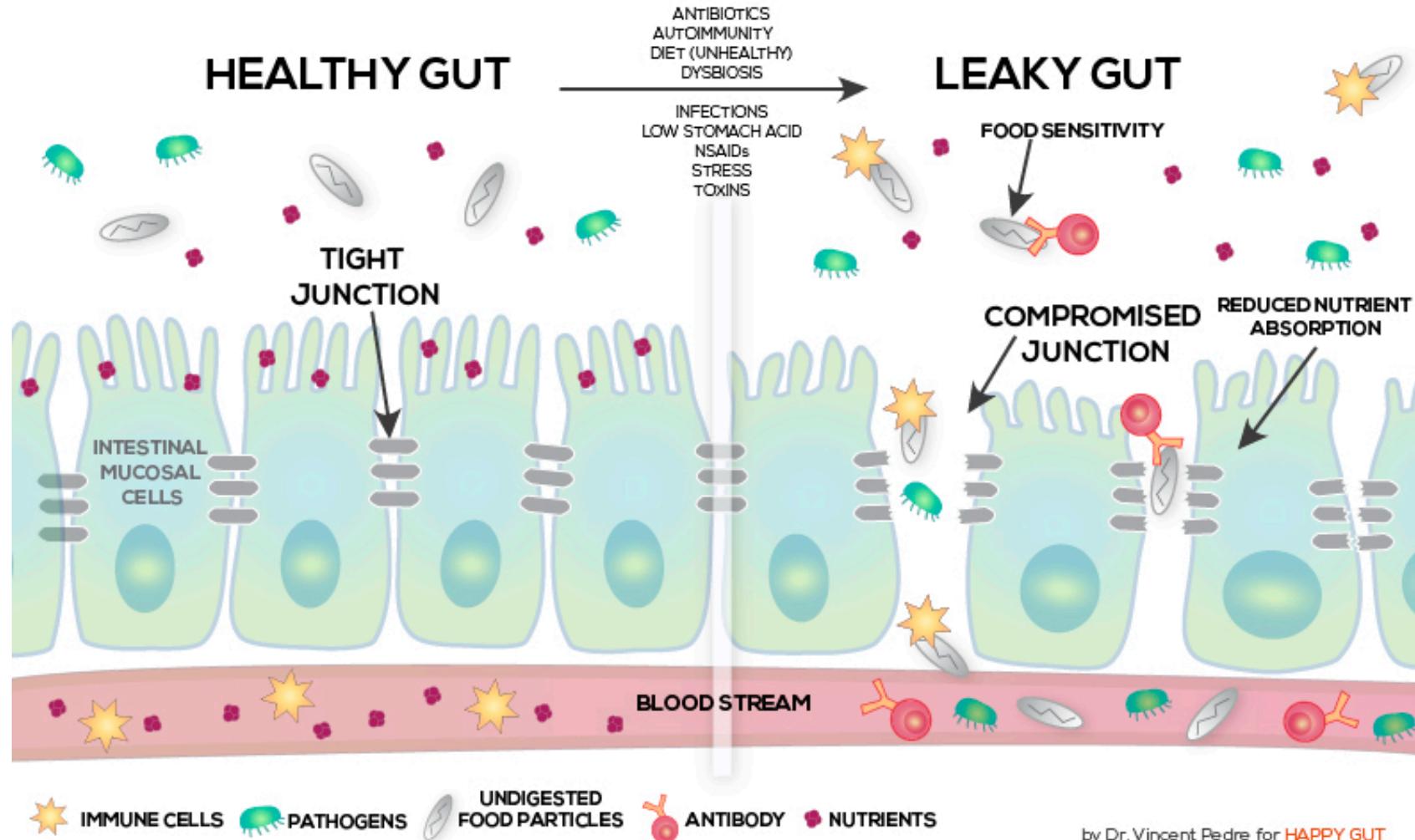
- ▶ Sterilizes the food bolus (kills unwanted microbes)
- ▶ Acid environment favors unfolding or denaturation of proteins
 - ▶ Starts the enzymatic action of proteins and prepares them for degradation

“Leaky Gut”

- ▶ Translocation
 - ▶ The process of a large molecule moving through a biologic barrier
 - ▶ May result in allergy, autoimmunity, or high levels of inflammation.
 - ▶ Can overwhelm the liver “detox” mechanisms

HEALTHY GUT VERSUS LEAKY GUT

A healthy gut works like a cheese cloth, allowing only nutrients through, but keeping larger food particles and pathogenic bacteria, yeast and parasites out. In a leaky gut, the tight junctions are loosened so undigested food particles and pathogens can get through and activate the immune system, causing inflammation and food sensitivities.



Food Allergy or Sensitivity

- ▶ Class Food Allergy
 - ▶ Classic IgE response
- ▶ Food Sensitivities
 - ▶ Delayed IgE (atopic dermatitis) or
 - ▶ Cell mediated (both delayed and chronic, ex celiac disease)
 - ▶ Some evidence for IgG mediated reactions.
- ▶ Persistent activation of the GALT
 - ▶ Destroys mucosal barriers
 - ▶ Leads to Th2 allergic response or Th1 auto-immune response
 - ▶ Triggers inflammation!

Underlying causes of Functional GI Conditions

- ▶ An overgrowth of bacteria in the small intestine
- ▶ An imbalance between “good” and “bad” microbes in the gut
- ▶ A permeable gut barrier (leaky gut)
- ▶ Chronic bacterial, parasitic, or fungal infections (such as *H. pylori*, *Blastocystis hominis*, *Candida albicans*)
- ▶ Low stomach acid or digestive enzyme production
- ▶ Sensitivity, allergy, or intolerance to certain foods
- ▶ Impaired communication between the gut and the brain

Environmental Factors

- ▶ Diet
 - ▶ High sugar, processed foods
- ▶ Frequent infections/antibiotic use
- ▶ Low Vitamin D
- ▶ Low rates of breastfeeding

Effects of Stress on Gut Physiology

- ▶ Altered motility
- ▶ Increased visceral perception
- ▶ Changes in gastrointestinal secretions
- ▶ Increased intestinal permeability
- ▶ Reduced regenerative capacity and mucosal blood flow
- ▶ Altered intestinal microbiota
- ▶ Catecholamines alter growth, motility and virulence of pathogenic and commensal bacteria



A Focus on Gut Microbiota

Gut Microbes in Pathogenesis is of IBD

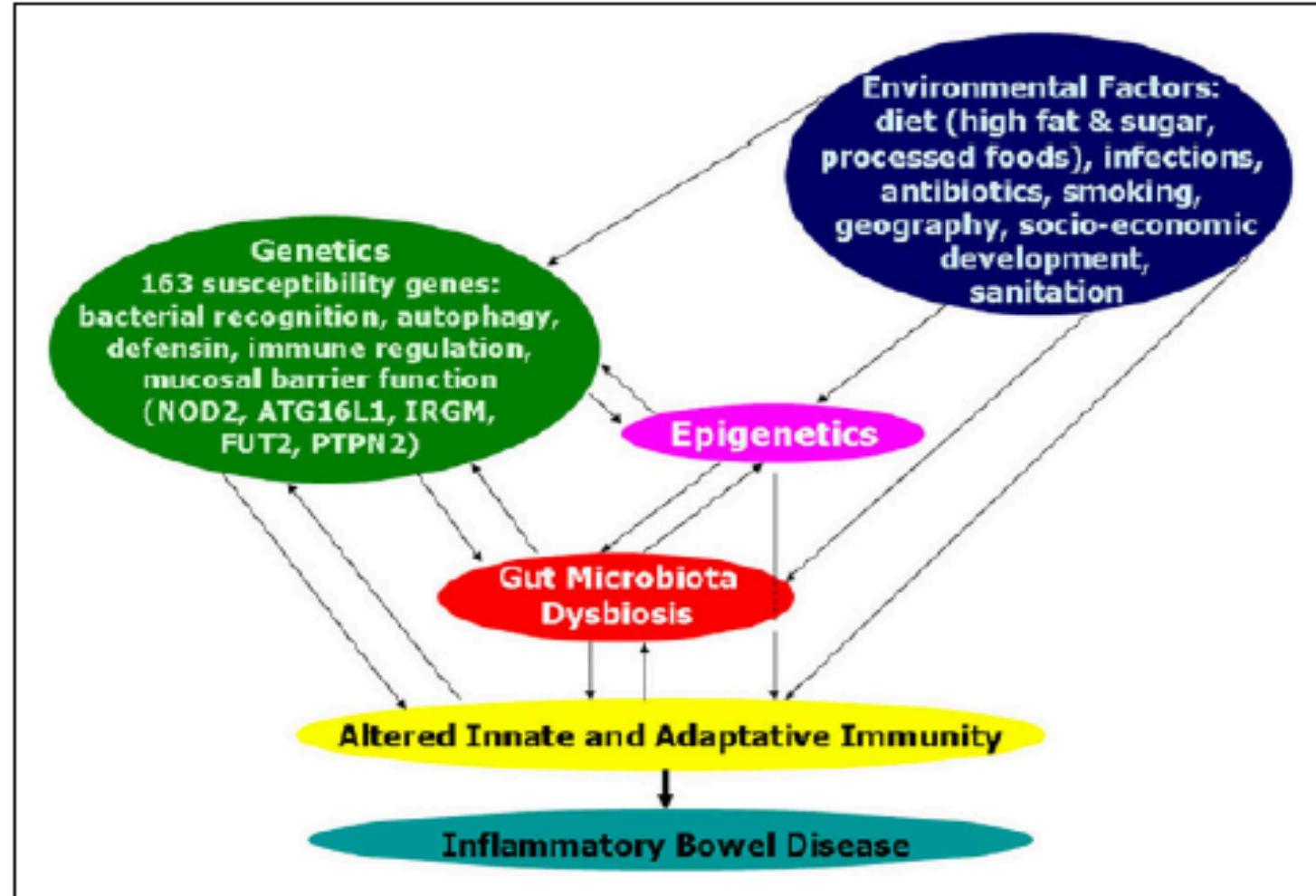
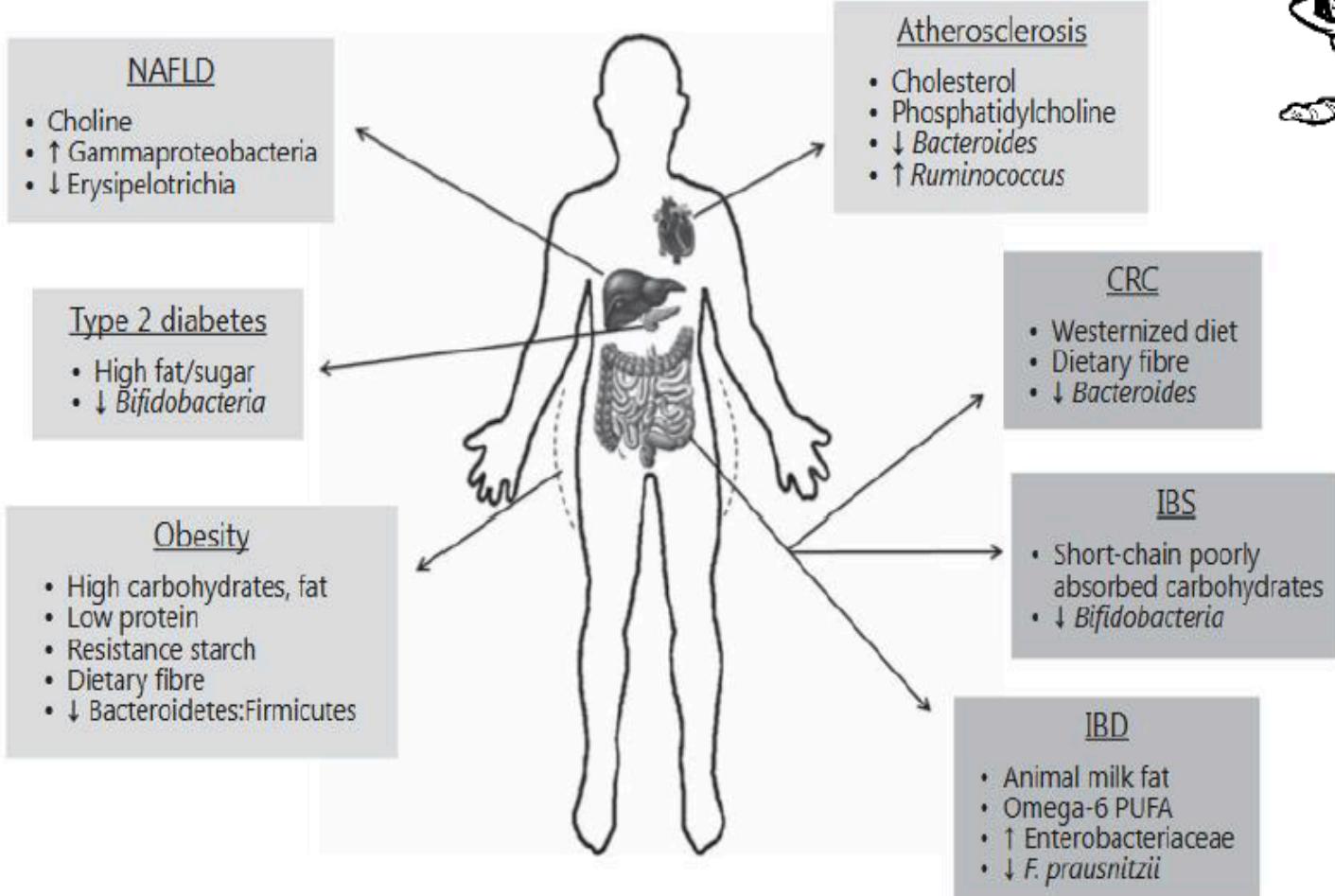


Figure 1. Complex interactions in the pathogenesis of inflammatory bowel disease.

Diet-induced dysbiosis and disease



Microbiota in Inflammatory Bowel Disease Pathogenesis and Therapy: Is It All About Diet?

Daniela Elena Serban, MD, PhD¹

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“...theory (“the bacterial penetration cycle”) proposes that CD may arise from a sequence of events involving changes in the microbiome and intestinal permeability, leading to bacterial adherence or penetration of the epithelium, as well as subsequent stimulation of the adaptive immune response, with consecutive tissue damage”

“Studies have shown an overall decrease in the biodiversity and stability of both mucosa-associated bacteria and fecal bacteria in patients with CD and UC vs HCs. In both CD and UC, the fecal microbiota (combination of shed mucosal bacteria and a separate nonadherent luminal population) differs from the mucosa-associated bacteria”

Diverse Microbiome is a good foundation!

- ▶ Reduced bacterial diversity of the infant's intestinal flora was associated with increased risk of allergic sensitization, allergic rhinitis, and peripheral blood eosinophilia, in the first 6 years of life. These results support the general hypothesis that an imbalance in the intestinal microbiome is influencing the development of lifestyle-related disorders, such as allergic disease.
 - ▶ Bisgaard Hans, et. al. (2011). Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. *J Allergy Clin Immunol*.

Dysbiosis

- ▶ Increases intestinal permeability (IP)!
- ▶ Increased IP has been associated with immune reactions from gram negative bacteria.
 - ▶ *endotoxin* and *lipopolysaccharide* (LPS) are used interchangeably and refer to the major cell wall component of Gram-negative bacteria
- ▶ Causes Inflammation
 - ▶ Linked to Depression

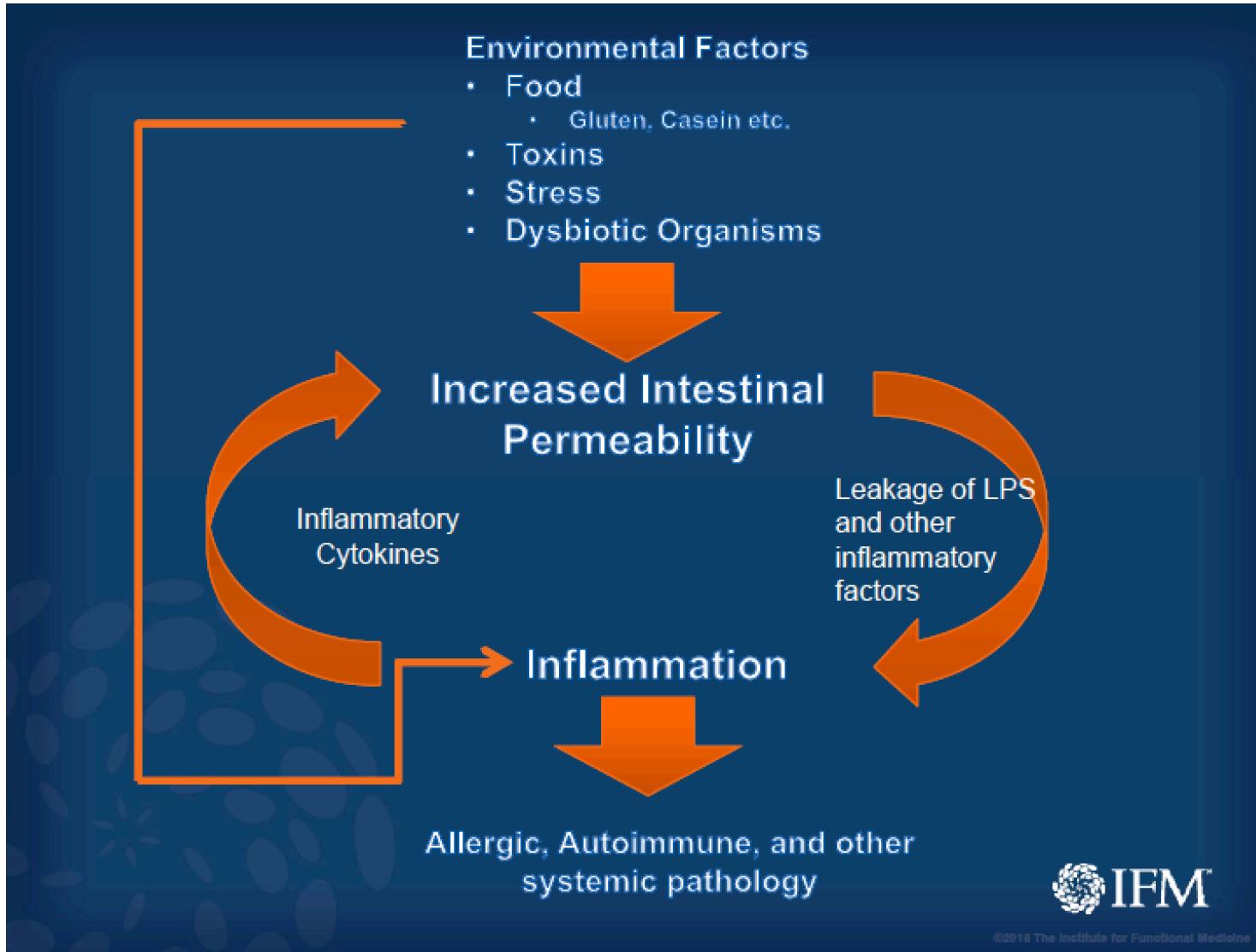
Dagci, H et al. *Acta Tropica*. doi:10.1016/S0001-706X(01)00191-7.

Maes M, et al. *Journal of Affective Disorders*. doi:10.1016/j.jad.2006.08.021.

Guo S, et al. *The American Journal of Pathology*. doi:10.1016/j.ajpath.2012.10.014.

Risk Factors for Dysbiosis and SIBO/SIFO

- ▶ **Depressed immune system**, such as HIV infection, cancer, diabetes mellitus, and use of anti-cancer chemotherapy, immunosuppressant drugs, steroids, or antibiotics
- ▶ **Tobacco use**
- ▶ **Anatomical abnormalities** such as small intestinal diverticulosis;
- ▶ **Postsurgical structural changes** such as ileocecal valve resection, gastric bypass, and Roux-en-Y
- ▶ **Medications that slow the gut motility** such as narcotics, anticholinergics, and anti-diarrheals
- ▶ **Hypo- or achlorhydria** due to surgery, autoimmune gastritis, or proton pump inhibitors
- ▶ **Small bowel dysmotility** irrespective of the cause (e.g., inflammatory bowel disease, celiac disease, radiation enteritis, small bowel adhesions, and systemic diseases associated with dysmotility such as scleroderma, diabetes, and amyloidosis)



Small Intestinal Bacterial Overgrowth

- ▶ Diagnosis is challenging
- ▶ When typical functions of the GI tract fail (Gastric Acid Secretion & Motility)
 - ▶ Small Intestine can become colonized with bacteria that aren't typically there
- ▶ Symptoms:
 - ▶ diarrhea (the most frequent, 13-89% across different studies)
 - ▶ abdominal pain
 - ▶ bloating
 - ▶ Flatulence/Steatorrhea
- ▶ Bacterial population in the small intestine exceeding 10^5 - 10^6 organisms/mL
 - ▶ Normally, less than 10^3 organisms/mL are found in the upper small intestine, majority of these are Gram-positive organisms.

Small Intestinal Bacterial Overgrowth.. The Problem...

- ▶ The bacteria interfere with our normal digestion and absorption of food and are associated with damage to the lining or membrane of the SI (leaky gut syndrome, which I prefer to call leaky SI in this case).
- ▶ They consume some of our food which over time leads to deficiencies in their favorite nutrients such as iron and B12, causing anemia.
- ▶ They consume food unable to be absorbed due to SI lining damage, which creates more bacterial overgrowth (a vicious cycle).
- ▶ After eating our food, they produce gas/ expel flatus, within our SI. The gas causes abdominal bloating, abdominal pain, constipation, diarrhea or both (the symptoms of IBS). Excess gas can also cause belching and flatulence.
- ▶ They decrease proper fat absorption by deconjugating bile leading to deficiencies of vitamins A & D and fatty stools.
- ▶ Through the damaged lining, larger food particles not able to be fully digested, enter into the body which the immune system reacts to. This causes food allergies/ sensitivities.
- ▶ Bacteria themselves can also enter the body/bloodstream. Immune system reaction to bacteria and their cell walls (endotoxin) causes chronic fatigue and body pain and burdens the liver.
- ▶ Finally, the bacteria excrete acids which in high amounts can cause neurological and cognitive symptoms.

SIBO Diagnostic Tests

- ▶ Duodenal fluid has been widely used and considered as the ‘gold standard’ for SIBO diagnosis, it is limited by low sensitivity and specificity as well as by technical heterogeneity, high costs and invasiveness
- ▶ Hydrogen or Methane Breath Tests
 - ▶ The excretion of these two gases in the expired air (samples taken at 15-minutes intervals) is quantified after the ingestion of a defined quantity of carbohydrates, and compared to basal values.

5 R Framework

- ▶ Remove
 - ▶ Pathogens?
 - ▶ Stress?
 - ▶ Food allergies?
- ▶ Replace
 - ▶ Digestive Enzymes/Bile
 - ▶ Fiber
- ▶ Reinoculate
 - ▶ Re-introduce desirable flora
- ▶ Repair
 - ▶ Nutritional Support for healing GI mucosa
- ▶ Rebalance
 - ▶ Stress relief/Mindfulness/Heart Rate Variability/Yoga
 - ▶ Psychotherapy

SIBO treatment

- ▶ Table 1 (Ponzianai et al.)
- ▶ Good Eradication Rates (50%)/Non-absorbable Antibiotic
 - ▶ Rifaxamin 1200-1600 mg daily.
 - ▶ Neomycin 500 mg BID X 10 days
- ▶ Systemic Antibiotics (Eradication 44-100%)
 - ▶ Ciprofloxacin
 - ▶ Metronidazole 750 mg daily (in divided doses, usually 250 mg TID)
 - ▶ Sometimes given in combination with Rifaxamin.

Rifaxamin Dosing

- ▶ 1600 mg per day x 10 days- 70-85% success normalizing LBT, 82% success normalizing GBT (Scarpellini)
- ▶ 1650 mg per day x 14 days (Pimentel)
 - ▶ 550 mg tid.
- ▶ 1200 mg per day x 14 days- 87-91% success normalizing GBT, 90-94% symptom improvement (Lombardo)
- ▶ 1200 mg per day x 10 days with 5 g per day Partially Hydrolyzed Guar Gum
 - ▶ 87% success normalizing GBT, 91% symptom improvement (Furnari)
- ▶ Rifaximin 1600 mg per day + Neomycin 1000 mg per day x 10 days, 87% success normalizing LBT (Low- this study used 1200 mg Rifaximin x 10 days but Dr Pimentel currently uses 1650 mg/day).

Scarpellini E, et al. Aliment Pharmacol Ther 2007; 25(7): 781-786

Pimentel M, et al. N Engl J Med. 2011 Jan 6;364(1):22-32.

Lombardo L, et al. Clin Gastroenterol Hepatol. 2010; 8 (6): 504-508.

Fumari M, et al. Aliment Pharmacol Ther. 2010 Oct;32(8):1000-6. Epub 2010 Aug 18.

Low K, et al. J Clin Gastroenterol. 2010 Sep;44(8):547-50.

Herbal Treatment

- ▶ Limited Evidence
 - ▶ Multi-center study (n=140) did find herbal therapy to be equivalent to Rifaxamin
 - ▶ Preparations used in next slide.
 - ▶ 2 herbal combination formulas together, at a dose of 2 caps 2 x day x 4 weeks, for each formula.
 - ▶ Biotics FC Cidal with Biotics Dysbiocide, or
 - ▶ Metagenics Candibactin-AR with Metagenics Candibactin-BR
- ▶ Dr. Pimental/Siebecker's team uses
- ▶ 1-3 of the following herbs x 4 weeks per course, at highest levels suggested on product labels.
 - ▶ Allicin from Garlic (the highest potency formula I know of is Allimed)
 - ▶ Oregano
 - ▶ Berberine- found in Goldenseal, Oregon Grape, Barberry, Coptis, Phellodendron
 - ▶ Neem
 - ▶ Cinnamon

Herbal Preparations for the Treatment of Small Intestine Bacterial Overgrowth

FC Cidal	Dysbiocide	Candidactin-AR	Candidactin-BR
Proprietary blend - 500 mg: 1 capsule	Proprietary Blend 950 mg per 2 capsules	One Capsule contains:	Two Capsules contain:
Tinospora cordifolia (stem)	Dill seed	Red Thyme oil (<i>thymus vulgaris</i> , providing 30%-50% thymol) 0.2 mL	Coptis root and rhizome extract (<i>coptis chinensis</i> , containing berberine) 30 mg
Equisetum arvense (stem)	Stemona Sessilifolia powder and extract	Oregano Oil (<i>origanum vulgare</i> , providing 55% to 75% carvacrol) 0.1 mL	Indian Barberry root extract (<i>berberis aristata</i> , containing berberine) 70 mg
Pau D'Arco (inner bark)	Artemisia Absinthium shoots and leaves extract,	Sage leaf 5.5:1 extract (<i>salvia officinalis</i>) 75 mg	Berberine Sulfate 400 mg • Proprietary 4:1 Extract 300 mg: Coptis root and rhizome (<i>coptis chinensis</i>)
Thymus vulgaris (aerial part)	Pulsatilla Chinensis rhizome powder and extract	Lemon Balm leaf 5:1 extract (<i>melissa officinalis</i>) 50 mg	Chinese Skullcap root (<i>scutellaria baicalensis</i>)
Artemisia dracunculus (leaf)	Brucea Javanica powder and extract		Philodendron bark (<i>phellodendron chinense</i>)
Sida cordifolia (aerial part)	Picrasma Excelsa bark extract		Ginger rhizome (<i>zingiber officinale</i>)
Olea europaea (leaf)	Acacia Catechu stem extract Hedyotis Diffusa powder and extract Yarrow leaf and flower extract (<i>achillea millefolium</i>).		Chinese Licorice root (<i>glycyrrhiza uralensis</i>) Chinese Rhubarb root and rhizome (<i>rheum officinale</i>) Chinese Rhubarb root and rhizome (<i>rheum officinale</i>).

Other SIBO Treatment Options

► Elemental Diet

- ▶ This approach seeks to starve the bacteria, but feed the person, by replacing meals for 2 weeks with an Elemental Formula. Elemental formulas are powdered nutrients in pre-digested, easily absorbed form.
 - ▶ The formula studied for SIBO is Vivonex Plus. It contains protein as amino acids, carbohydrate as maltodextrin, fat as various oils, and vitamins & minerals.
 - ▶ 80-84% success in eradicating of SIBO.

► Drawbacks

- ▶ Expensive
- ▶ High carbohydrate/sugar %
- ▶ Unpleasant taste
- ▶ No eating for duration of treatment (2-3 weeks)
- ▶ Weight loss (a dangerous drawback for those of low weight)

Prevent SIBO from reoccurring

- ▶ In 2006 Dr Pimentel shared his prevention protocol which includes a prokinetic drug (motility agent) and a lower carbohydrate diet. The combined use of these two (#'s 1 & 2 below) are of key importance for prevention.
- 1. The main strategies for prevention are:
- 2. Stimulate the migrating motor complex (MMC, the bacterial cleansing wave of the SI, with a prokinetic drug)
- 3. Follow a SIBO diet ongoing
- 4. Supplement with Hydrochloric Acid (HCl), the antibacterial acid of the stomach, if deficient
- 5. Remove proton pump inhibiting drugs (PPI's), and antacids, a cause of reduced HCl and risk factor for SIBO
- 6. Correct Ileocecal Valve Syndrome (IVC), the physical barrier to bacterial backflow from the large intestine (LI)
- 7. Correct neurological deficits and dysfunctions, including sympathetic dominance
- 8. Treat any concomitant diseases that contribute to SIBO

Low FODMAP

- ▶ FODMAP stands for fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, all of which are particular types of carbohydrate.
- ▶ **Excess fructose:** honey, apple, mango, pear, watermelon, high-fructose corn syrup, agave syrup, dried fruit, fruit juice
- ▶ **Fructans:** artichokes (globe), artichokes (Jerusalem), asparagus, beetroot, broccoli, Brussels sprouts, cabbage, eggplant, fennel, okra, chicory, dandelion leaves, garlic (in large amounts), leek, onion (brown, white, Spanish, onion powder), radicchio, lettuce, spring onion (white part), wheat, rye, pistachio, inulin, fructo-oligosaccharides.
- ▶ **Lactose:** milk, ice cream, custard, dairy desserts, condensed and evaporated milk, milk powder, yogurt, soft unripened cheeses (such as ricotta, cottage, cream, and mascarpone cheese).
- ▶ **Galactans:** legumes (such as baked beans, kidney beans, soybeans, lentils, chickpeas).
- ▶ **Polyols:** apple, apricot, avocado, blackberry, cherry, longan, lychee, nectarine, pear, plum, prune, mushroom, sorbitol, mannitol, xylitol, maltitol, and isomalt.

Specific Carbohydrate Diet

- ▶ Allowed: meat/fish/poultry, eggs, some beans, lactose-free dairy, non-starchy vegetables, ripe fruit, nuts/seeds, honey and saccharine.
- ▶ Not Allowed: grains, starchy vegetables, lactose, some beans and any sweeteners other than honey, saccharine and occasional stevia.
- ▶ An Introduction diet is recommended to start with.
- ▶ Then the diet is progressive as the intestines heal. At the beginning, cooked vegetables, cooked ripe fruit, no beans and very little nuts are recommended.
- ▶ Personal tailoring of the diet within the allowed foods is recommended as individuals vary greatly as to what they can tolerate.
- ▶ The SCD has a 75% to 84% success rate (for SIBO if followed strictly. Originally used for children with Celiac Disease (as defined before the discovery of gluten), it was found that they could return to eating an unrestricted diet after following the diet for 1 year after the disappearance of symptoms. Adults may need to stay on the diet to remain symptom free.

GAPS Diet

- ▶ (Gut and Psychology Syndrome)
- ▶ Gaps diet is the SCD with a few modifications:
- ▶ A few less beans, no baking soda or store bought juice.
- ▶ The dairy protein casein is begun more slowly - cultured vegetables are emphasized in place of yogurt.
- ▶ It incorporates the [nutritional guidelines of the Weston Price Foundation.](#)
- ▶ An Introduction diet is recommended to start with which is more clearly defined then the SCD Intro.

Healing Gut Protocols

Manage Stress!

- ▶ Mindfulness
- ▶ Hypnotherapy
- ▶ Acupuncture
- ▶ Yoga
- ▶ Biofeedback

Supplements

- ▶ To help break down food:
 - ▶ Digestive Enzymes
 - ▶ Betaine HCL/Pepsin

Supplements

- ▶ **To restore the gut barrier**
 - ▶ **L-glutamine:** glutamine is an important nutritional substance for healthy intestinal cells, particularly in the gut, and it's essential in maintaining proper intestinal barrier function.
 - ▶ 2-4 grams per day intestinal healing
 - ▶ 10-40 grams per day critically ill
 - ▶ **MSM and quercetin:** these anti-inflammatory substances can reduce chronic inflammation, which is a major cause of leaky gut.
 - ▶ **N-acetyl glucosamine:** N-acetyl glucosamine helps support proper health of the gut mucosa and reduces intestinal permeability.
 - ▶ **Mucin:** mucin is a particular kind of protein (glycoprotein) that is normally produced by the intestinal cells. It protects the intestinal lining and reduces inflammation.
 - ▶ **DGL, slippery elm, marshmallow, chamomile, and cat's claw:** these botanicals produce a soothing, gel-like substance that coats the digestive tract, which can help heal ulcers and inflamed tissue.

Supplements

- ▶ Anti-inflammatory
 - ▶ Omega-3's
 - ▶ 3 grams per day
 - ▶ Vitamin D
 - ▶ Boswellia: shows non-inferiority to medication (ASA/6MP) induction
 - ▶ Polyphenols: Phytochemicals that are derived from plants
 - ▶ Curcumin (turmeric)
 - ▶ Resveratrol (grapes, wine)
 - ▶ EGCG (Epigallocatechin gallate) (green tea)
 - ▶ Quercetin (apples, onions, leafy veggies, tea)

Probiotics

- ▶ Consume probiotic rich foods
 - ▶ Kefir
 - ▶ Raw Sauerkraut
 - ▶ Kimchi
- ▶ Probiotic Supplement Success
 - ▶ It must contain strains that are normally found in the human gut.
 - ▶ It must be able to survive the acidic environment of the stomach and capable of colonizing (i.e., establishing residence in) the G.I. tract.
 - ▶ It must be supplemented in concentrations higher than what is found in the gut.
- ▶ In clinical trials, probiotics appear to be useful for the treatment of various clinical conditions such as food allergy, atopic dermatitis, and allergic rhinitis.
- ▶ Some studies even show improvement in depression symptoms with probiotics

Bischoff SC, et al. (2014). *BMC Gastroenterology*, 14, 189.

Messaoudi, M. (2011). Beneficial psychological effects of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in healthy human volunteers. *Gut Microbes*, 2, 256-261.

Probiotic Supplements

- ▶ Soil-Based Organisms
 - ▶ Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria. (Product example Prescript Assist)
 - ▶ May be helpful/better tolerated for patients with SIBO since overgrowth can sometimes be from common bacteria such as lactobacillus species
- ▶ *Saccharomyces boulardii*
 - ▶ Good for preventing and treating diarrhea
 - ▶ Recurrent C-Diff (with other antibiotics)
 - ▶ IBD
- ▶ VSL #3 (3.6 trillion bacteria per day)
 - ▶ Good evidence in treatment of Ulcerative Colitis (Am J Gastroenterol. 2005 Jul;100(7):1539-46)
 - ▶ Remission achieved in 53% of patients.
 - ▶ Response in 24%

Prebiotics

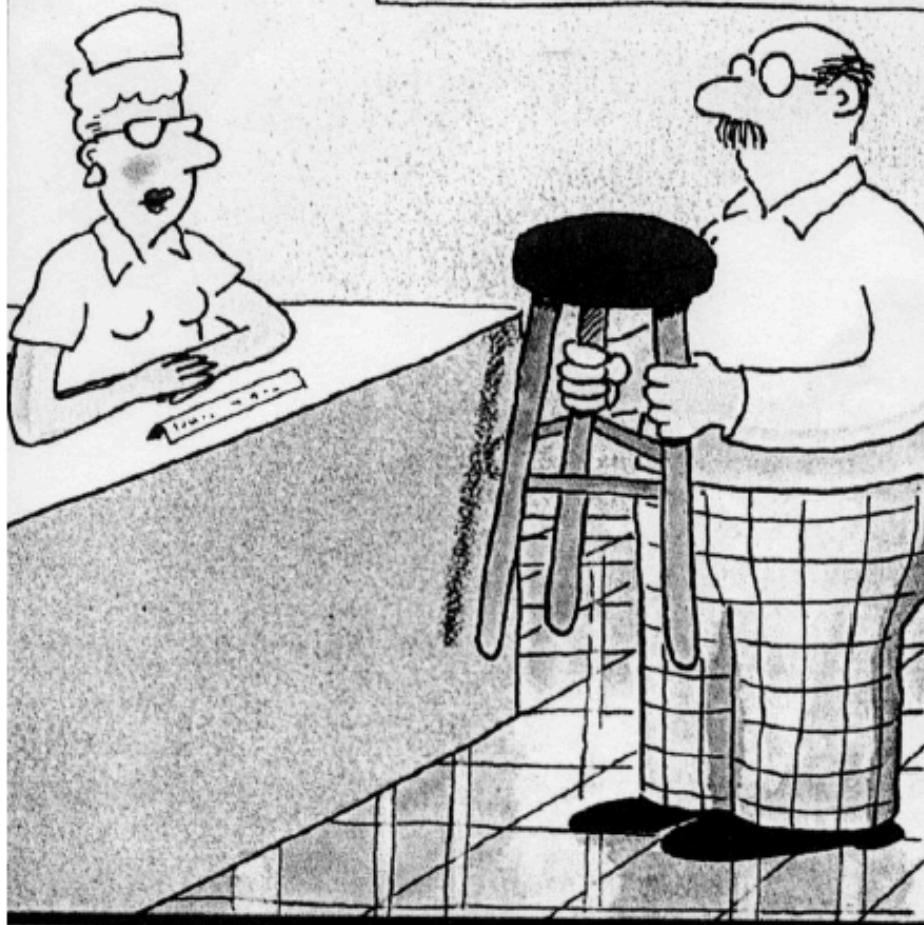
- ▶ Prebiotics are food ingredients that cannot be digested by humans but can be digested by the bacteria in our gut
- ▶ Prebiotics are FODMAPs
 - ▶ Start low and go slow!
- ▶ Example Formula Prebiogen:
 - ▶ synergistic blend of arabinogalactan, beta-glucan, inulin, and oligofructose

Fecal Transplants

- ▶ High efficacy in eradicating C. Diff
- ▶ Available evidence is limited and weak, it suggests that fecal microbiota transplantation has the potential to be an effective and safe treatment for IBD
 - ▶ Majority in review experienced
 - ▶ Reduction of Symptoms
 - ▶ Cessation of IBD meds
 - ▶ Disease remission
- ▶ Big focus of research!

MENDENHALL

LABORATOR TESTING

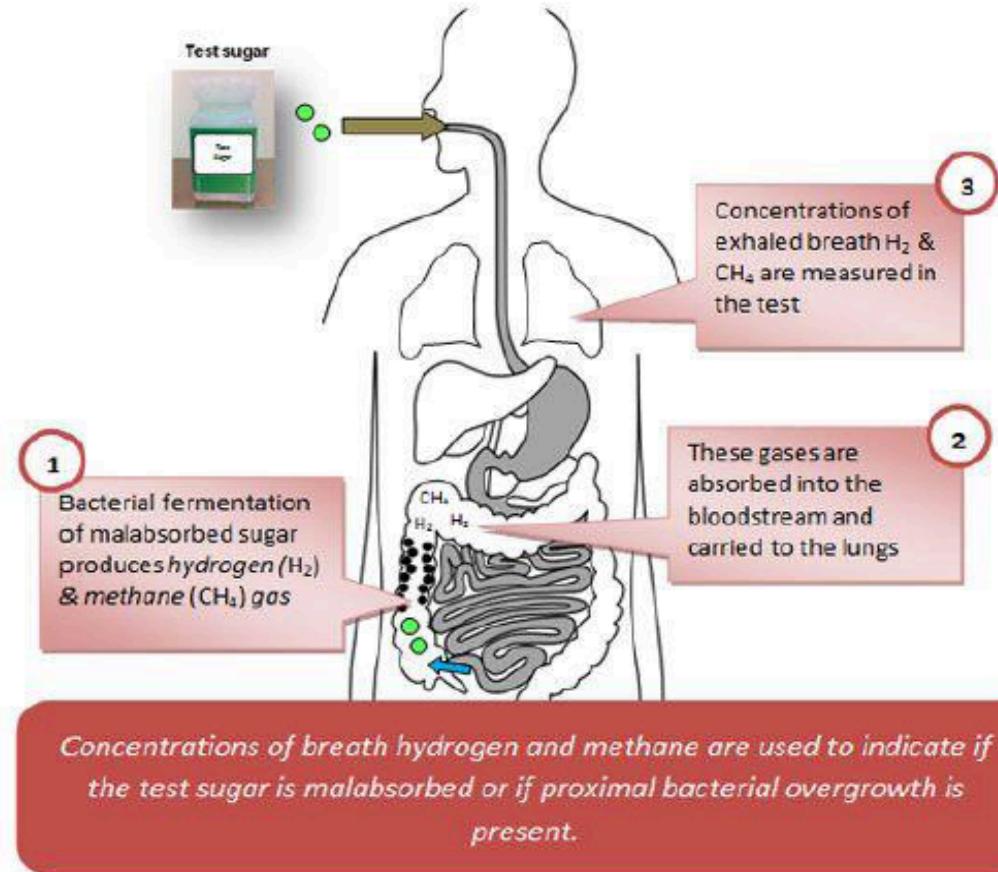


"That's not quite the stool sample we had in mind, Mr. O'Donnell."

Examples of Diagnostic Testing Options

- ▶ Genova
 - ▶ GI Effects
- ▶ Diagnostics Solutions Laboratory
- ▶ Doctor's Data
- ▶ Breath Testing
- ▶ Great Plains Laboratory
 - ▶ Organic Acids Test (OAT)

More on Breath Testing



Time for a Case: Meet Joan

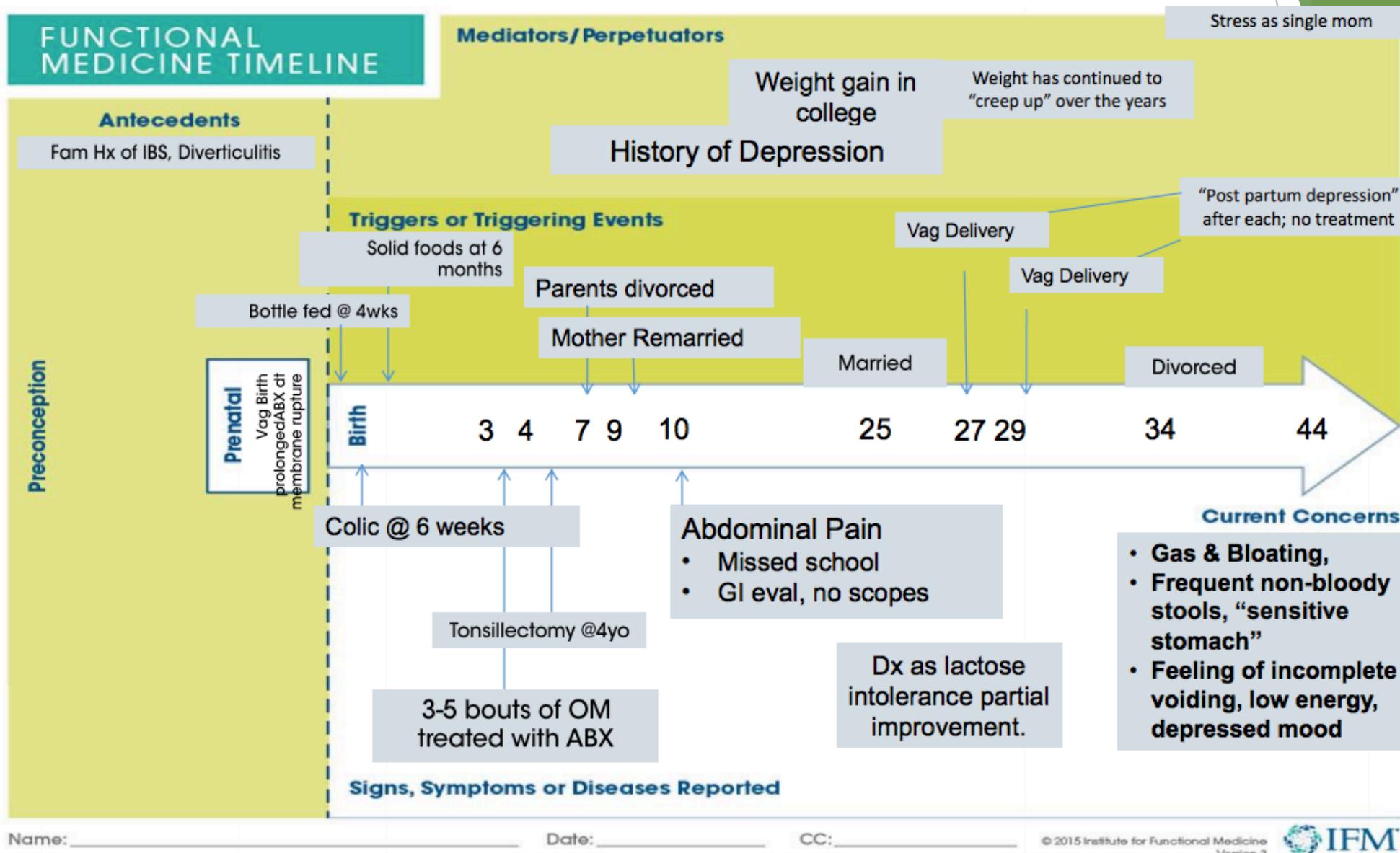
- ▶ Joan presents as a 44 year old woman in no acute distress. She complains of what she calls “IBS” or a “nervous stomach” that manifests mainly as Gas and Bloating with frequent non-bloody stools.
- ▶ There is a family history of IBS, as well as diverticulitis, though she cannot recall specifics. She also mentions she feels “blah”, has low energy, no stamina with low energy and a depressed/low mood.
- ▶ Her medical history includes chronic episodes of abdominal pain since 10 years old which caused her to miss school frequently. The diagnosis at the time was Lactose Intolerance and avoidance of dairy products yielded partial improvements. She does not recall any extensive diagnostic work up for this, denies any scopes.

Joan's Case

Laboratory:

- Primary Care
 - sCBC: WNL
 - Ferritin: 75 mg/dl
 - TSH: 2.1
 - 25 OH vitamin D: 47 ng/dl
- Gastroenterologist
 - Celiac Serology
 - IGA/Immunoglobulin A (IgA): normal
 - TTGA / Tissue Transglutaminase (tTG) IgA: negative
 - Gliadin (Deamidated) IgA: negative
 - Endomysial Antibody IgA: negative
 - SIBO breath testing: WNL

Case 1 Joann



Joan's Case

	DIGESTION / ABSORPTION		
	Within	Outside	Reference Range
Elastase	 	129	> 200 µg/mL
Fat Stain	Few	 	None - Mod
Muscle fibers	None	 	None - Rare
Vegetable fibers	Few	 	None - Few
Carbohydrates	Neg	 	Neg
	Within	Outside	Reference Range
% Acetate	67	 	36 - 74 %
% Propionate	22	 	9 - 32 %
% Butyrate	 	8.4	9 - 39 %
% Valerate	2.7	 	1 - 8 %
Butyrate	 	0.36	0.8 - 3.8 mg/mL
Total SCFA's	4.3	 	4 - 14 mg/mL
	Within	Outside	Reference Range
Lactoferrin	2.6	 	< 7.3 µg/mL
Calprotectin*	20	 	10 - 50 µg/g
Lysozyme*	271	 	<= 600 ng/mL
White Blood Cells	None	 	None - Rare
Mucus	Neg	 	Neg

GI Markers

	INFLAMMATION			
	Within	Outside	Reference Range	
Lactoferrin	< 0.5		< 7.3 µg/mL	Lactoferrin and Calprotectin are reliable markers for differentiating organic inflammation (IBD) from functional symptoms (IBS) and for management of IBD. Monitoring levels of fecal lactoferrin and calprotectin can play an essential role in determining the effectiveness of therapy, are good predictors of IBD remission, and can indicate a low risk of relapse. Lysozyme* is an enzyme secreted at the site of inflammation in the GI tract and elevated levels have been identified in IBD patients. White Blood Cells (WBC) and Mucus in the stool can occur with bacterial and parasitic infections, with mucosal irritation, and inflammatory bowel diseases such as Crohn's disease or ulcerative colitis.
Calprotectin*	< 10		≤ 50 µg/g	
Lysozyme*	267		≤ 600 ng/mL	
White Blood Cells	None		None - Rare	
Mucus	Neg		Neg	

	IMMUNOLOGY			
	Within	Outside	Reference Range	
Secretory IgA*		9.9	51 - 204 mg/dL	Secretory IgA* (sIgA) is secreted by mucosal tissue and represents the first line of defense of the GI mucosa and is central to the normal function of the GI tract as an immune barrier. Elevated levels of sIgA have been associated with an upregulated immune response.

Inflammation and Immunology

Calprotectin ↑



Eosinophil Protein X (EPX)↑



Fecal Calprotectin Testing

≤ 50 µg/g

No inflammation,
IBS likely

50 - 200 µg/g

Mild inflammation
present, consider re-
testing or other
gastrointestinal
diseases

≥ 200 µg/g

Inflammation is present
in the gastrointestinal
tract, further
investigative measures
are required

Joan's Case

BACTERIOLOGY CULTURE		
Expected/Beneficial flora	Commensal (Imbalanced) flora	Dysbiotic flora
3+ <i>Bacteroides fragilis</i> group	2+ Alpha hemolytic strep	
3+ <i>Bifidobacterium</i> spp.	4+ Gamma hemolytic strep	
4+ <i>Escherichia coli</i>	1+ <i>Klebsiella oxytoca</i>	
NG <i>Lactobacillus</i> spp.	1+ <i>Pseudomonas aeruginosa</i>	
NG <i>Enterococcus</i> spp.		
2+ <i>Clostridium</i> spp.		
NG = No Growth		

YEAST CULTURE	
Normal flora	Dysbiotic flora
1+ <i>Candida parapsilosis</i>	
1+ <i>Rhodotorula mucilaginosa</i>	

Joan's case

Comprehensive Stool Analysis / Parasitology x3

PARASITOLOGY/MICROSCOPY*			PARASITOLOGY INFORMATION
Sample 1 Mod Blastocystis hominis Rare Yeast			<p>Intestinal parasites are abnormal inhabitants of the gastrointestinal tract that have the potential to cause damage to their host. The presence of any parasite within the intestine generally confirms that the patient has acquired the organism through fecal-oral contamination. Damage to the host includes parasitic burden, migration, blockage and pressure. Immunologic inflammation, hypersensitivity reactions and cytotoxicity also play a large role in the morbidity of these diseases. The infective dose often relates to severity of the disease and repeat encounters can be additive.</p> <p>There are two main classes of intestinal parasites, they include protozoa and helminths. The protozoa typically have two stages; the trophozoite stage that is the metabolically active, invasive stage and the cyst stage, which is the vegetative inactive form resistant to unfavorable environmental conditions outside the human host. Helminths are large, multicellular organisms. Like protozoa, helminths can be either free-living or parasitic in nature. In their adult form, helminths cannot multiply in humans.</p> <p>In general, acute manifestations of parasitic infection may involve diarrhea with or without mucus and or blood, fever, nausea, or abdominal pain. However these symptoms do not always occur. Consequently, parasitic infections may not be diagnosed or eradicated. If left untreated, chronic parasitic infections can cause damage to the intestinal lining and can be an unsuspected cause of illness and fatigue. Chronic parasitic infections can also be associated with increased intestinal permeability, irritable bowel syndrome, irregular bowel movements, malabsorption, gastritis or indigestion, skin disorders, joint pain, allergic reactions, and decreased immune function.</p> <p>In some instances, parasites may enter the circulation and travel to various organs causing severe organ diseases such as liver abscesses and cysticercosis. In addition, some larval migration can cause pneumonia and in rare cases hyper infection syndrome with large numbers of larvae being produced and found in every tissue of the body.</p> <p>One negative parasitology x1 specimen does not rule out the possibility of parasitic disease, parasitology x3 is recommended. This exam is not designed to detect <i>Cryptosporidium</i> spp., <i>Cyclospora cayetanensis</i> or <i>Microsporidia</i> spp.</p>
Sample 2 Few Blastocystis hominis Rare Yeast			
Sample 3 Many Blastocystis hominis			

*A trichrome stain and concentrated iodine wet mount slide is read for each sample submitted.

GIARDIA/CRYPTOSPORIDIUM IMMUNOASSAY				
	Within	Outside	Reference Range	
Giardia intestinalis	Neg		Neg	<p>Giardia intestinalis (<i>lamblia</i>) is a protozoan that infects the small intestine and is passed in stool and spread by the fecal-oral route. Waterborne transmission is the major source of giardiasis.</p>
Cryptosporidium	Neg		Neg	<p>Cryptosporidium is a coccidian protozoa that can be spread from direct person-to-person contact or waterborne transmission.</p>

Blastocystis hominis

- ▶ Screening of a large population group for protozoa infections revealed that 515 were infected with the single protozoa *Blastocystis hominis*.
- ▶ However, only 239 (46%) were found to be symptomatic, suggesting differential pathogenicity.
 - ▶ 43 of these symptomatic patients were treated with metronidazole.
 - ▶ All patients became asymptomatic with negative stools on follow-up.
 - ▶ Treatment should be considered if patients are symptomatic
- ▶ Symptoms
 - ▶ IBS and/or cutaneous (urticaria, pruritus- perianal, intense palmoplantar itching)
 - ▶ Mast cell degranulation- ↑ histamine release
 - ▶ Short-term exacerbation with die off is not uncommon
- ▶ The increase in intestinal permeability in patients with *Blastocystis hominis* suggests that it can be a pathogenic protozoal infection and have systemic consequences.

Summary Of Joan's Stool Analysis Results

- ▶ Potentially impaired digestive function
 - ▶ Reduced Pancreatic Elastase
- ▶ Evidence of Dysbiosis based on
 - ▶ Presence of opportunistic organisms
 - ▶ Presence of *Blastocystis hominis*
 - ▶ Reduced diversity in her microbiome
 - ▶ Reduced N-butyric acid
- ▶ Possibility of increased Intestinal Permeability
 - ▶ Even though we do not have direct laboratory evidence for this, there is a pattern that makes us suspicious.

FUNCTIONAL MEDICINE MATRIX

Retelling the Patient's Story

Antecedents

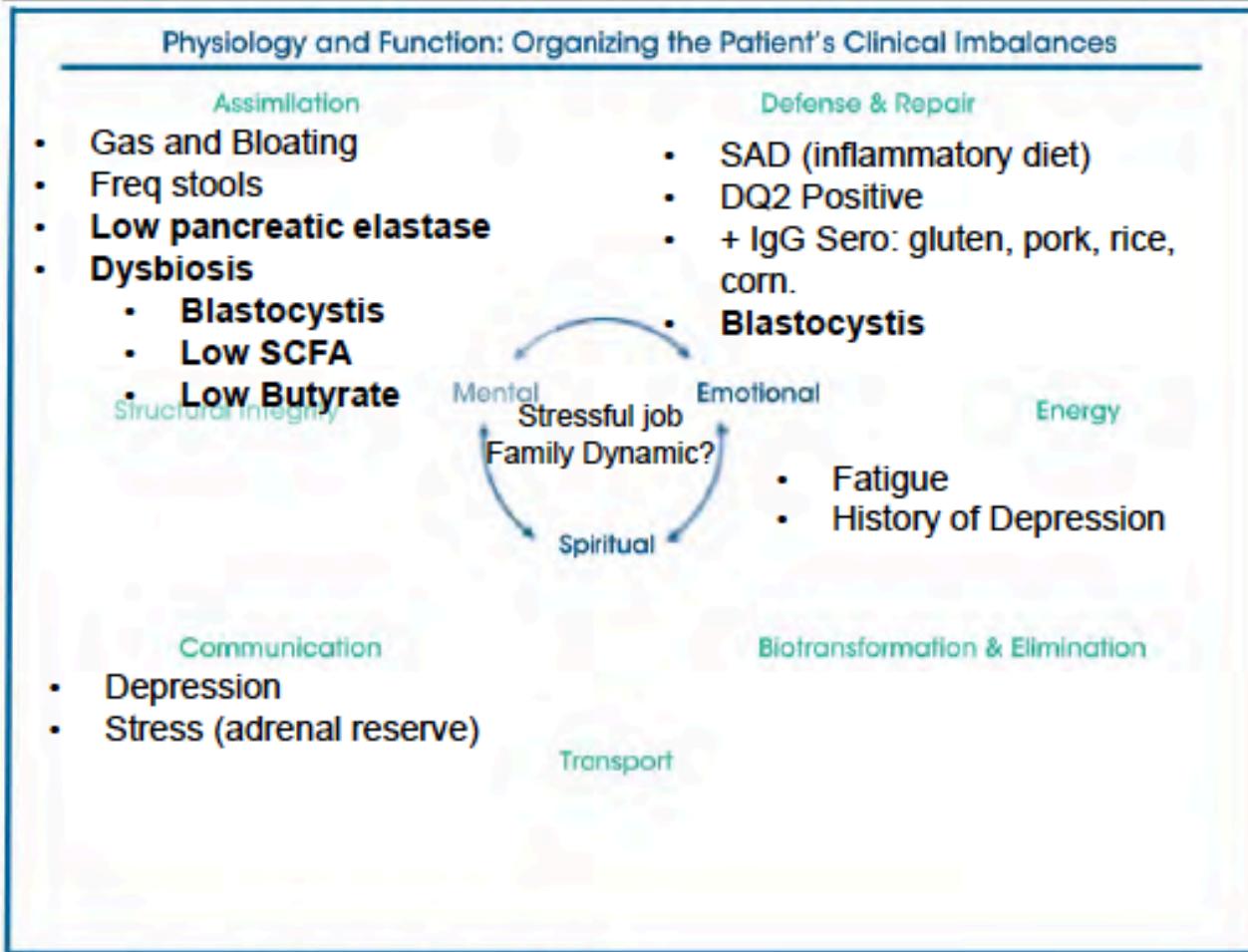
Mother SAD	Fm Hx IBS, Diverticulitis
Bottle @ 4 wk; Solid food @6mo	Hx OM Rx ABX
Tonsillectomy @ 4yo	

Triggering Events

Parents divorced @7	
Abdominal pain @10	
Lactose Intolerant	
Sensitive to tomato	
2 kids @27&29 wt post part dep.	
Divorced at 34yo (two teen boys)	

Mediators/Perpetuators

SAD	
Weight gain in college	



Modifiable Personal Lifestyle Factors

Sleep & Relaxation	Exercise & Movement	Nutrition	Stress	Relationships
Poor quality and quantity; has to be up to get the kids ready	NONE; "no time"	SAD; quick meals due to being busy Eats out often	Kids are a "handful" Job is stressful as bank exec asst.	Not dating and rarely has time to socialize

Name:

Date:

CC:

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Nervous System Effect On GI Function

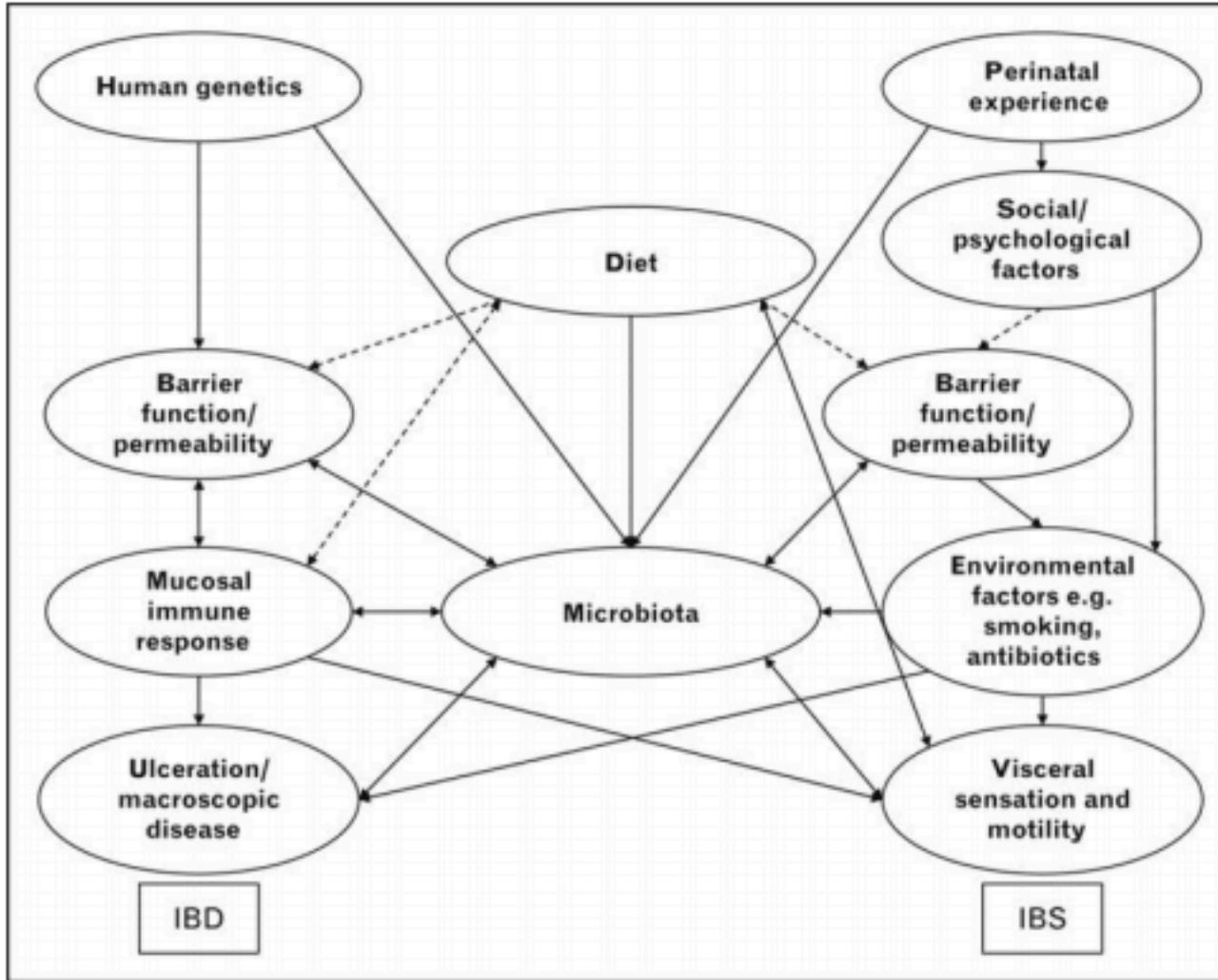
- ▶ Alterations in gastrointestinal motility
- ▶ Increase in visceral perception
- ▶ Changes in gastrointestinal secretion
- ▶ Increase in intestinal permeability
- ▶ Negative effects on regenerative capacity of gastrointestinal mucosa
- ▶ Negative effects on intestinal microbiota
- ▶ Portal of entry of pathogens into the CNS

Joan's treatment plan

- ▶ Oligoantigenic elimination diet
- ▶ Anti-parasitic protocol
 - ▶ Prescriptive medication: metronidazole
 - ▶ Botanical combination: Saccharomyces boulardii
- ▶ Pancreatic enzymes
- ▶ Probiotics/Prebiotics
- ▶ Repair medical food/individual nutrients
- ▶ Immune support for decreased SIgA
- ▶ Modify attitude and lifestyle to promote a healthier way of living

Other GI Disorders

IBS vs IBD

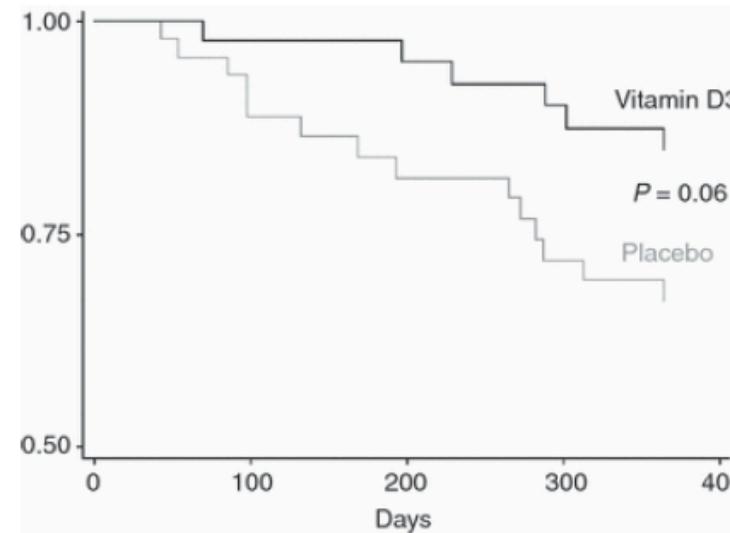


Major G, Spiller R. Irritable bowel syndrome, inflammatory bowel disease and the microbiome. *Current Opinion in Endocrinology, Diabetes, and Obesity*. 2014;21(1):15-21. doi:10.1097/MED.0000000000000032.

Source IFM

Clinical trial: vitamin D3 treatment in Crohn's disease: a randomized double-blind placebo-controlled study

**Percentage of patients
reaching primary
endpoint (clinical relapse)
in the vitamin D3 vs.
placebo group.**



108 patients with Crohn's disease in remission, of which fourteen were excluded later.
Patients were randomized to receive either 1200 IU vitamin D3 (n = 46) or placebo (n = 48) once daily during 12 months. The primary endpoint was clinical relapse.

IBD

Ulcerative Colitis and Probiotics



IBD

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DOI: 10.1111/apt.14203

WILEY AP&T Alimentary Pharmacology & Therapeutics

Systematic review with meta-analysis: the efficacy of probiotics in inflammatory bowel disease

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Summary

Background: Ulcerative colitis (UC) and Crohn's disease (CD) are inflammatory bowel diseases (IBD). Evidence implicates disturbances of the gastrointestinal microbiota in their pathogenesis.

Aim: To perform a systematic review and meta-analysis to examine the efficacy of probiotics in IBD.

“VSL#3 may be effective in inducing remission in active UC. Probiotics may be as effective as 5-ASAs in preventing relapse of quiescent UC. The efficacy of probiotics in CD remains uncertain, and more evidence from RCTs is required before their utility is known.”

may be as effective as 5-ASAs in preventing relapse of quiescent UC. The efficacy of probiotics in CD remains uncertain, and more evidence from RCTs is required before their utility is known.

GERD

PPI Risks

- ▶ Reduce acid secretion → reduce symptoms
- ▶ Impaired Nutrient Absorption
- ▶ Osteoporosis
- ▶ Kidney Disease
- ▶ Dementia and Functional Decline
- ▶ Pneumonia
- ▶ C. Difficile
- ▶ Heart Attack
- ▶ Stroke

Natural Treatments

- ▶ Relieve symptoms
- ▶ Decrease esophageal inflammation & promote esophageal healing
- ▶ Eliminate/minimize exacerbating factors
 - ▶ address dietary factors
 - ▶ address lifestyle factors
- ▶ Promote antioxidant defenses
- ▶ Improve salivary gland function/esophageal acid clearance
- ▶ Speed gastric emptying
- ▶ Prevent esophageal cancer
- ▶ Support the nervous system

Product	Directions	Rationale
Apple Cider Vinegar ²⁷	Take 1-2 teaspoons in a glass of water before meals. (drink with a straw to avoid erosion to teeth)	Some theories for how heartburn develops suggest that heartburn can happen as a result of not having enough stomach acid to properly digest food. Adding a small amount of the acidic apple cider vinegar may help reduce symptoms.
Probiotics ²⁷	Aim for at least 10 to 20 billion CFUs per day.	Heartburn symptoms could be due to an imbalance of GI bacteria. Probiotics can help restore the balance of GI flora and improve digestion. Various bacteria play different roles in digestion.
Digestive Enzymes ²⁸	Take 1 capsule with meals.	Poor digestion may make heartburn symptoms worse. Adding digestive enzymes can aid digestion and prevent symptoms.
DGL ²⁹⁻³¹	Take 1 capsule once daily with a meal.	Soothes gut lining, stimulates proper digestion.
GI Revive ²⁹⁻³⁵ (Contains DGL and other ingredients)	Take 7 capsules daily; These can be spaced out however the patient tolerates them. It may be beneficial to take them with meals.	GI Revive can help heal the gut if damage or “leaky gut” is suspected. The theory is that since most of the immune system lies in the gut, if there is damage and large inflammatory particles get through, patients will experience inflammation and GI symptoms.
DGL by OrthoMolecular ^{29-31, 36-40}	1-2 tablets per day	Soothes gut lining, stimulates proper digestion. Marshmallow root has a long history of providing a soothing property to mucous membranes. Slippery elm bark also helps protect the GI tract and promotes a healthy cycle of inflammation. Aloe Vera has studies that show it helps balance gastric acid secretion and at low doses protects the membranes from excess acid.
Heartburn Essentials ^{29-31, 36-37}	1 capsule with each meal	Has DGL, marshmallow root, slippery elm, artichoke, and turmeric plus digestive enzymes.

Additional References

- ▶ Kresser C. Clinican's Guide to Digestive Disorders. Available from:
<https://kresserinstitute.com> (posted to Moodle)
- ▶ Francesca Romana Ponziani, Viviana Gerardi & Antonio Gasbarrini(2016) Diagnosis and treatment of small intestinal bacterial overgrowth, Expert Review of Gastroenterology & Hepatology, 10:2, 215-227, DOI: 10.1586/17474124.2016.1110017
- ▶ Siboinfo.com
- ▶ <https://www.youtube.com/watch?v=Mp6y2UwWyPg>
- ▶ <https://www.functionalmedicine.org>

How Can I Learn More?

- ▶ Kresser Institute: Some Free Content
 - ▶ <https://kresserinstitute.com>
 - ▶ Chris Kresser's Podcast <https://itunes.apple.com/us/podcast/revolution-health-radio/id372257397?mt=2>
- ▶ Designs for Health Podcast
 - ▶ <https://itunes.apple.com/us/podcast/designs-for-health-educational-podcasts/id1003341898?mt=2>
- ▶ Integrative Practitioner
 - ▶ <https://www.integrativepractitioner.com/resources/webinars/>
- ▶ Emerson Ecologics
 - ▶ <https://www.emersonecologics.com/Webinars-DrKalish>
- ▶ <http://www.pointinstitute.org>
- ▶ Conferences
 - ▶ A4M, IFM, Supplement Company Sponsored
- ▶ Pharmacists: Izabella Wentz PharmD, Suzy Cohen RPh, Jim LaValle RPh CCN, Grace Liu PharmD, Anh Nguyen, PharmD BCACP

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