THE INSTITUTE FOR FUNCTIONAL MEDICINE®

Treatment of GI Dysfunction in the Context of the Functional Medicine Matrix

TOM SULT, MD

Applying Functional Medicine in Clinical Practice

Disclosure

Tom Sult, MD disclosed he is a consultant for Mend After and is on the Scientific Advisory Board of Nutrition Dynamics.

Evidence Icons: Key

Clinical Disclaimers:

Association, not causation

Lab test
(Labs not generally accepted in conventional care)

Clinical experience
(Intervention warranted by historical clinical experience of educator and/or functional medicine community of practitioners in the context of evidentiary paucity)

Clinical judgment
(Intervention warranted by clinical judgment of educator and/or functional medicine community of practitioners in the context of evidentiary paucity)

Conflict of interest

Study Types:

Animal study

In vitro study

n of 1, or single-case study

In silico *(Computerized molecular modeling)*

Performance Objectives

Following this activity, successful participants will be able to…

1. Review and clarify the Functional Medicine Timeline, Matrix, and the concepts of Antecedents, Triggers, and Mediators.
2. Discuss the importance of understanding the patient's individual story.
3. Identify key "leverage points" to utilize therapeutically with individual patients.

Performance Objectives

Following this activity, successful participants will be able to…

4. Define the components of the 5R framework (Remove, Replace, Re-inoculate, Repair, Rebalance).
5. Select and interpret functional GI laboratory evaluation to help guide personalized implementations of the 5R approach in patient with gastrointestinal dysfunction.
6. Develop individual treatment protocols for patients with gastrointestinal dysfunction, using a framework of remove, replace, reinoculate, repair, rebalance.
7. Recognize how laboratory evaluation can help guide the implementation of the 5R approach.

Review

- The GI system is an integral and central "node" of the complex web of functional medicine.
- Dysregulation of the GI system can have a profound impact on health.

We Have Reviewed the Key Functional Roles of the Gut and How To Evaluate Them:

Digestion / Absorption

Intestinal Permeability

Gut microbiota / Dysbiosis

Immune Modulation/Inflammation

Nervous System (Enteric Division)

The Case of Joan

- Recall the case as first presented by Dr. Hughes
- Recall the case as expanded by Dr. Hanaway
- Recall the case Timeline
- Recall the case Matrix

Gather Oneself & Information

Organize on the Matrix, Time Line

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Gather Oneself & Information

Organize on the Matrix, Time Line…

Tell the Patient's Story

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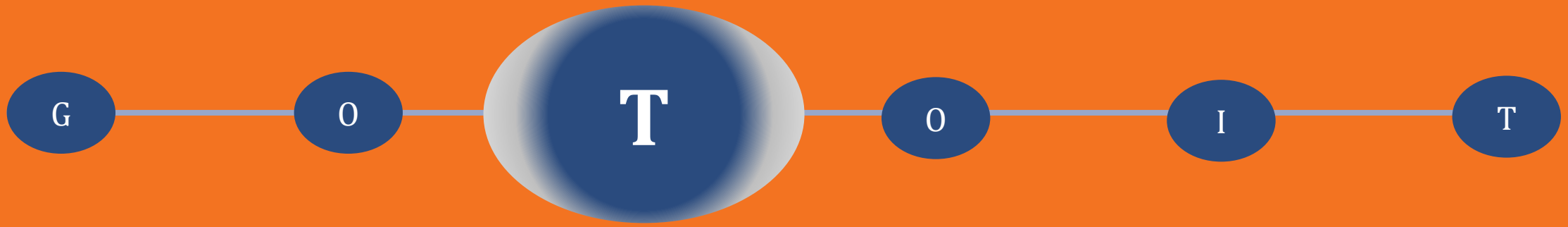


Tell

the story back to the patient in your own words to ensure accuracy and understanding.

The re-telling of the patient's story is a *dialogue* about the case highlights including the antecedents, triggers, and mediators identified in the history, correlating them to the timeline and matrix. The patient is asked to join in correcting and amplifying the story, engendering a context of true partnership.

Quilligan S, Silverman J. The skill of summary in clinician-patient communication: a case study. Patient Educ Couns. 2012 Mar;86(3):354-9. doi: 10.1016/j.pec.2011.07.009.
Finefrock D, et al. Patient-Centered Communication Behaviors That Correlate With Higher Patient Satisfaction Scores. J Patient Exp. 2018 Sep;5(3):231-235. doi: 10.1177/2374373517750414.

Mastering The Story:
The Science and Art Of Healing

- Think deeply about the context of the story.
- Think deeply about the physiology behind the story.
- Be patient: allow the story to unfold.
- Be the audience: don't interrupt; only at appropriate points ask thoughtful probing questions.
- Help them amplify their story.

Muneeb A, Jawaid H, Khalid N, Mian A. The Art of Healing through Narrative Medicine in Clinical Practice: A Reflection. Perm J. 2017;21:17–013. doi:10.7812/TPP/17-013
Zaharias G. What is narrative-based medicine? Narrative-based medicine 1. *Can Fam Physician*. 2018;64(3):176–180.

Mastering The Story:
The Science and Art Of Healing

- Be inclusive vs. exclusive in the history
- Look for patterns that connect
- Retell the story: re-create meaning
- Connect, educate, inspire, motivate
- Assess the readiness to change
- Activate nature – the greatest pharmacy

What Is Joan's Story – How Would You Tell It?

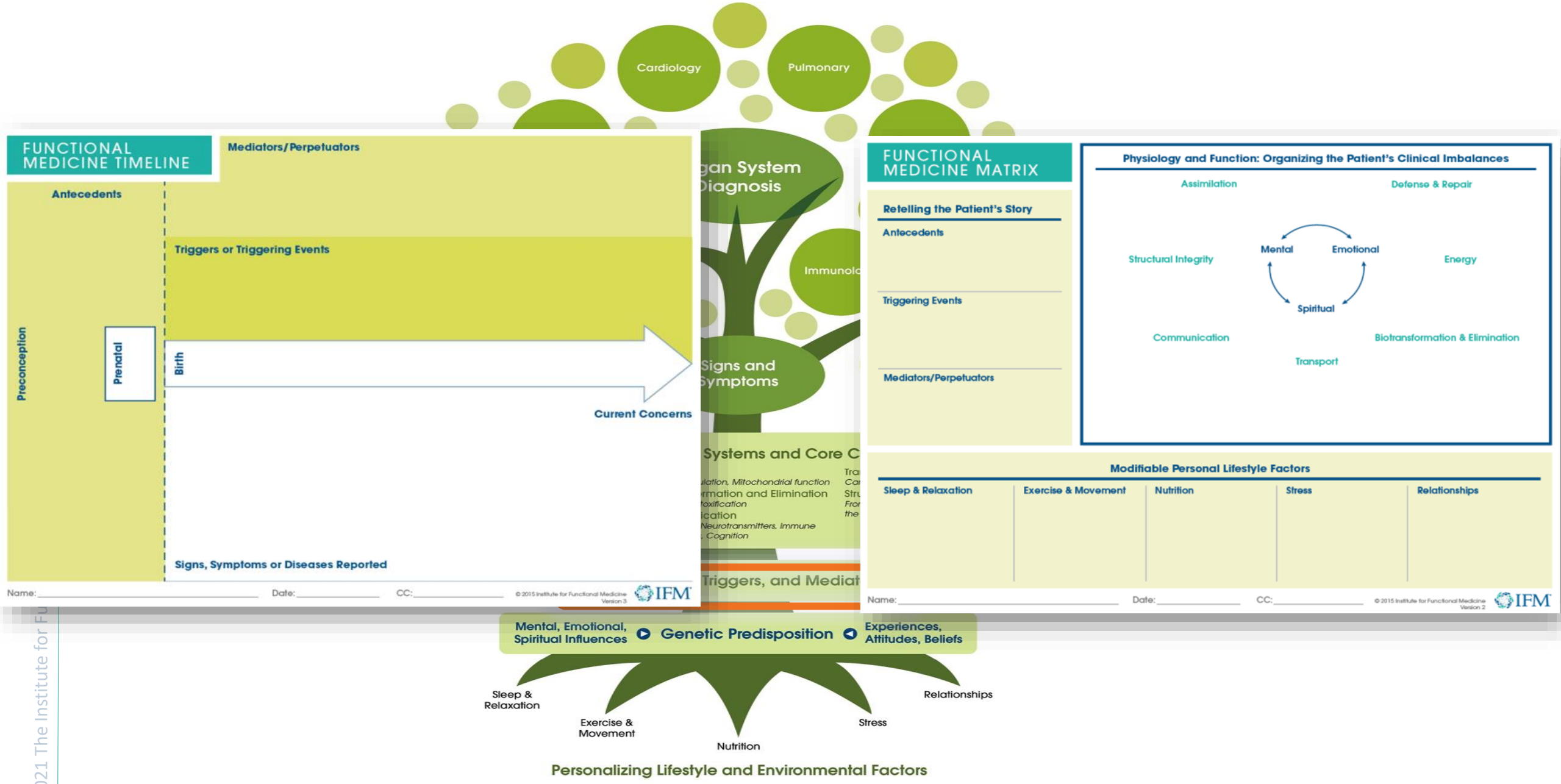
What is the conventional retelling of the story?

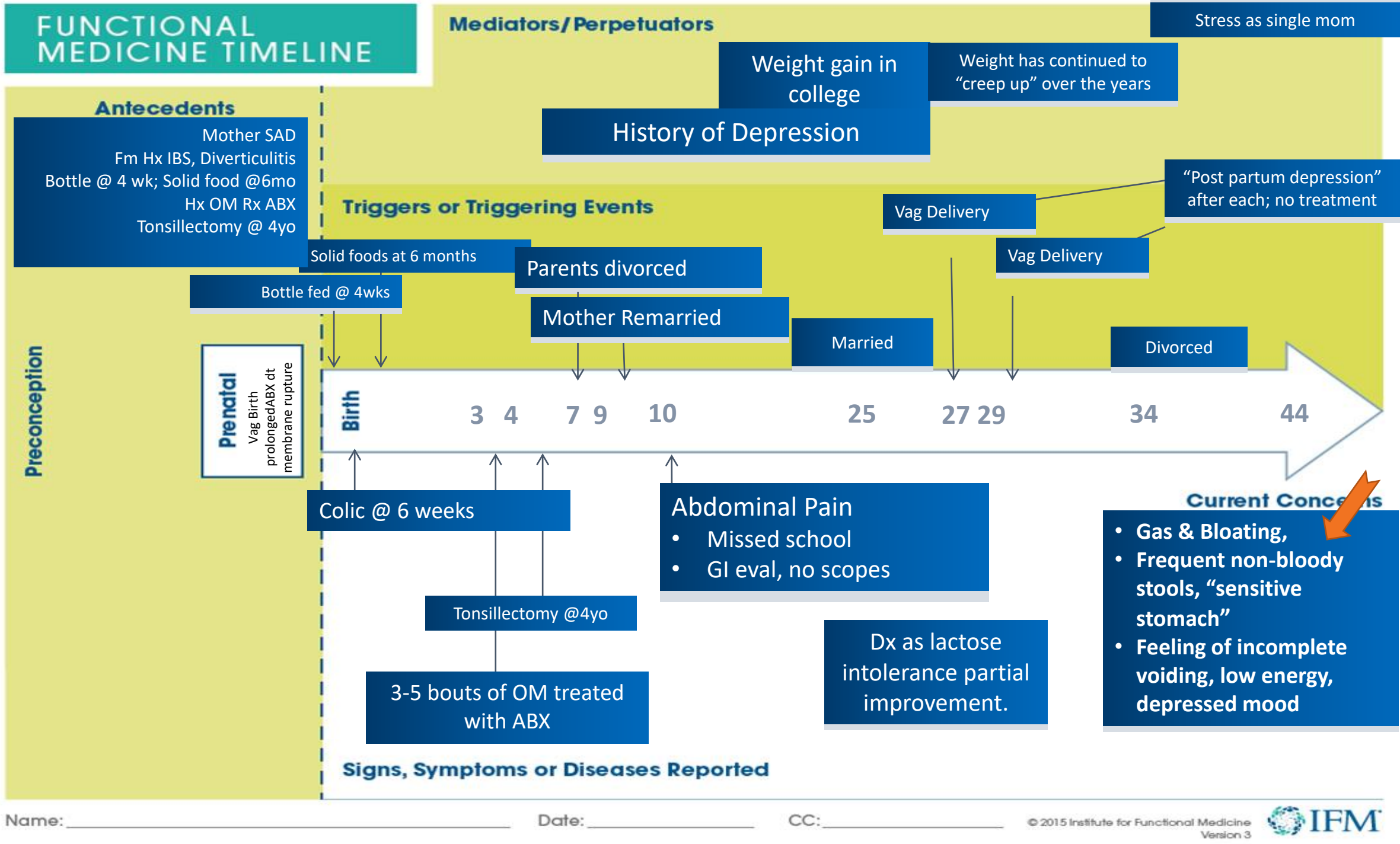
- Joan, you appear to have IBS and Depression.
- The good news is that we have an opportunity to “kill two birds with one stone” so to speak.
- An antidepressant will help your depression.
- The same antidepressant will also help your IBS.
- Pick up your med at the pharmacy and let’s follow up in a few weeks
- If you are not improved, I think a new GI work up is in order.

How might you now retell the story?

What tools do you use to retell the story?

- ATMs
- Timeline
- Matrix





Clarifying The Most Important **Antecedents, Triggers, And Mediators**

Antecedents:

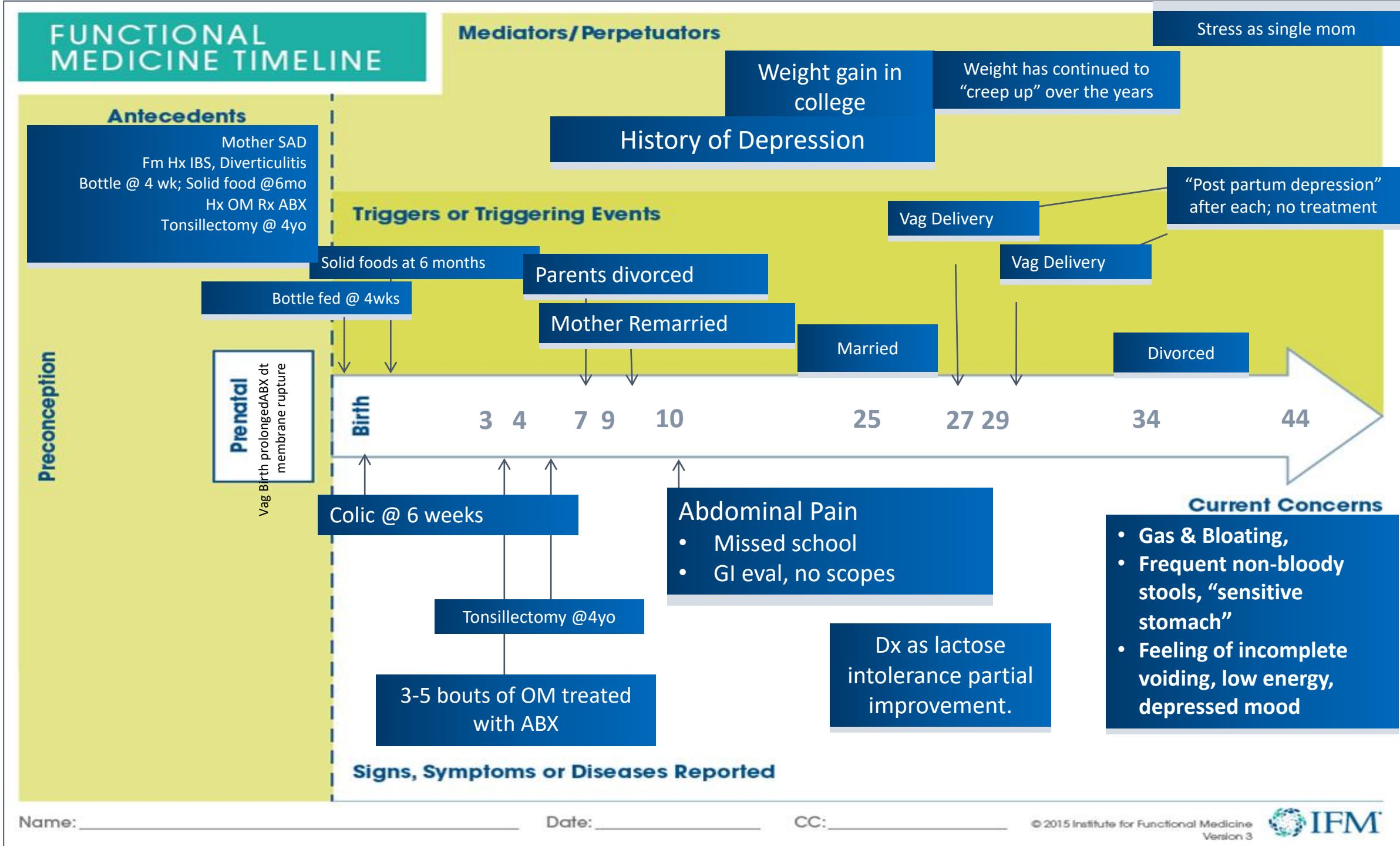
- Fm Hx IBS, Diverticulitis
- Bottle @ 4 wk
- Solid food @ 6 mo
- Hx OM Rx ABX
- Tonsillectomy @ 4yo

Triggers:

- Multiple antibiotics
- Standard American Diet
- Impaired digestion by lab
- *Blastocystis hominis*, dysbiosis presumed
- Increased IP

Mediators:

- Adiposity
- Depression
- Nutritional insufficiencies



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
2 kids @27&29 wt post part dep.
Divorced at 34yo (two teen boys)

Mediators/Perpetuators

SAD
Weight gain in college

Physiology and Function: Organizing the Patient's Clinical Imbalances

Assimilation

- Gas and Bloating
- Freq stools

Defense & Repair

- SAD (inflammatory diet)

Structural Integrity

Energy

- Fatigue
- History of Depression

Communication

- Depression
- Stress (adrenal reserve)

Biotransformation & Elimination

Transport

Modifiable Personal Lifestyle Factors

Sleep & Relaxation

Poor quality and quantity; has to be up to get the kids ready

Exercise & Movement

NONE; "no time"

Nutrition

SAD; quick meals due to being busy
Eats out often

Stress

Kids are a "handful"
Job is stressful as bank exec asst.

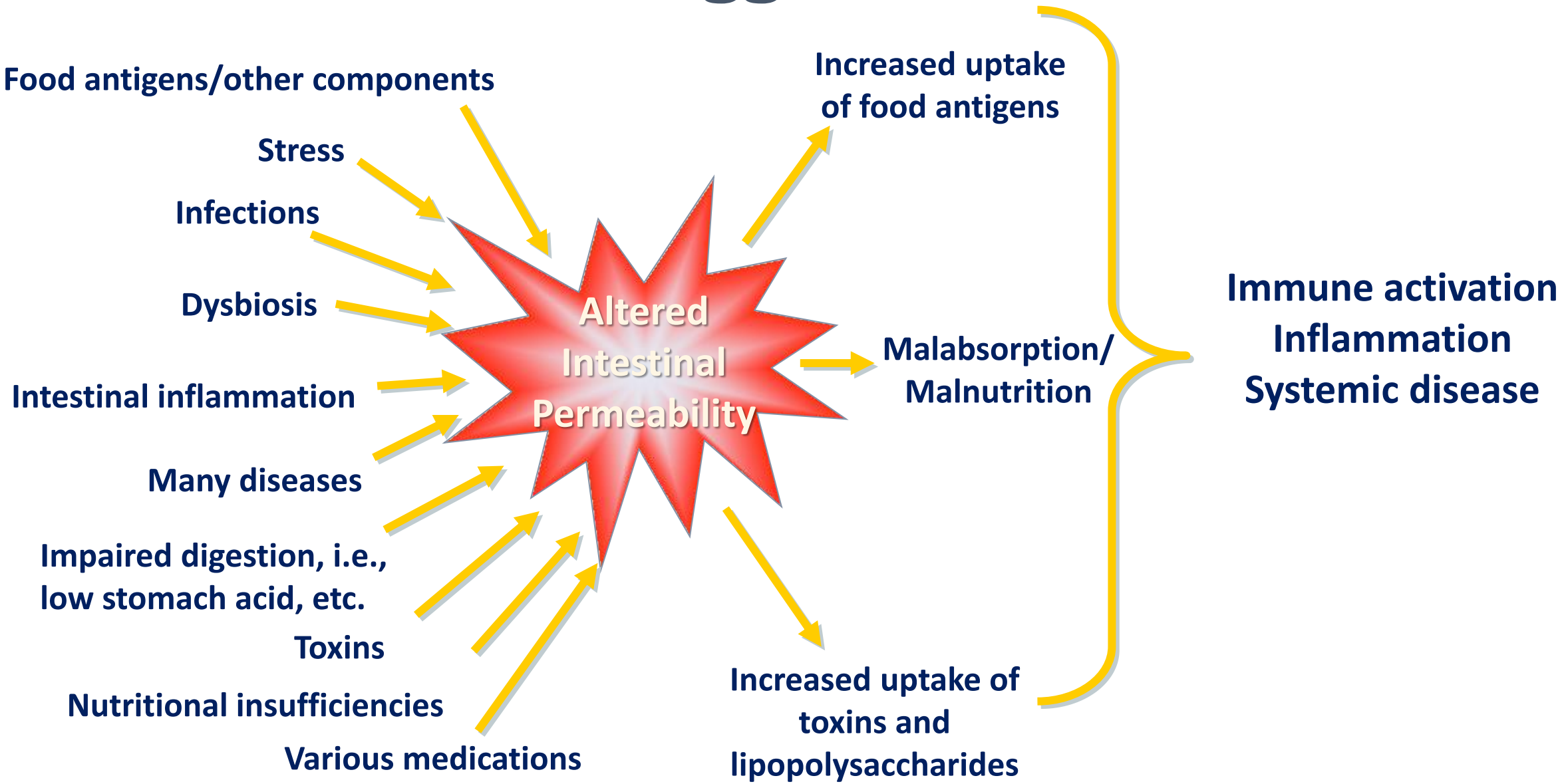
Relationships

Not dating and rarely has time to socialize

Name: _____ Date: _____ CC: _____

IFM

What Are The Triggers of Increased IP?



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Gather Oneself & Information

Organize on the Matrix, Time Line

Tell the Patient's Story

Order your Priorities

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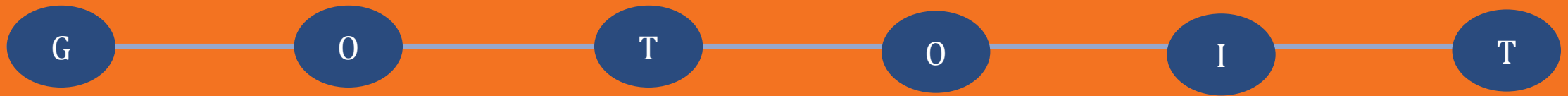

Unless there is a compelling reason to do otherwise –

TREAT THE GUT.

Treatment Approaches for Gut Dysfunction: **The 5R Program**

A conceptual framework designed to:

- Supply a scaffold to build targeted, individualized intervention
- Systematize a process to normalize critical gastrointestinal functions

The 5R Framework

- **R**emove
- **R**eplace
- **R**einoculate
- **R**epair
- **R**ebalance

The Conceptual Approach **Asks 5 Basic Questions**:

1. What does this patient need to have ***Removed?***
2. What does this patient need to have ***Replaced?***
3. What does this patient need in terms of support and/or re-establishment of a healthy balance of microflora; that is, what does he/she require to ***Reinoculate*** the gut?
4. What does this patient require to support healing and ***Repair*** of the GI epithelial barrier?
5. What does this patient need to do to ***Rebalance*** their lifestyle; that is, are there ways to modify their attitude and lifestyle to promote a healthier way of living, and thus healthier gut balance?

"Remove"

Remove refers to the elimination of factors such as:

- **Foods** to which an individual is sensitive, intolerant, or allergic
- **Pathogenic microflora** (e.g., bacteria, fungi, parasites)
- **Environmental stressors** such as pollutants
- **Stress**

Clinical approaches may include:

- Oligoantigenic elimination diet
- Botanical antimicrobials or bacteriostatic/bacteriocidal phytonutrients
- Antibiotics/Antifungal medications
- Removal of toxins and stressors

"Replace"

Replace refers to the replacement of factors that may be inadequate or lacking.

Clinical approaches may include:

- Digestive factors
- Hydrochloric acid
- Pancreatic enzymes
- Bile salts
- Fiber to support transit and general GI function

"Reinoculate"

Reinoculate refers to the **reintroduction of desirable GI microflora** (prebiotics, probiotics, synbiotics) to obtain a more desirable balance to the intestinal milieu.

Clinical approaches may include:

Probiotics may include:

- *Bifidobacteria* strains
- *Lactobacillus* strains
- *Saccharomyces boulardii*

Prebiotics may include:

- Inulin or fructooligosaccharides (FOS)
- Various other soluble fibers

Synbiotics may include:

- Bifidobacteria and FOS
- Lactobacillus and inulin

"Repair"

Repair refers to **providing nutritional support for healing and regeneration of the GI mucosa.**

Clinical approaches may include:

- Nutrients important for GI repair and healing: glutamine, arginine, vitamin A, vitamin D, vitamin C, zinc, pantothenic acid, vitamin E, carotenoids
- Mucosal lining support (e.g., phosphatidylcholine)
- Mucosal secretion protectants such as phosphatidylcholine, plantain, polysaccharides
- Support for GALT function (e.g., lactoferrin, lactoperoxidase, whey immunoglobulins)
- Antioxidants known to function in the GI (e.g., catechins)
- Nutritional and phytonutritional anti-inflammatories (e.g., curcumin, EPA, and DHA)

"Rebalance"

Rebalance refers to **providing support for restorative processes in a patients life.**

Clinical approaches may include:

- 'Scheduling' relaxation
- Mindful eating and better choices
- Heart rate variability/ biofeedback
- Yoga, meditation, prayer, breathing, or other centering practices
- Psychotherapy

How Can We Use The 5R's To Help Joan?

Gather Oneself & Information

Organize on the Matrix, Time Line

Tell the Patient's Story

Order your Priorities

Initiate Assessment and Care

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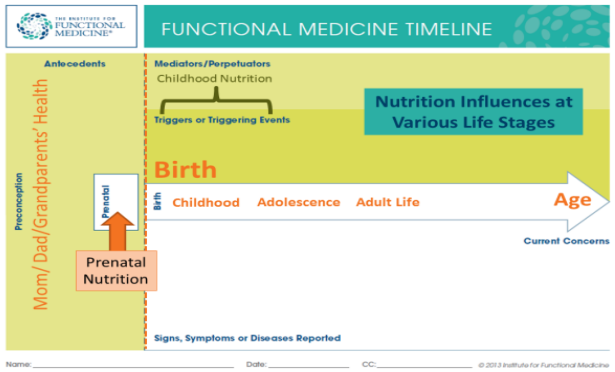
MEDICAL SYMPTOMS QUESTIONNAIRE (MSQ)

LUNGS	1	Chest congestion	
	0	Asthma, bronchitis	
	0	Shortness of breath	
	0	Difficulty breathing	Total 1
DIGESTIVE TRACT	3	Nausea, vomiting	
	4	Diarrhea	
	3	Constipation	
	3	Bloated feeling	
	2	Belching, passing gas	
	1	Heartburn	
	3	Intestinal/stomach pain	Total 19
JOINTS/MUSCLE	1	Pain or aches in joints	
	0	Arthritis	
	3	Stiffness or limitation of movement	
	0	Pain or aches in muscles	
	1	Feeling of weakness or tiredness	Total 5
WEIGHT	0	Binge eating/drinking	
	3	Craving certain foods	
	3	Excessive weight	
	0	Compulsive eating	
	0	Water retention	
	0	Underweight	Total 6
ENERGY/ACTIVITY	2	Fatigue, sluggishness	
	0	Apathy, lethargy	
	0	Hyperactivity	
	1	Restlessness	Total 3
MIND	1	Poor memory	
	0	Confusion, poor comprehension	
	1	Poor concentration	
	0	Poor physical coordination	
	0	Difficulty in making decisions	
	0	Stuttering or stammering	
	0	Slurred speech	
	0	Learning disabilities	Total 2
EMOTIONS	1	Mood swings	
	1	Anxiety, fear, nervousness	
	0	Anger, irritability, aggressiveness	
	3	Depression	Total 5
OTHER	0	Frequent illness	
	0	Frequent or urgent urination	
	0	Genital itch or discharge	Total 0
			Grand Total 64

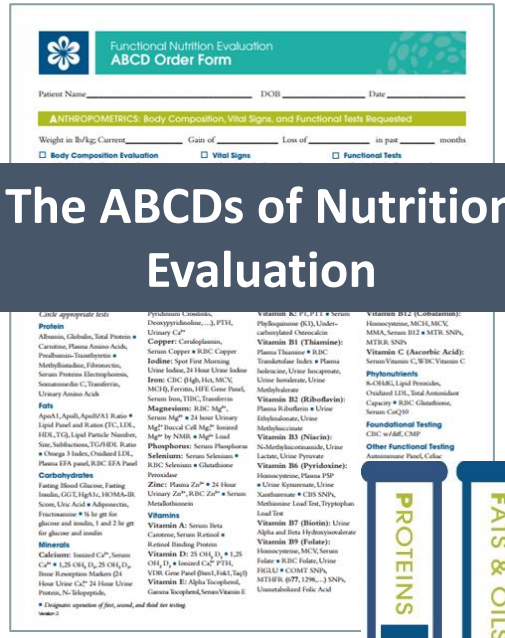
Practical Applications Using The "5R" Approach

What does Joan need to have ***Removed***?

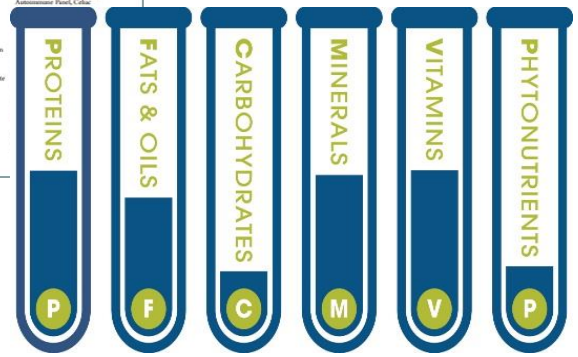
- **Foods** to which an individual is sensitive, intolerant, or allergic
- **Pathogenic microflora** (e.g., bacteria, fungi, parasites)
- **Environmental toxins** such as pollutants
- **Stress**



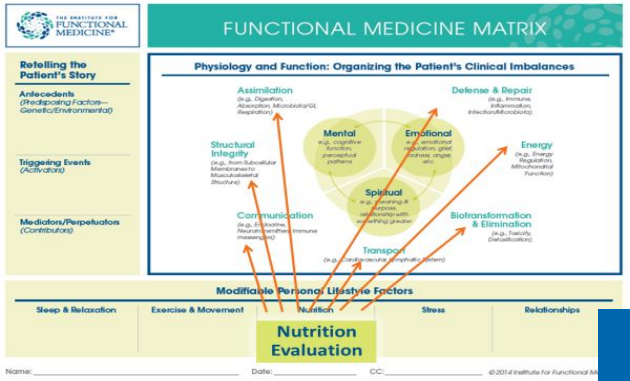
Nutrition Assessments



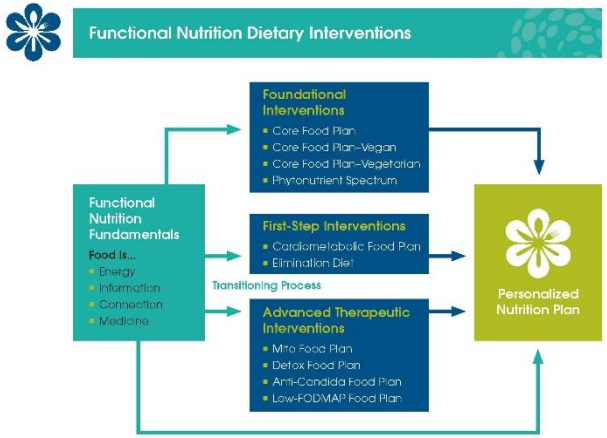
The ABCDs of Nutrition Evaluation



Gather
Organize
Re-Tell
Order/Prioritize
Initiate



Nutrition Therapeutic Interventions

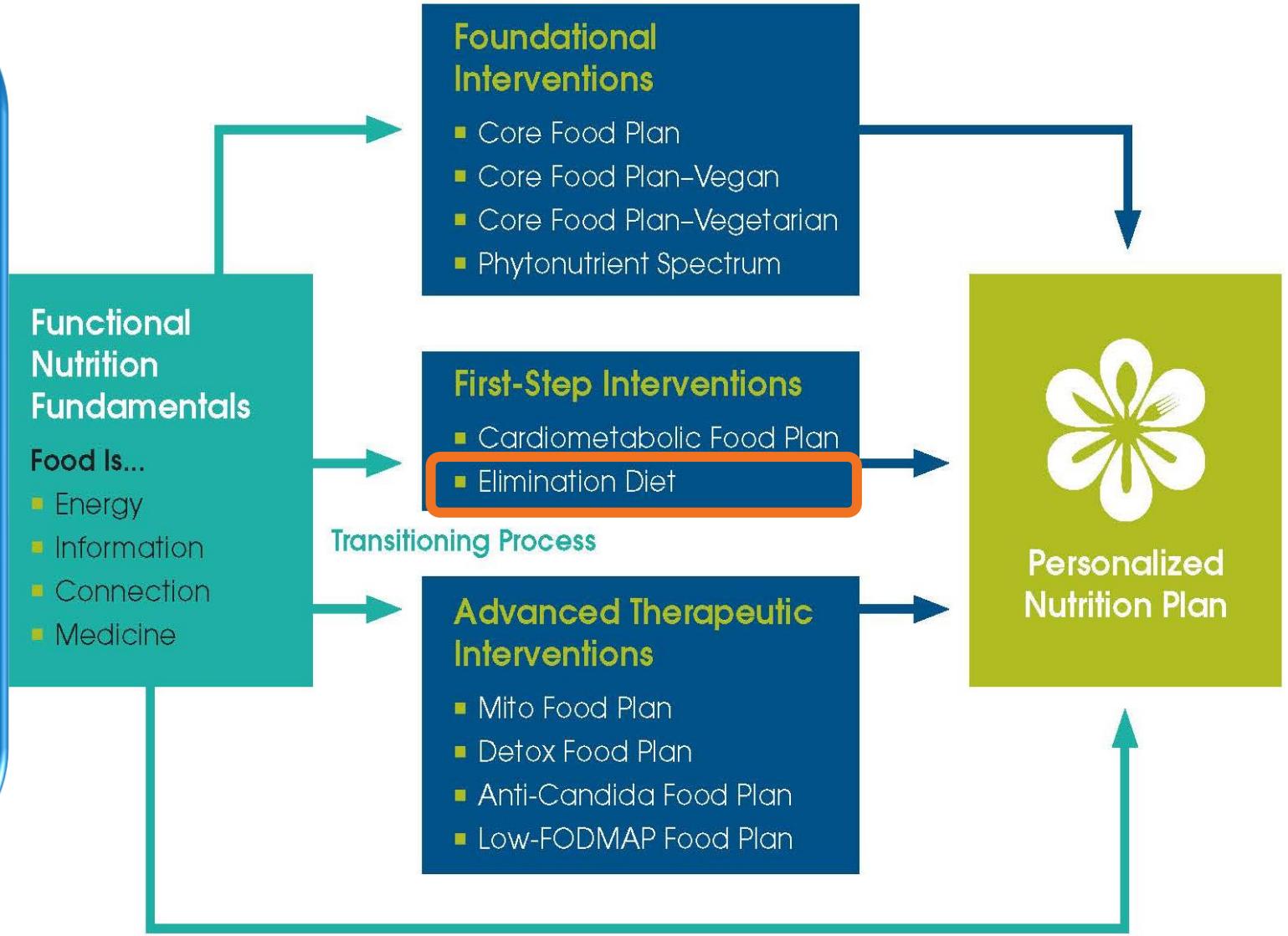


Functional Nutrition Dietary Interventions

Who: Those who haven't been successful with conventional medical therapy.

Expected Length: Short-term (for at least 3 weeks or until symptoms resolve followed by Reintroduction Phase)

Aspects of the Diet: gut/microbiome healing and support, food trigger identification, reduction of inflammation, DF/GF, increased phytonutrients, toxic burden reduction (from genes, toxic exposures, dietary exposures), increased body awareness of food, no calorie restriction



Introducing the **Elimination Diet**

Reducing foods that can trigger systemic reactions in order to reduce inflammation, lower the allergenic load, and provide the gut with a dietary base to allow for restoration

See References: Supporting Research for Elimination Diet

References: Supporting Research for Elimination Diet

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Elimination Diet Food Plan

PROTEINS *Proteins*

Servings/day_____

Lean, free-range, grass-fed, organically grown animal protein; non-GMO, organic plant protein; and wild-caught, low-mercury fish preferred.

Animal Proteins:

- ☐ Fish: Halibut, herring,● mackerel, salmon, sardines,● tuna, etc.–*1 oz*
- ☐ Meat: All wild game, buffalo, elk, lamb, venison–*1 oz*
- ☐ Poultry (skinless): Chicken, Cornish hen, turkey–*1 oz*

Plant Protein:

- ☐ Spirulina–*2 T*

Protein Powder:

- ☐ Check label for # grams/scoop (*1 protein serving=7 g*) Hemp, pea, rice

1 serving as listed = 35–75 calories, 5–7 g protein, 3–5 g fat, 0–4 g carbs

Average protein serving is 3–4 oz (size of palm of hand).

Eliminate

Beef/veal, canned meats, cold cuts, eggs, frankfurters, pork, shellfish, whey, soy (miso, natto, tempeh, tofu, textured vegetable protein)

LEGUMES *Proteins/Carbs*

Servings/day_____

Organic, non-GMO preferred

- ☐ Bean soups–*¾ c*
- ☐ Dried beans, peas, or lentils (cooked)–*½ c*
- ☐ Flour, legume–*¼ c*
- ☐ Green peas (cooked)–*½ c*
- ☐ Hummus or other bean dip–*⅓ c*
- ☐ Refried beans, vegetarian–*½ c*

1 serving = 90–110 calories, 3–7 g protein, 0 fat, 15 g carbs

Eliminate

Soybean products (edamame, miso, soy sauce, tamari, tempeh, tofu, soy milk, soy yogurt, textured vegetable protein)

Version 9

DAIRY ALTERNATIVES *Proteins/Carbs*

Servings/day_____

Unsweetened, organic preferred

- ☐ Kefir: Coconut (plain)●▲–*4-6 oz*
- ☐ Milk: Almond, coconut, flaxseed, hazelnut, hemp, rice–*8 oz*
- ☐ Yogurt: Coconut (cultured)●▲–*4-6 oz*

1 serving = 25–90 calories, 1–9 g protein, 1–4 g carbs (nutritional values vary)

Eliminate

Butter, cheese, cottage cheese, cream, frozen yogurt, ice cream, milk, non-dairy creamers, soy milk, yogurt (dairy and soy), whey

NUTS & SEEDS *Proteins/Fats*

Servings/day_____

Unsweetened, unsalted, organic preferred

- ☐ Almonds–*6*
- ☐ Brazil nuts–*2*
- ☐ Cashews●–*6*
- ☐ Chia seeds–*1 T*
- ☐ Coconut (dried)–*3 T*
- ☐ Flaxseed (ground)–*2 T*
- ☐ Hazelnuts–*5*
- ☐ Hemp seeds–*1 T*
- ☐ Macadamias–*2-3*
- ☐ Nut and seed butters–*½ T*
- ☐ Pecan Halves–*4*
- ☐ Pine nuts–*1 T*
- ☐ Pistachios–*16*
- ☐ Pumpkin seeds–*1 T*
- ☐ Sesame seeds–*1 T*
- ☐ Sunflower seeds●–*1 T*
- ☐ Walnut halves●–*4*

1 serving = 45 calories, 5 g fat

Eliminate

Mixed nuts (with peanuts), peanuts, peanut butter

FATS & OILS *Fats*

Servings/day_____

Minimally refined, cold-pressed, organic, non-GMO preferred

- ☐ Avocado●–*2 T or ⅛ whole*
- ☐ Coconut milk, regular (canned)–*1½ T*
- ☐ Coconut milk, light (canned)–*3 T*
- ☐ Ghee/clarified butter (grass-fed)–*1 t*
- ☐ Olives:● Black, green, kalamata–*8*
- ☐ Oils, cooking: Avocado, coconut, grapeseed, olive (extra virgin), rice bran, sesame–*1 t*
- ☐ Oils, salad: Almond, avocado, flaxseed, grapeseed, hempseed, olive (extra virgin), pumpkin, safflower (high-oleic), sunflower (high-oleic), sesame, walnut–*1 t*
- ☐ Prepared salad dressing with acceptable oils–*2 T*

1 serving = 45 calories, 5g fat

Eliminate

Butter, corn oil, cottonseed oil, margarine/spreads, mayonnaise, peanut oil, shortening, soybean oil

KEY

● High Histamine ■ Nightshades ▲ Fermented Foods

Notes: *Nutritional amounts are based on average values for the variety of foods within each food category.*

Dietary prescription is subject to the discretion of the health practitioner.

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dandelion, kale, mustard, turnip, etc.

1 serving = ½ c, 1 c raw greens = 25 calories, 5 g carbs

VEGETABLES Starchy *Carbs*

Servings/day_____

- ☐ Acorn squash (cubed)–*1 c*
- ☐ Butternut squash (cubed)–*1 c*
- ☐ Plantain–*⅓ c or ½ whole*
- ☐ Potato: Purple, red, sweet, white, yellow–*½ med*
- ☐ Potatoes (mashed, made with non-dairy milk)–*½ c*
- ☐ Root vegetables: Parsnip, rutabaga–*½ c*
- ☐ Yam–*½ med*

1 serving = 80 calories, 15 g carbs

Eliminate

Corn, Potato (if avoiding nightshades)

FRUITS *Carbs*

Servings/day_____

Unsweetened, no sugar added

- ☐ Apple–*1 sm*
- ☐ Applesauce–*½ c*
- ☐ Apricots–*4*
- ☐ Banana–*½ med*
- ☐ Blackberries–*¾ c*
- ☐ Blueberries–*¾ c*
- ☐ Dried fruit● (no sulfites)–*2 T*
- ☐ Figs–*3*
- ☐ Grapes–*15*
- ☐ Grapefruit–*½ med*
- ☐ Juices (diluted)–*½ c*
- ☐ Kiwi–*1 med*
- ☐ Kumquats–*4*
- ☐ Lemon–*1*
- ☐ Lime–*1*
- ☐ Melon, all–*1 c*
- ☐ Mango–*½ sm*
- ☐ Nectarine–*1 sm*
- ☐ Orange–*1 med*
- ☐ Papaya–*1 c*
- ☐ Peach–*1 sm*
- ☐ Pear–*1 sm*
- ☐ Persimmon–*½*
- ☐ Pineapple–*¾ c*
- ☐ Plums–*2 sm*
- ☐ Pomegranate seeds –*½ c*
- ☐ Prunes–*3 med*
- ☐ Raisins–*2 T*
- ☐ Raspberries●–*1 c*
- ☐ Tangerines–*2 sm*

1 serving = 60 calories, 15 g carbs

Eliminate

Citrus fruits (if directed by your healthcare provider)

Organic, non-GMO fruits, vegetables, herbs and spices preferred

GLUTEN-FREE GRAINS *Carbs*

Servings/day_____

Unsweetened, sprouted, organic preferred

- ☐ Amaranth–*¾ c*
- ☐ Brown rice cakes–*2*
- ☐ Buckwheat/kasha–*½ c*
- ☐ Crackers: (nut, seed, rice)–*3-4*
- ☐ Flours for baking: Arrowroot, sorghum, tapioca–*3 T*
- ☐ Millet–*½ c*
- ☐ Oats: Rolled, steel-cut–*½ c*
- ☐ Quinoa–*½ c*
- ☐ Rice–*⅓ c*
- ☐ Teff–*¾ c*

All grain servings are for cooked amounts.

1 serving = 75-110 calories, 15 g carbs

Eliminate

Barley, corn, emmer, farro, kamut, rye, spelt, triticale, wheat

BEVERAGES, SPICES & CONDIMENTS

Unsweetened, no sugar added

- ☐ Filtered water
- ☐ Sparkling/mineral water
- ☐ Unsweetened coconut water
- ☐ Green tea
- ☐ Fresh juiced fruits/vegetables
- ☐ Herbs and Spices, all
- ☐ Condiments: Mustard,● vinegars●▲ –*use sparingly, suggest 1 T or less per serving*

KEY

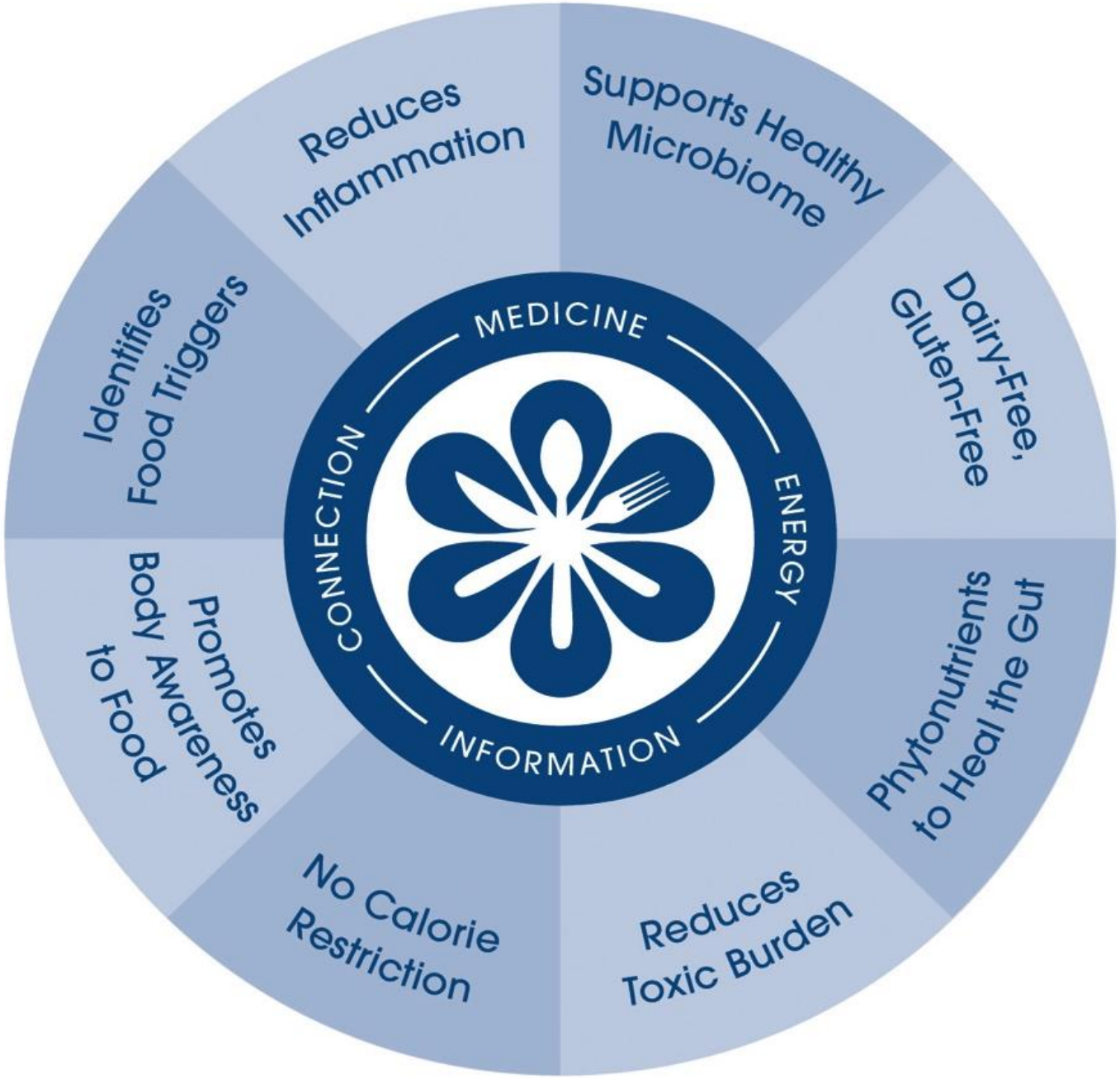
● High Histamine ■ Nightshades ▲ Fermented Foods

IFM

How will an Elimination Diet help Joan?

What parts of the Functional Medicine Matrix will an Elimination Diet touch?

An Elimination Diet touches the entire Matrix



Elimination Diet

"It's hard to do an elimination diet."

- Actually it is relatively easy but requires planning. Most don't plan to fail, they fail to plan.
- Plan your work and work your plan!
- **More discussion with Dr. Boham about the Comprehensive Elimination Diet in the presentation titled "Prescribing an Elimination Diet"**
- **We recommend you experience an elimination diet YOURSELF; watch for communications regarding opportunities for Elimination Diet experientials**

Laboratory: What do we know about Joan?

- **Primary Care**
  - CBC: 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 (Deaminated) IgA: negative
    - Endomysial Antibody IgA: negative
  - SIBO breath testing: WNL

Can we rule out Celiac disease?

Can we rule out wheat allergy?

Can we rule out non-Celiac gluten sensitivity?

Practical Applications Using The "5R" Approach

What does Joan need to have ***Removed***?

- **Foods to which an individual is sensitive, intolerant, or allergic**
- **Pathogenic microflora** (e.g., bacteria, fungi, parasites)
- **Environmental toxins** such as pollutants
- **Stress**

Comprehensive Stool Analysis / Parasitology x3

PARASITOLOGY/MICROSCOPY *
Sample 1
M[illegible] Blastocystis hominis
Rare Yeast
Sample 2
F[illegible] Blastocystis hominis
Rare Yeast
Sample 3
M[illegible]y Blastocystis hominis

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

PARASITOLOGY INFORMATION

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.

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.

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.

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.

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 Cryptosporidium spp, Cyclospora cayetanensis or Microsproridia spp.

GIARDIA/CRYPTOSPORIDIUM IMMUNOASSAY

	Within	Outside	Reference Range
Giardia intestinalis	Neg		Neg
Cryptosporidium	Neg		Neg

Giardia intestinalis (lamblia) 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.
Cryptosporidium is a coccidian protozoa that can be spread from direct person-to-person contact or waterborne transmission.

What do we know about *Blastocystis hominis*?

Can we link Joan's symptoms to Blastocystis in particular?

How Common is Blastocystis?

- In 2000, a study found that *B. hominis* infected 23% of the 2,896 patients throughout the US. It is the most prevalent mono-infection in symptomatic patients in the US.
- Studies using DNA-based methods to assess the positive rate in different cohorts have seen prevalence rates ranging from about **50% in healthy adults in highly industrialized countries** to 100% in healthy Senegalese children.
- Statistics from one lab 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%)

See References: How Common is Blastocystis?

References: How Common is Blastocystis?

1. Amin OM. Seasonal prevalence of intestinal parasites in the United States during 2000. Am J Trop Med Hyg. 2002 Jun;66(6):799-803.
2. Scanlan PD, et al. 15 September 2014. The microbial eukaryote Blastocystis is a prevalent and diverse member of the healthy human gut microbiota. FEMS Microbiol Ecol doi:10.1111/1574-6941.12396.
3. El Safadi D, et al. 2014. Children of Senegal River Basin show the highest prevalence of Blastocystis sp. ever observed worldwide. BMC Infect Dis 14:164. doi:10.1186/1471-2334-14-164.

Is Blastocystis a Pathogen?

- 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.

Qadri SM, al-Okaili GA, al-Dayel F. Clinical significance of Blastocystis hominis. J Clin Microbiol. 1989 Nov;27(11):2407-9.

Is Blastocystis a Pathogen?: Update

Human pathogenicity of Blastocystis sp. remains controversial as it can be found in both symptomatic and asymptomatic patients.

- It may be associated with certain subtypes of organism which impacts Blastocystis protease activity.
- The host specificity and the pathogenic potential of different *B. hominis* isolates correlate with sequence variations in the SSU-rRNA gene.

Additional Considerations: The occurrence of gut microbiota appears to be important for the pathogenic countenance of Blastocystis infections.

- Gut microbiota influences the survival and outcome of many parasitic infections.
- Commensal yeasts and bacteria can play an important role in reducing pathogenicity of parasites as they prevent the colonization of pathogenic agents on intestinal mucosa.

See References: Is Blastocystis a Pathogen? Update

References: Is Blastocystis a Pathogen? Update

1. Skotarczak B. Genetic diversity and pathogenicity of Blastocystis. Ann Agric Environ Med. 2018 Sep 25;25(3):411-416. doi: 10.26444/aaem/81315.
2. Noël C, et al. Molecular phylogenies of Blastocystis isolates from different hosts: implications for genetic diversity, identification of species, and zoonosis. J Clin Microbiol. 2005 Jan;43(1):348-55.
3. Berrilli F, Di Cave D, Cavallero S, D'Amelio S. Interactions between parasites and microbial communities in the human gut. Front Cell Infect Microbiol. 2012; 2: 141. doi:10.3389/fcimb.2012.00141
4. Lepczyńska M, Białkowska J, Dzika E, Piskorz-Ogórek K, Korycińska J. Blastocystis: how do specific diets and human gut microbiota affect its development and pathogenicity? Eur J Clin Microbiol Infect Dis. 2017 Sep;36(9):1531-1540. doi: 10.1007/s10096-017-2965-0.

B. Hominis
Differential pathogenicity

Blastocystis: 17 subtypes, immunosuppressed patients most affected

- *Treatment should be considered if patients are symptomatic*
- *OR* if one of the more virulent subtypes is detected by PCR:
  - > Sub-Type 3 had a strong correlation with symptomatic disease.
  - > Sub-Type 1, 2, 4 and 6 have also been isolated from symptomatic patients.

Symptoms:

- IBS and/or cutaneous (uticaria, pruritus- perianal, *intense* palmoplantar itching)
- Mast cell degranulation: **↑ histamine release**
- Short-term *exacerbation* with die off is not uncommon

1. Roberts T, Stark D, Harkness J, Ellis J. Update on the pathogenic potential and treatment options for Blastocystis sp. *Gut Pathog*. 2014;6:17. doi:10.1186/1757-4749-6-17
2. Tan KS. New insights on classification, identification, and clinical relevance of Blastocystis spp. *Clin Microbiol Rev*. 2008; 21(4):639-65. doi: 10.1128/CMR.00022-08.
3. Yakoob J, et al. Irritable bowel syndrome: is it associated with genotypes of Blastocystis hominis. *Parasitol Res*.2010;106(5):1033-8. doi: 10.1007/s00436-010-1761-x.
4. Kick G, Rueff F, Przybilla B. Palmoplantar pruritus subsiding after Blastocystis hominis eradication. *Acta Derm Venereol.* 2002;82(1):60.doi:10.1080/000155502753600948
5. Kurt Ö, Doğruman Al F, Tanyüksel M. Eradication of Blastocystis in humans: Really necessary for all? Parasitol Int. 2016 Dec;65(6 Pt B):797-801. doi: 10.1016/j.parint.2016.01.010.
6. El Safadi D, et al. (2013) Molecular epidemiology of *Blastocystis* in Lebanon and correlation between subtype 1 and gastrointestinal symptoms. Am J Trop Med Hyg 88:1203–1206. doi:10.4269/ajtmh.12-0777

Lab Test for *B. hominas* Subtypes

INFECTION

Dientamoeba fragilis
Blastocystis spp.

Parasitology

PCR Parasitology - Protozoa**

Methodologies: DNA by PCR, Next Generation Sequencing

Organism	Result	Units		Expected Result
Blastocystis spp.	6.00e2	femtograms/microliter C&S stool	**Detected**	Not Detected
Cryptosporidium spp.	<4.87e2	genome copies/microliter C&S stool	Not Detected	Not Detected
Cyclospora cayetanensis	<2.65e2	genome copies/microliter C&S stool	Not Detected	Not Detected
Dientamoeba fragilis	6.40e2	genome copies/microliter C&S stool	**Detected**	Not Detected
Entamoeba histolytica	<1.14e3	genome copies/microliter C&S stool	Not Detected	Not Detected
Giardia	<1.57e2	genome copies/microliter C&S stool	Not Detected	Not Detected

***Blastocystis* spp. Reflex Subtyping**

Type 1:	Not Detected	Type 4:	Not Detected	Type 7:	Not Detected
Type 2:	Detected	Type 5:	Not Detected	Type 8:	Not Detected
Type 3:	Not Detected	Type 6:	Not Detected	Type 9:	Not Detected

B. Hominis Sub-type Differences of Pathogenicity

- Blastocystis exhibits host specificity and strain-to-strain variation in pathogenicity. The subtype (ST) differences are an important factor affecting the pathogenesis of Blastocystis sp.
  - ST6, which is reported limitedly in our country, was found in patients with GIS complaints.
  - ST1 and ST2: higher in the patient group
  - Blastocystis ST-7 (but not ST-4) significantly increased apoptosis in enterocytes, suggesting that Blastocystis exhibits host specificity and strain-to-strain variation in pathogenicity.

1. Cakir F, Cicek M, Yildirim IH. Determination the Subtypes of Blastocystis sp. and Evaluate the Effect of These Subtypes on Pathogenicity. Acta Parasitol. 2019 Mar;64(1):7-12. doi: 10.2478/s11686-018-00002-y.
2. Wu Z, Mirza H, Teo JD, Tan KS. Strain-dependent induction of human enterocyte apoptosis by blastocystis disrupts epithelial barrier and ZO-1 organization in a caspase 3- and 9-dependent manner. Biomed Res Int. 2014;2014:209163. doi: 10.1155/2014/209163.

Does Blastocystis Have Systemic Effects? Does it Increase Intestinal Permeability?

- Increased intestinal permeability in patients with protozoan infections vs. controls, especially in the Giardia and Blastocystis groups (not in Entamoeba coli group).
    - **The increase in intestinal permeability in patients with *Blastocystis hominis* suggests that it can be a pathogenic protozoal infection and have systemic consequences.**
- Blastocystis spp. also have immuno-modulatory effects:
    - Degradation of IgA
    - Inhibition of iNOS
    - Upregulation of proinflammatory cytokines

1. Dagci H, Ustun S, Taner MS, Ersoz G, Karacasu F, Budak S. Protozoon infections and intestinal permeability. Acta Trop. 2002 Jan;81(1):1-5.
2. Ajjampur SS, Tan KS. Pathogenic mechanisms in Blastocystis spp. – Interpreting results from in vitro and in vivo studies. Parasitol Int. 2016 Dec;65(6 Pt B):772-779. doi: 10.1016/j.parint.2016.05.007.

Can Other Protozoal Infections Increase Intestinal Permeability?

- Adhesion of *Giardia duodenalis* trophozooites to intestinal cells was shown to induce disturbances of their tight, adherens, and desmosomal junction proteins.
- Giardia Cysteine Proteases (CPs) are directly involved in intestinal epithelial junctional complex disruption, intestinal epithelial cell apoptosis, and degradation of host immune factors, including chemokines and immunoglobulins.

1. Maia-Brigagao C, Mordgado-Diaz JA, De Souza W. Giardia disrupts the arrangement of tight, adherens and desmosomal junction proteins of intestinal cells. *Prasitol Int.* 2012;*61*(2), 280-7. doi: 10.1016/j.parint.2011.11.002.
2. Allain T, Fekete E, Buret AG. Giardia Cysteine Proteases: The Teeth behind the Smile. Trends Parasitol. 2019 Aug;35(8):636-648. doi: 10.1016/j.pt.2019.06.003

Other Protozoal Infections and Intestinal Permeability

In vitro study:

- Protozoan parasite Cryptosporidium parvum (CP) infection increased paracellular permeability in Caco-2 cell monolayers and substantially decreased the protein levels of occludin, claudin 4, and E-cadherin.

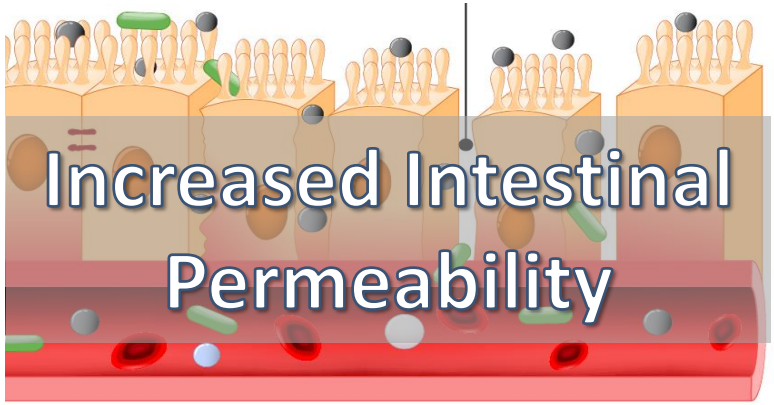
Animal study:

- A mouse model of malaria/NTS co-infection showed increased gut mastocytosis and increased ileal and plasma histamine levels that were temporally associated with increased gut permeability and bacterial translocation.
- Malaria/NTS co-infection in **mast cell-deficient mice was associated with a reduction in gut permeability and bacteremia.**
- **Antihistamine treatment reduced bacterial translocation and gut permeability in mice with malaria**, suggesting a contribution of mast cell-derived histamine to GI pathology and enhanced risk of bacteremia during malaria/NTS co-infection.

1. Kumar A, et al. Cryptosporidium parvum disrupts intestinal epithelial barrier function via altering expression of key tight junction and adherens junction proteins. Cell Microbiol. 2018 Jun;20(6):e12830. doi: 10.1111/cmi.12830.
2. Potts RA, et al. Mast cells and histamine alter intestinal permeability during malaria parasite infection. Immunobiology. 2016 Mar;221(3):468-74. doi: 10.1016/j.imbio.2015.11.003.

Is Inflammation Linked To Increased Intestinal Permeability?

- Food (gluten, casein, etc.)
- Toxins
- Stress
- Dysbiotic Organisms



Inflammatory Cytokines

Leakage of LPS and other inflammatory factors

Inflammation

Allergic, Autoimmune, and other systemic pathology

Michielan A, D'Incà R. Intestinal Permeability in Inflammatory Bowel Disease: Pathogenesis, Clinical Evaluation, and Therapy of Leaky Gut. Mediators of Inflammation. 2015;2015:628157. doi:10.1155/2015/628157

Is Inflammation Linked To Depression?

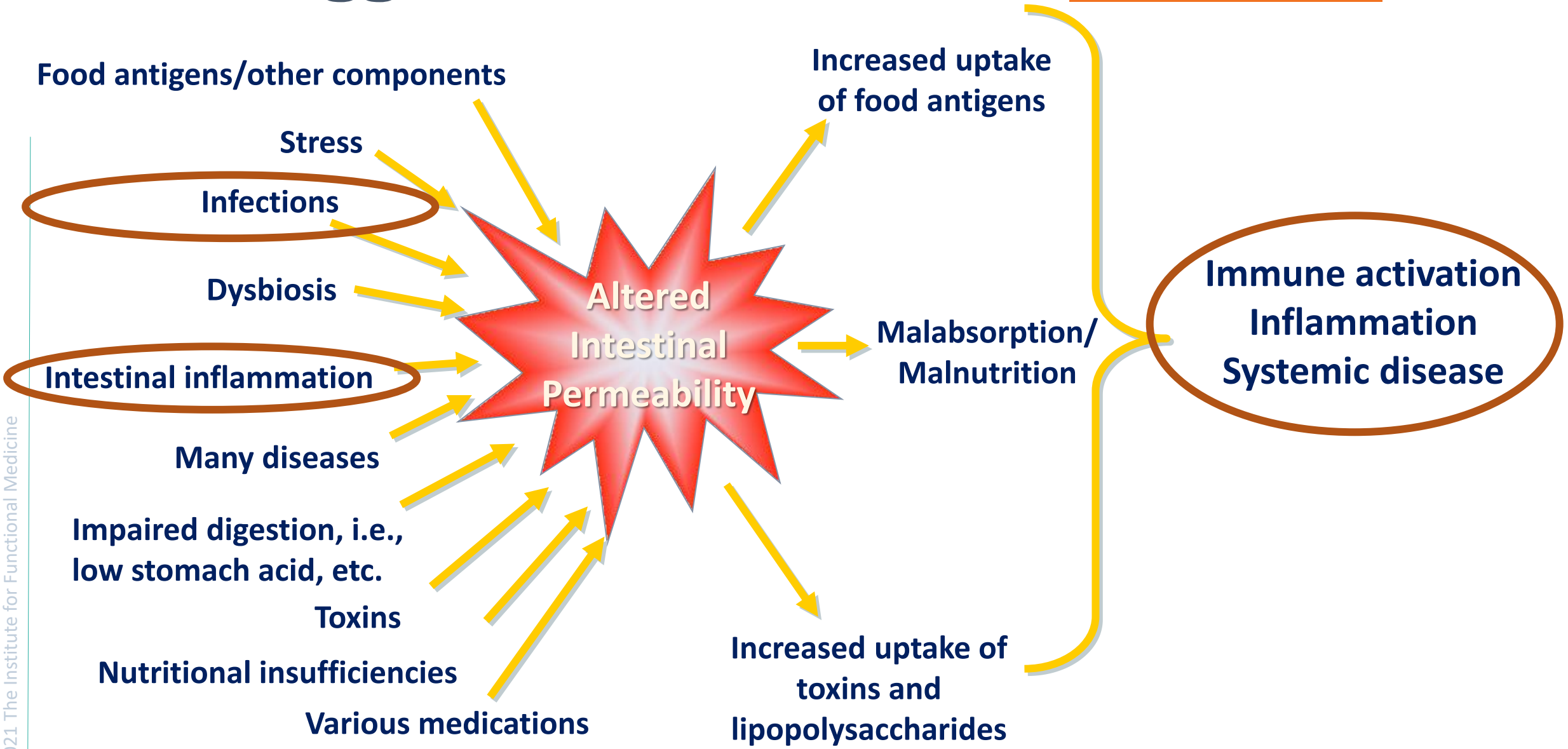
1. Miller AH, Maletic V, Raison CL. Inflammation And Its Discontents: The Role Of Cytokines In The Pathophysiology Of Major Depression. *Biological Psychiatry.* 2009;65(9):732-741. doi: 10.1016/j.biopsych.2008.11.029.
2. Leonard B, Maes M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. Neurosci Biobehav Rev. 2012;36(2):764-85. doi: 10.1016/j.neubiorev.2011.12.005.
3. Slavich GM, Irwin MR. From Stress to Inflammation and Major Depressive Disorder: A Social Signal Transduction Theory of Depression. Psychological bulletin. 2014;140(3):774-815. doi:10.1037/a0035302.
4. Akhondzadeh S, et al. Clinical trial of adjunctive celecoxib treatment in patients with major depression: a double blind and placebo controlled trial. Depress Anxiety. 2009;26(7):607-11. doi: 10.1002/da.20589.
5. Köhler O, et al. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatry. 2014 Dec 1;71(12):1381-91. doi: 10.1001/jamapsychiatry.2014.1611.

So… can intestinal permeability be linked to depression… and potentially some of Joan's health issues?

Intestinal mucosal dysfunction characterized by increased LPS translocation may induce specific "sickness behavior" including symptoms of depression.

Maes M, Kubera M, Leunis J. The gut-brain barrier in major depression: Intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. *Neuroendocrinology Letter.* 2008; 29(1):117-24.

Triggers of Increased IP: Joan's Case



FUNCTIONAL MEDICINE TIMELINE

Mediators/Perpetuators

Stress as single mom

Weight gain in college

Weight has continued to "creep up" over the years

History of Depression

Antecedents

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

Triggers or Triggering Events

"Post partum depression" after each; no treatment

Vag Delivery

Vag Delivery

Solid foods at 6 months

Parents divorced

Bottle fed @ 4wks

Mother Remarried

Married

Divorced

Preconception

Prenatal

Vag Birth prolongedABX dt membrane rupture

Birth

3 4 7 9 10 25 27 29 34 44

Colic @ 6 weeks

Abdominal Pain
- Missed school
- GI eval, no scopes

Current Concerns
- **Gas & Bloating,**
- **Frequent non-bloody stools, "sensitive stomach"**
- **Feeling of incomplete voiding, low energy, depressed mood**

Tonsillectomy @4yo

Dx as lactose intolerance partial improvement.

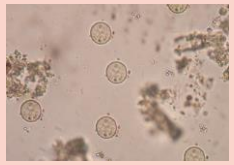
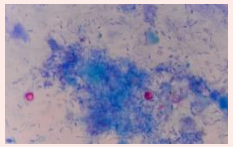
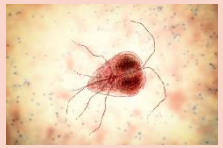
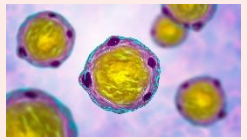
3-5 bouts of OM treated with ABX

Signs, Symptoms or Diseases Reported

Name: _____ Date: _____ CC: _____

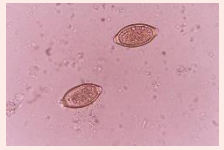
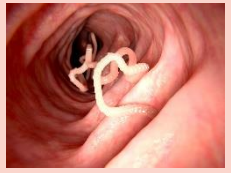
IFM

Specific Pharmaceutical Treatment of Parasites

PARASITE	MEDICAL TX
E. Histolytica 	Flagyl 750 TID 10 D W Iodoquinol 650 mg 20 D
Cryptosporidium 	Alinia 500 mg BID 14 days
Giardiasis 	Alinia 500 mg BID or Flagyl 250 TID x 7 days
Blastocystis hominis 	Flagyl 750 mg TID or Alinia 500 mg BID x 10 days

1. https://www.pdr.net/drug-summary/Flagyl-Capsules-metronidazole-1047
2. https://www.pdr.net/drug-summary/Alinia-nitazoxanide-1235
3. https://www.pdr.net/drug-summary/Quinja-iodoquinol-aloe-polysaccharide-24118
4. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Nitazoxanide. [Updated 2020 Apr 30] Available from: https://www.ncbi.nlm.nih.gov/books/NBK548943/

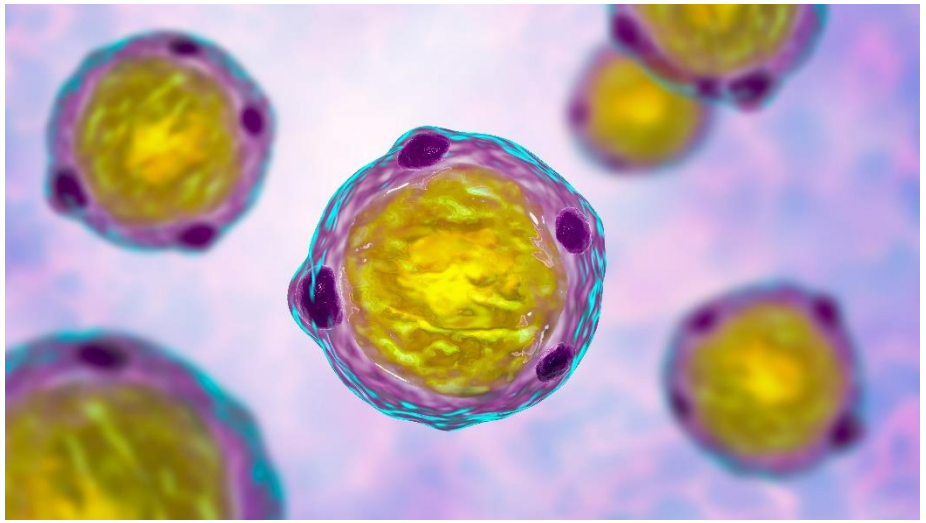
Specific Pharmaceutical Treatment of Parasites

PARASITE	MEDICAL TX
Strongyloidiasis 	Ivermectin 200 mg/kg/D plus broad spectrum antibiotics for 14 days
Trichuris trichiura 	Flagyl 500 TID x 7-10 days or albendazole 400 mg single dose
Tapeworm 	Praziquantel 20 mg/kg 4-6x per day for 21 days
Balantidium coli 	Tetracycline 500 TID for 10 days

1. Campbell S, Soman-Faulkner K. Antiparasitic Drugs. [Updated 2019 Dec 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544251/
2. Viswanath A, Yarrarapu SNS, Williams M. Trichuris Trichiura (Whipworm, Roundworm) [Updated 2020 Jul 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK507843/
3. Lesh EJ, Brady MF. Tapeworm (Taenia Solium, Taenia Saginata, Diphyllobothrium, Cysticercosis, Neurocysticercosis) [Updated 2019 Dec 2]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537154/
4. https://www.cdc.gov/dpdx/balantidiasis/tx.html

Pharmaceutical Options for Parasites

- **Nitozoxanide** (Alinia)
- **Metronidazole** (Flagyl)
- **Tinidazole** (Tindamax)
- **Iodoquinol** (Yodoxin)
- **Paromomycin** (Humatin)



Treatment time: varies

1. Campbell S, Soman-Faulkner K. Antiparasitic Drugs. [Updated 2019 Dec 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK544251/
2. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Nitazoxanide. [Updated 2020 Apr 30] Available from: https://www.ncbi.nlm.nih.gov/books/NBK548943/. 3. https://www.pdr.net/drug-summary/Alinia-nitazoxanide-1235

Additional Botanical Options for Parasites

- **Black walnut** (*Juglans nigra)*
- **Wormwood** *(Artemisia absinthium/annua)*
- **Bitterwood** (*Quassia amara)*
- **Garlic** *(Allium sativum)*
- **GoldThread** *(Coptis chinensis)[Huang lian]*
- **Olive leaf** *(Olea europaea)*
- **Citrus Seed Extract**

Artemisia annua

Coptis chinensis

1. Heron, Silena & Yarnell, Eric. (1999). Treating Parasitic Infections with Botanical Medicines. Alternative and Complementary Therapies. 5. 214-224. 10.1089/act.1999.5.214.
2. Fallahi S, Rostami A, Delfan B, Pournia Y, Rashidipour M. Effect of olive leaf, Satureja khuzestanica, and Allium sativum extracts on Giardia lamblia cysts compared with metronidazole in vitro. J Parasit Dis. 2016;40(4):1204-1209. doi:10.1007/s12639-015-0650-8.
3. Ionescu G, Kiehl R, Wichmann-Kunz F, Williams CH, Bauml LM, Levine S. Oral citrus seed extract. J Orthomol Med. 1990;5:230–238
4. Kim SY, Shin KS. Antimicrobial Activity of Trifoliate Orange (Poncirus trifoliate) Seed Extracts on Gram-Negative Food-borne Pathogens. Prev Nutr Food Sci. 2012;17(3):228-233. doi:10.3746/pnf.2012.17.3.228

Specific Botanical Treatments for Parasites

- **Oregano** (*Origanum vulgare*) encapsulated oil, 200 mg TID
- **Thyme** (*Thymus vulgaris*) standardized to contain thymol, 100-200 mg TID
- **Goldenseal** (*Hydrastis canadensis*) standardized to contain berberine, 200-400 mg TID
- **Artemesia/Chinese Wormwood** (*Artemesia annua*) 1-3 grams TID

Treatment time: 4-6 weeks

1. Sakkas H, Papadopoulou C.Antimicrobial Activity of Basil, Oregano, and Thyme Essential Oils. J. Microbiol. Biotechnol. (2017), 27(3), 429–438 https://doi.org/10.4014/jmb.1608.08024
2. Heron, Silena & Yarnell, Eric. (1999). Treating Parasitic Infections with Botanical Medicines. Alternative and Complementary Therapies. 5. 214-224. 10.1089/act.1999.5.214.

Is there something else with Joan we need to remove?

Bacteria and/or Yeast?

BACTERIOLOGY CULTURE

Expected/Beneficial flora	Commensal (Imbalanced) flora	Dysbiotic flora
3+ Bacteroides fragilis group	2+ Alpha hemolytic strep	
3+ Bifidobacterium spp.	4+ Gamma hemolytic strep	
4+ Escherichia coli	1+ Klebsiella oxytoca	
NG Lactobacillus spp.	1+ Pseudomonas aeruginosa	
NG Enterococcus spp.		
2+ Clostridium spp.		

NG = No Growth

YEAST CULTURE

Normal flora	Dysbiotic flora
1+ Candida parapsilosis	
1+ Rhodotorula mucilaginosa	

What do we know about dysbiosis in Joan?

Does Joan have ‘dysbiosis?’

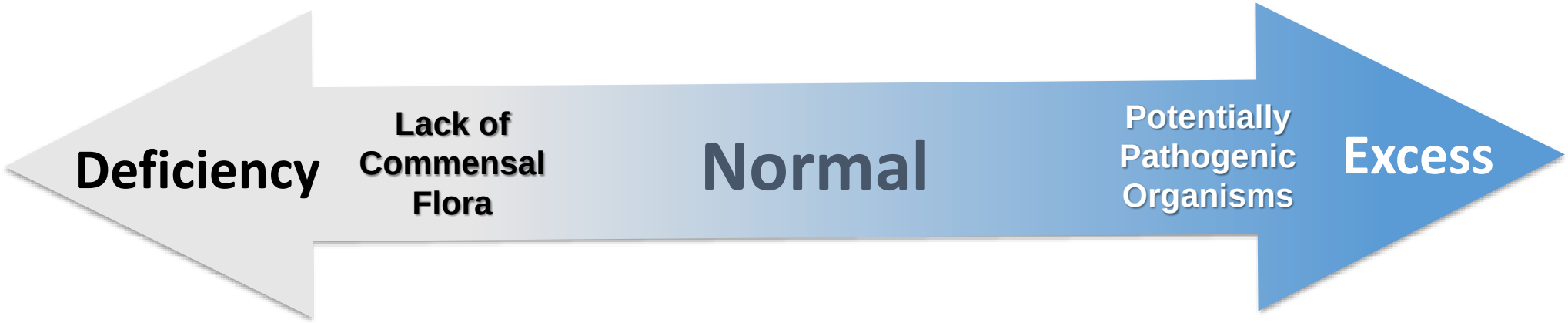
Dysbiosis

- **We are not looking for classic "infection"**
- 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.***

Treating Pathogenic Organisms vs. Treating Dysbiosis

- For dysbiosis, consider a continuum for affecting change in the gastrointestinal milieu:
  - **Dietary changes**
  - **Pre- and probiotics**
  - **Anti-microbial botanicals**
  - **Anti microbial medications**
- Anti-microbial pharmaceutical and/or botanical treatments should be reserved for significant and persisting dysbiosis and for patients with true pathogenic infections.

Altering The Intestinal Milieu



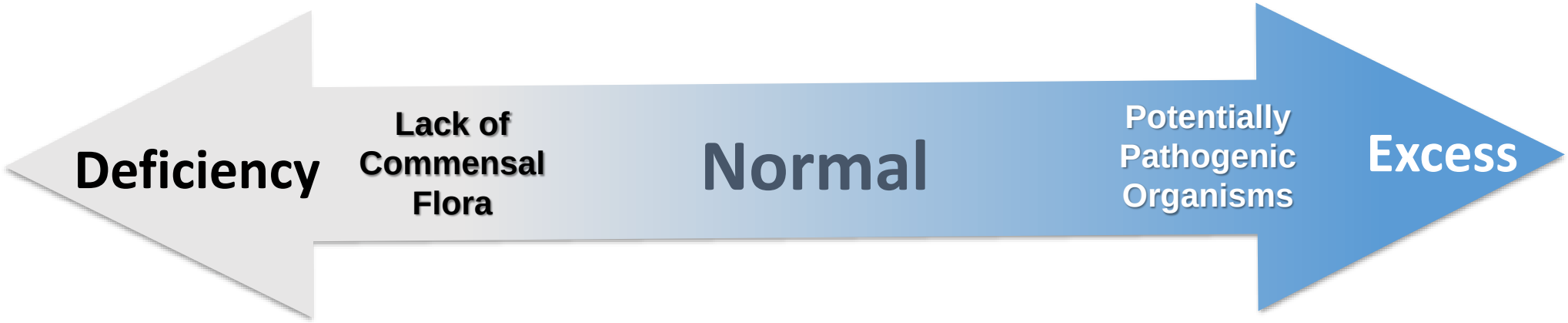
Treatment:

- Diet
- Fermented foods
- Soluble fiber
- Prebiotics
- Probiotics

Treatment:

- Antibiotics
- Antifungals
- Antimicrobials (Botanical)

Altering The Intestinal Milieu



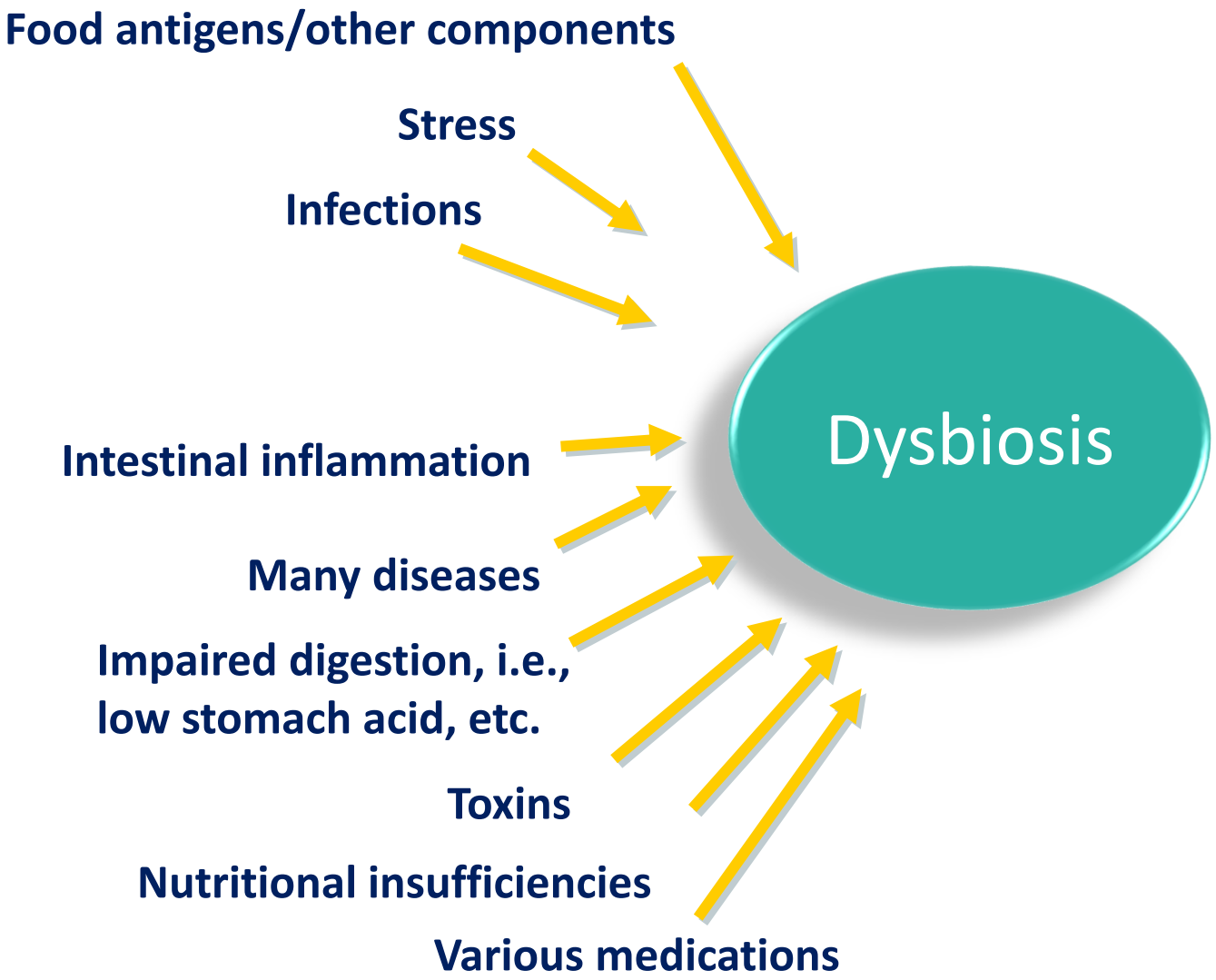
Treatment:

- SEED
- FEED

Treatment:

- WEED

Contributors to Dysbiosis



See References: Contributors to Dysbiosis

References: Contributors to Dysbiosis

1. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. Nature Reviews Immunology. 2009;9(5):313-323. doi:10.1038/nri2515.
2. Carding S, Verbeke K, Vipond DT, Corfe BM, Owen LJ. Dysbiosis of the gut microbiota in disease. *Microbial Ecology in Health and Disease*. 2015;26:10.3402/mehd.v26.26191. doi:10.3402/mehd.v26.26191.
3. Al Nabhani Z, Lepage P, Mauny P, et al. Nod2 Deficiency Leads to a Specific and Transmissible Mucosa-associated Microbial Dysbiosis Which Is Independent of the Mucosal Barrier Defect. J Crohns Colitis. 2016 Dec;10(12):1428-1436.
4. Arrieta M-C, Stiemsma LT, Amenyogbe N, Brown EM, Finlay B. The Intestinal Microbiome in Early Life: Health and Disease. *Frontiers in Immunology*. 2014;5:427. doi:10.3389/fimmu.2014.00427.
5. Matsuoka K, Kanai T. The gut microbiota and inflammatory bowel disease. *Seminars in Immunopathology*. 2015;37:47-55. doi:10.1007/s00281-014-0454-4.

WEEDING:
Removing Bacteria, Yeast and Protozoa in the 5R Program

Summary

- Antimicrobials for bacteria, yeast and protozoal/parasite infections should be used judiciously, and generally supported by objective information from laboratory evaluation.
- When employing antimicrobial therapy, incorporating (1) dietary and (2) prebiotic/probiotic treatments should almost always be used concurrently.

Summary: Removing **Bacteria**

Laboratory stool culture assessment showing elevated **pathogenic bacteria** should result in:

- Antimicrobial therapy guided by sensitivity
- Dietary recommendations incorporating prebiotics and probiotics
- Supplemental recommendations incorporating prebiotics and probiotics

Summary: Removing **Bacteria**

Laboratory stool culture assessment showing elevated **potentially pathogenic bacteria** should result in:

- Dietary recommendations incorporating prebiotics and probiotics
- Supplemental recommendations incorporating prebiotics and probiotics AND
- Consideration of antimicrobial therapy depending on other signs/symptoms

Summary: Removing **Bacteria**

- Treatment of pathogenic or potential pathogenic bacteria using antimicrobial agents should generally be guided by objective laboratory evaluation.
- Botanical and/or nutraceutical antimicrobial treatments should generally be considered first line treatments for bacterial dysbiosis.
- Based upon clinical experience, treatment should include combination botanical therapies for 6-12 weeks, along with diet and probiotics/prebiotics.

Summary: Removing **Bacteria**

- Pharmaceutical antibiotic treatment should generally be reserved for acute pathogenic bacteria infections, and/or recalcitrant non-responsive cases of chronic bacterial dysbiosis.
- Because of the risk of antimicrobial resistance, both botanical/nutraceutical and pharmaceutical agents should be used judiciously and for the shortest time possible.

Summary: Removing **Bacteria**

When treating with bacterial antimicrobials, reevaluation of pathogenic and potentially pathogenic bacteria by stool culture is recommended.

Removing Bacteria

Laboratory stool culture assessment shows:	Next steps for both:	What else to consider:	Overview:
Elevated pathogenic bacteria	**Prebiotics/Probiotics** 1) Dietary recommendations 2) Supplemental recommendations	**Antimicrobial therapy guided by sensitivity**	Treatment of pathogenic or potential pathogenic bacteria using antimicrobial agents should generally be guided by objective laboratory evaluation.
			Botanical and/or nutraceutical antimicrobial treatments should generally be considered first line treatments for bacterial dysbiosis.
Potentially pathogenic bacteria		**Consider antimicrobial therapy depending on other signs/symptoms**	Based upon clinical experience, treatment should include combination botanical therapies for 6-12 weeks, along with diet and probiotics/prebiotics.
			Pharmaceutical antibiotic treatment should generally be reserved for acute pathogenic bacteria infections, and/or recalcitrant non-responsive cases of chronic bacterial dysbiosis.
			Because of the risk of antimicrobial resistance, both botanical/nutraceutical and pharmaceutical agents should be used judiciously and for the shortest time possible.
			When treating with bacterial antimicrobials, reevaluation of pathogenic and potentially pathogenic bacteria by stool culture is recommended.

Summary: Removing **Yeast**

- Yeast dysbiosis is difficult to objectify with laboratory evaluation alone; therefore diagnosis is often made with a combination of laboratory coupled with suggestive signs and symptoms.
- Treatment generally involves
    1. **A low carbohydrate dietary approach**
    2. **Probiotics and**
    3. **Antifungal agent(s)**
- As some yeast feed competitively on prebiotics, administration of prebiotics may be delayed.

Summary: Removing **Yeast**

- Initial antifungal treatment generally is started with prescription nystatin and/or botanical/nutraceutical combinations.
- Antifungal treatment often requires a 4-8 week course.
- Using systemic pharmaceutical antifungals is generally reserved for recalcitrant cases.
- Because yeast dysbiosis is difficult to objectify with laboratory evaluation, follow-up reevaluation may or may not require laboratory.

	Diagnosis:	Next Steps:	What else to consider:	Follow-Up:
Removing Yeast	Combination of laboratory coupled with suggestive signs and symptoms	Treatment generally involves: 1) Low carb diet 2) Probiotics 3) Antifungal agents *(often prescription nystatin and/or botanical/nutraceutical combinations for 4-8 week course)* *Note: As some yeast feed competitively on *prebiotics*, administration of prebiotics may be delayed	Systemic pharmaceutical antifungals is generally reserved for recalcitrant cases.	Because yeast dysbiosis is difficult to objectify with laboratory evaluation, follow-up reevaluation may or may not require laboratory.

Summary: Removing **Parasites**

- Treatment of parasitic infections using prescription pharmaceuticals or botanicals/nutraceuticals should generally be guided by objective laboratory information of infection.
- Parasitic infections are generally most effectively treated using prescription pharmaceuticals.

Summary: Removing **Parasites**

- Based upon clinical experience, combinations of botanical/nutraceutical agents for extended treatment (6-12 weeks) have shown efficacy against parasitic infections.
- Laboratory evaluation of eradication of a parasitic infection is recommended.

Removing Parasites

Diagnosis:	Next Steps:	Follow-Up:
Objective laboratory information of infection	**Treatment generally involves:** 1) Parasitic infections are generally most effectively treated using prescription pharmaceuticals. 2) Based upon clinical experience, combinations of botanical/nutraceutical agents for extended treatment (6-12 weeks) have shown some efficacy against parasitic infections.	Laboratory evaluation of eradication of a parasitic infection is recommended.

"Remove" Summary: Joan

- *Remove* refers to the elimination of factors such as:
  - **Foods** to which an individual is sensitive, intolerant, or allergic ✔
  - **Pathogenic microflora** (e.g., bacteria, fungi, **parasites**) ✔
  - **Environmental stressors** such as pollutants
  - **Stress**

- **Clinical approaches may include:**
  - Oligoantigenic elimination diet ✔
  - Botanical antimicrobials or bacteriostatic/bacteriocidal phytonutrients
  - Antibiotics/Antifungal medications
  - Removal of toxins and stressors

Part 2

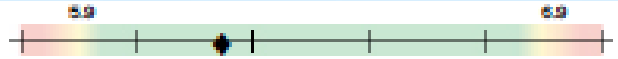
Practical Applications Using The "5R" Approach

What does Joan need to have ***Replaced***?

Determine need for digestive support

What else have we learned about Joan's GI function from her stool analysis?

Additional Tests

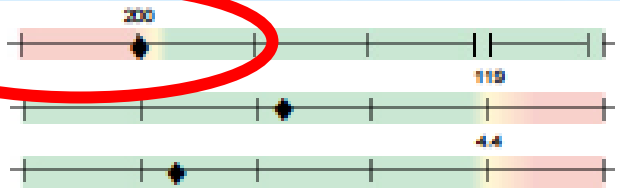


pH	6.2		5.7-7.1
RBCs	Negative		Negative
Color	Brown		

Additional Tests

pH is influenced by numerous factors, but it is strongly related to the bacterial release of pH-lowering organic acids and pH-raising ammonia. Positive RBCs can signify GI tract bleeding. Color (other than brown) abnormalities can be due to upper GI bleeding, or bile duct blockage, steatorrhea or antibiotic use.

Digestion

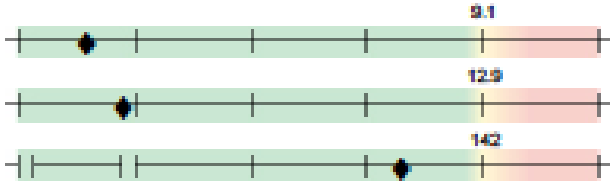


Elastase 1	194 L		> 100 ug/g
Triglycerides	77		<= 181 mg/dL
Putrefactive SCFA	1.6		<= 7.4 mM/g
Vegetable Fibers	Rare		None-Few

Digestion

Pancreatic elastase 1 levels below 100 are strongly correlated with severe pancreatic insufficiency; levels of 100-200 identify moderate pancreatic insufficiency. High triglycerides signify fat maldigestion. Putrefactive SCFA are a result of bacterial fermentation of undigested protein. High numbers of vegetable fibers indicate maldigestion.

Absorption



LCFAs	2.4		<= 15.1 mmol/L
Total Fat	5.7		<= 18.9 mmol/L
Cholesterol	96		<= 191 mg/dL

Absorption

High LCFA indicates fat malabsorption due to pancreatic or biliary insufficiency, or acute bacterial infection that produces intestinal cell destruction. High total fat usually signals malabsorption, as does elevated fecal cholesterol.

*UC = Unable to Calculate

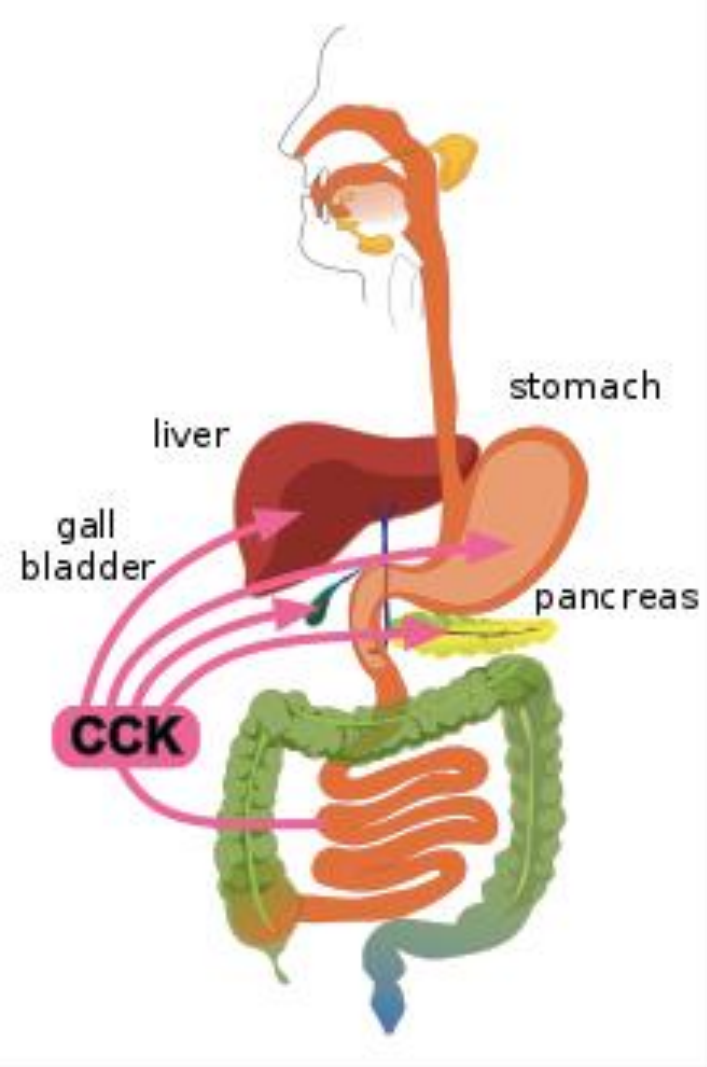
Decisions involving diagnosis and treatment are the responsibility of the clinician.

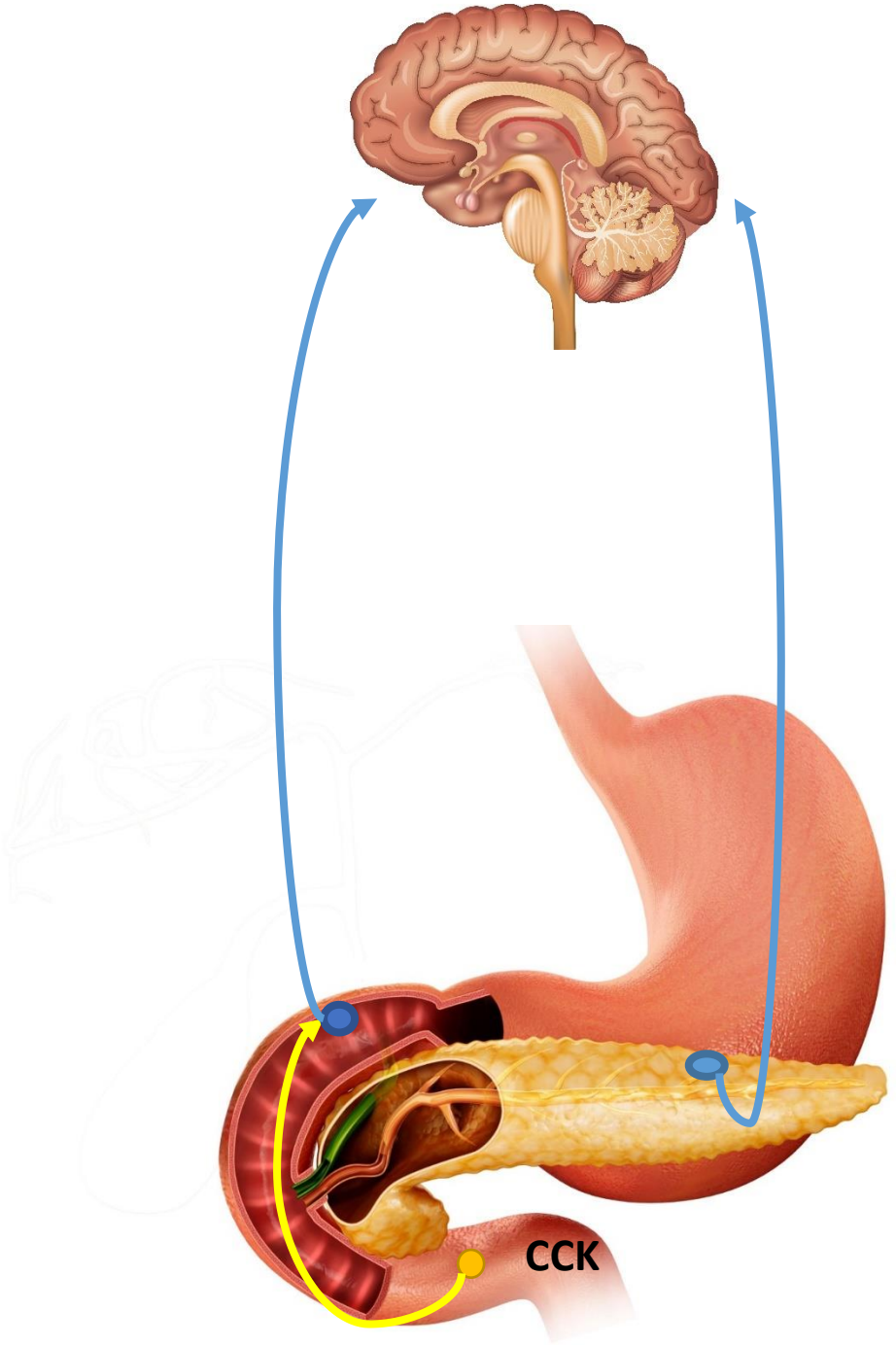
1. US National Library of Medicine. Stool Elastase. Medline Plus. Reviewed December 15, 2020. Accessed February 1, 2021. https://medlineplus.gov/lab-tests/stool-elastase/
2. Singh VK, Haupt ME, Geller DE, Hall JA, Quintana Diez PM. Less common etiologies of exocrine pancreatic insufficiency. World J Gastroenterol. 2017 Oct 21;23(39):7059-7076. doi: 10.3748/wjg.v23.i39.7059

Pancreatic Elastase 1

- Name confusion:
  - Chymotrypsin-like Elastase Family Member 3
- Exclusively human enzyme
- Not digested during transit
- Give information about the exocrine pancreatic function
- Regulated by CCK signaling pathway
- Related to brush border health

CCK (Cholecystokinin)



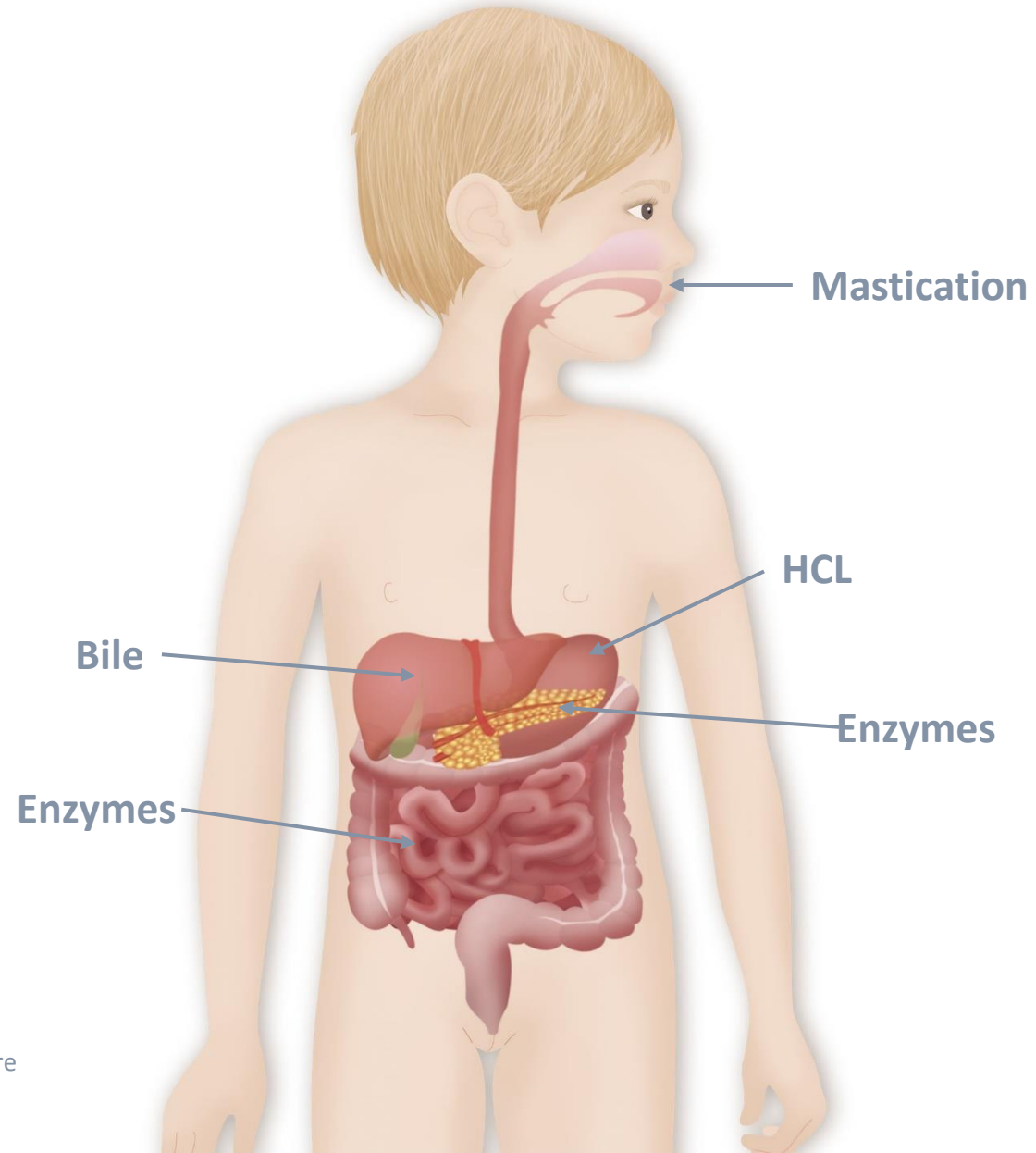


References: CCK (Cholecystokinin)

1. US National Library of Medicine. NCBI Gene Summary: CELA3B (chymotrypsin like elastase3B). Updated January 29, 2021. Accessed February 2, 2021. https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=DetailsSearch&Term=23436
2. Singh VK, Haupt ME, Geller DE, Hall JA, Quintana Diez PM. Less common etiologies of exocrine pancreatic insufficiency. World J Gastroenterol. 2017 Oct 21;23(39):7059-7076. doi: 10.3748/wjg.v23.i39.7059
3. Murphy JA, Criddle DN, Sherwood M, et al. Direct activation of cytosolic Ca2+ signaling and enzyme secretion by cholecystokinin in human pancreatic acinar cells. Gastroenterology. 2008 Aug;135(2):632-41. doi: 10.1053/j.gastro.2008.05.026

Maldigestion

- Adequate mastication
- Hypochlorhydria
- Pancreatic insufficiency
- Brush border injury
- Bile insufficiency



Zuvarox T, Belletieri C. Malabsorption Syndromes. [Updated 2020 Apr 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553106/

Signs and Symptoms Suggestive of . . .

Hypochlorhydria

- Bloating or belching immediately following a meal
- A sense of fullness after eating
- Itching around rectum
- Weak, peeling, or cracked fingernails
- Post-adolescent acne
- Undigested food in stool
- Dilated capillaries in face (acne rosacea)
- Iron deficiency
- Chronic intestinal infections
- Multiple food allergies

Pancreatic enzyme insufficiency

- Indigestion/fullness 2-4 hours after meal
- Bloating or flatulence 2-4 hours after meal
- Undigested food in stool

1. Fatima R. Achlorhydria. Stat Pearls. Updated January 22, 2021. Accessed February 11, 2021.
2. US National Library of Medicine. Stool Elastase. Medline Plus. Reviewed December 15, 2020. Accessed February 1, 2021. https://medlineplus.gov/lab-tests/stool-elastase/

Assessment of . . .

Hypochlorhydria

- Clinical signs & symptoms
- Betaine HCL challenge test
- Alka Selzer challenge test
- Heidelberg pH capsule

Pancreatic enzyme insufficiency

- Pancreatic elastase is measured in stool as a direct indicator of exocrine pancreatic insufficiency.

1. US National Library of Medicine. Stool Elastase. Medline Plus. Reviewed December 15, 2020. Accessed February 1, 2021. https://medlineplus.gov/lab-tests/stool-elastase/
2. US National Library of Medicine. Stomach Acid Test. Medline Plus. Updated January 5, 2021. Accessed February 8, 2021. https://medlineplus.gov/ency/article/003883.htm

Digestive Support

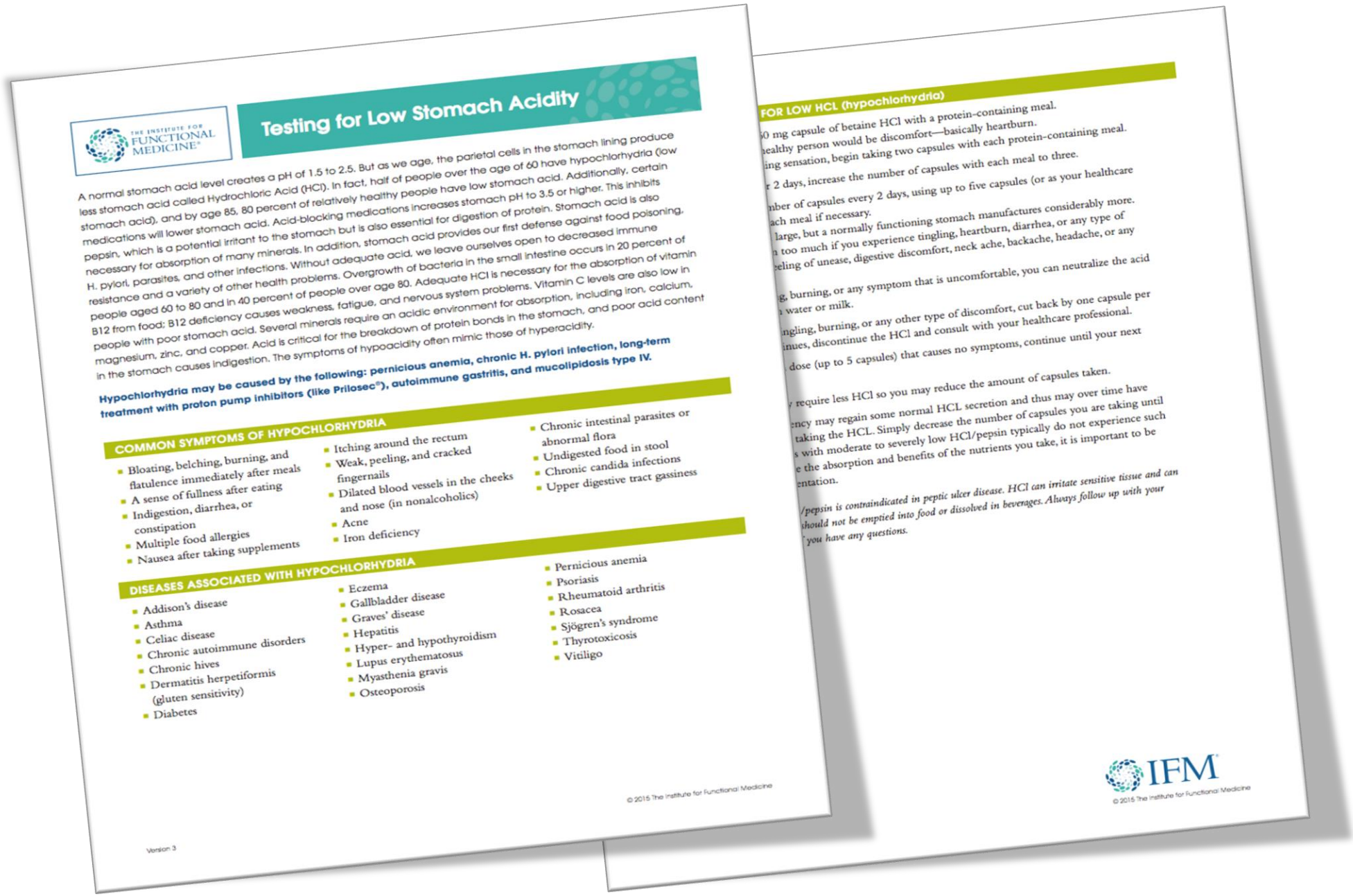
Maldigestion = incomplete processing of food

- Insufficient HCL
- Insufficient intestinal brush border enzymes
  - Decreased CCK stimulation of pancreas
- Insufficient pancreatic enzymes
- Insufficient bile acids

Supporting Gastric Acidity

- Betaine HCL tablets (350–3500 mg) with protein-containing meal (spaced before & throughout the meal)
- Umeboshi plums
- Digestive enzymes with acid pH range
- Swedish bitters
- Gentian root
- Vinegar
- Decrease stress!
  - Increase vagal tone
  - Heart rate variability biofeedback

1. Yago MR, Frymoyer AR, Smelick GS, et al. Gastric reacidification with betaine HCl in healthy volunteers with rabeprazole-induced hypochlorhydria. Mol Pharm. 2013 Nov 4;10(11):4032-7. doi: 10.1021/mp4003738
2. Olennikov DN, Kashchenko NI, Chirikova NK, Tankhaeva LM. Iridoids and Flavonoids of Four Siberian Gentians: Chemical Profile and Gastric Stimulatory Effect. Molecules. 2015;20(10):19172-19188. Published 2015 Oct 21. doi:10.3390/molecules201019172
3. Bonaz B, Sinniger V, Pellissier S. Vagal tone: effects on sensitivity, motility, and inflammation. Neurogastroenterol Motil. 2016 Apr;28(4):455-62. doi: 10.1111/nmo.12817



Testing for Low Stomach Acidity

A normal stomach acid level creates a pH of 1.5 to 2.5. But as we age, the parietal cells in the stomach lining produce less stomach acid called Hydrochloric Acid (HCl). In fact, half of people over the age of 60 have hypochlorhydria (low stomach acid), and by age 85, 80 percent of relatively healthy people have low stomach acid. Additionally, certain medications will lower stomach acid. Acid-blocking medications increases stomach pH to 3.5 or higher. This inhibits pepsin, which is a potential irritant to the stomach but is also essential for digestion of protein. Stomach acid is also necessary for absorption of many minerals. In addition, stomach acid provides our first defense against food poisoning, H. pylori, parasites, and other infections. Without adequate acid, we leave ourselves open to decreased immune resistance and a variety of other health problems. Overgrowth of bacteria in the small intestine occurs in 20 percent of people aged 60 to 80 and in 40 percent of people over age 80. Adequate HCl is necessary for the absorption of vitamin B12 from food; B12 deficiency causes weakness, fatigue, and nervous system problems. Vitamin C levels are also low in people with poor stomach acid. Several minerals require an acidic environment for absorption, including iron, calcium, magnesium, zinc, and copper. Acid is critical for the breakdown of protein bonds in the stomach, and poor acid content in the stomach causes indigestion. The symptoms of hypoacidity often mimic those of hyperacidity.

Hypochlorhydria may be caused by the following: pernicious anemia, chronic H. pylori infection, long-term treatment with proton pump inhibitors (like Prilosec®), autoimmune gastritis, and mucolipidosis type IV.

COMMON SYMPTOMS OF HYPOCHLORHYDRIA

- Bloating, belching, burning, and flatulence immediately after meals
- A sense of fullness after eating
- Indigestion, diarrhea, or constipation
- Multiple food allergies
- Nausea after taking supplements
- Itching around the rectum
- Weak, peeling, and cracked fingernails
- Dilated blood vessels in the cheeks and nose (in nonalcoholics)
- Acne
- Iron deficiency
- Chronic intestinal parasites or abnormal flora
- Undigested food in stool
- Chronic candida infections
- Upper digestive tract gassiness

DISEASES ASSOCIATED WITH HYPOCHLORHYDRIA

- Addison's disease
- Asthma
- Celiac disease
- Chronic autoimmune disorders
- Chronic hives
- Dermatitis herpetiformis (gluten sensitivity)
- Diabetes
- Eczema
- Gallbladder disease
- Graves' disease
- Hepatitis
- Hyper- and hypothyroidism
- Lupus erythematosus
- Myasthenia gravis
- Osteoporosis
- Pernicious anemia
- Psoriasis
- Rheumatoid arthritis
- Rosacea
- Sjögren's syndrome
- Thyrotoxicosis
- Vitiligo

Version 3

FOR LOW HCL (hypochlorhydria)

0 mg capsule of betaine HCl with a protein-containing meal.
ealthy person would be discomfort—basically heartburn.
ing sensation, begin taking two capsules with each protein-containing meal.
r 2 days, increase the number of capsules with each meal to three.
nber of capsules every 2 days, using up to five capsules (or as your healthcare
ach meal if necessary.
large, but a normally functioning stomach manufactures considerably more.
too much if you experience tingling, heartburn, diarrhea, or any type of
eling of unease, digestive discomfort, neck ache, backache, headache, or any

g, burning, or any symptom that is uncomfortable, you can neutralize the acid
water or milk.
ingling, burning, or any other type of discomfort, cut back by one capsule per
inues, discontinue the HCl and consult with your healthcare professional.
dose (up to 5 capsules) that causes no symptoms, continue until your next

require less HCl so you may reduce the amount of capsules taken.
ency may regain some normal HCL secretion and thus may over time have
taking the HCL. Simply decrease the number of capsules you are taking until
s with moderate to severely low HCl/pepsin typically do not experience such
e the absorption and benefits of the nutrients you take, it is important to be
entation.

/pepsin is contraindicated in peptic ulcer disease. HCl can irritate sensitive tissue and can
should not be emptied into food or dissolved in beverages. Always follow up with your
you have any questions.

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Digestive Support

Maldigestion = incomplete processing of food

- Insufficient HCL
- Insufficient intestinal brush border enzymes
  - Decreased CCK stimulation of pancreas
- Insufficient pancreatic enzymes
- Insufficient bile acids

Digestive Factors
(treatment time – long term)

Pancreatin

- 5000-24000 USP lipase activity;
- Mixture of lipases, proteases, and amylases
- Porcine or Bovine-derived
- Taken with meals

Bromelain (*Ananas comosus*)

- 1200-2400 MCU
- Taken with meals

1. Fieker, A., Philpott, J., & Armand, M. Enzyme replacement therapy for pancreatic insufficiency: present and future. *Clinical and experimental gastroenterology*, 2011:4(55).
2. Struyvenberg MR, Martin CR, Freedman SD. Practical guide to exocrine pancreatic insufficiency - Breaking the myths. BMC medicine. 2017;15(1):29.
3. Rathnavelu V, Alitheen NB, Sohila S, Kanagesan S, Ramesh R. Potential role of bromelain in clinical and therapeutic applications. Biomed Rep. 2016;5(3):283-288. doi:10.3892/br.2016.720

Digestive Support

Maldigestion = incomplete processing of food

- Insufficient HCL
- Insufficient intestinal brush border enzymes
  - Decreased CCK stimulation of pancreas
- Insufficient pancreatic enzymes
- Insufficient bile acids

Digestive Factors

Cholagogues/Choleretics - Agents that promote the flow or production of bile from the liver

Treatment time = variable

Dandelion root (*Taraxacum officinale*)

2-4 grams TID with food

5 ml 1:1 fluid extract TID with food

Bile salts (Ox bile)

500-1000 mg with food

Taurine

500-1000 mg with food

1. Pizzorno JE, Murray MT. Textbook of Natural Medicine. St. Louis, MO: Elsevier/Churchill Livingstone; 2013.
2. Singh, A., Malhotra, S., & Subban, R. (2008). Dandelion (Taraxacum officinale)-hepatoprotective herb with therapeutic potential. *Pharmacognosy Reviews*, 2008: *2*(3), 163.
3. Rowe KM, Schiller LR. Ileostomy diarrhea: Pathophysiology and management. Baylor Univ Med Cent Proc. 2020;33(2):218-226. doi:10.1080/08998280.2020.1712926

"Replace" Summary: Joan

Replace refers to the replacement of factors that may be inadequate or lacking.

Clinical approaches may include:

- Digestive factors
- Hydrochloric acid
- Pancreatic enzymes ✔
- Bile salts
- Fiber to support transit and general GI function

Recapping The Treatment Program So Far: Remove, Replace…

To start:

- Oligoantigenic elimination diet
- Anti-parasitic protocol
    - Prescriptive medication
    - Botanical combination
- Pancreatic enzymes

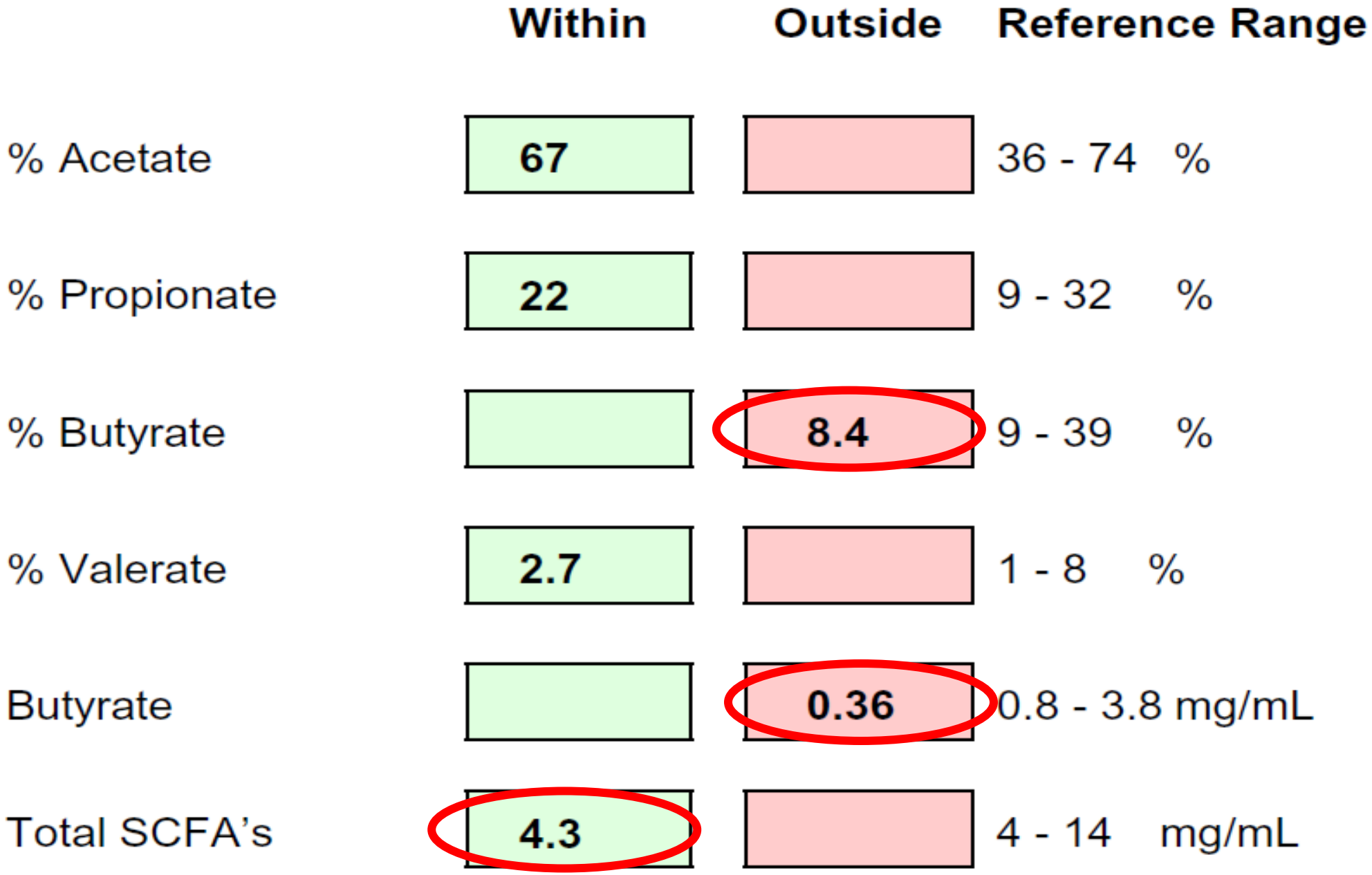
Practical Applications Using The "5R" Approach

Does Joan need to have gut flora ***'Reinoculated'***

(Feeding and Seeding the Microbiome)

Determine need for support of intestinal milieu

- Prebiotics
- Probiotics
- Synbiotics



1. Niccolai E, Baldi S, Ricci F, et al. Evaluation and comparison of short chain fatty acids composition in gut diseases. World J Gastroenterol. 2019;25(36):5543-5558. doi:10.3748/wjg.v25.i36.5543
2. (2018 cross-sectional study) Bridges KM, Diaz FJ, Wang Z, et al. Relating Stool Microbial Metabolite Levels, Inflammatory Markers and Dietary Behaviors to Screening Colonoscopy Findings in a Racially/Ethnically Diverse Patient Population. Genes (Basel). 2018;9(3):119. Published 2018 Feb 26. doi:10.3390/genes9030119

Feeding and Seeding the Microbiome

Laboratory stool assessment of low short chain fatty acids (SCFA) and/or low butyrate should result in:

- Dietary recommendations incorporating prebiotics and probiotics
- Supplemental recommendations incorporating prebiotics and probiotics

Feeding

“Re-balancing” Gut Flora

- **Diet** (Food as Medicine)
  - Prebiotics
  - Fermented foods
  - Specific carbohydrates
  - Soluble fiber
  - Synbiotics = Pre- + Pro-biotics

- **Probiotics** (Bugs as Drugs)
  - Dosage?
  - Strains?
  - Safety?

FEED: Diet and Microbiome

"Diet has the most powerful influence on gut microbial communities in healthy human subjects."

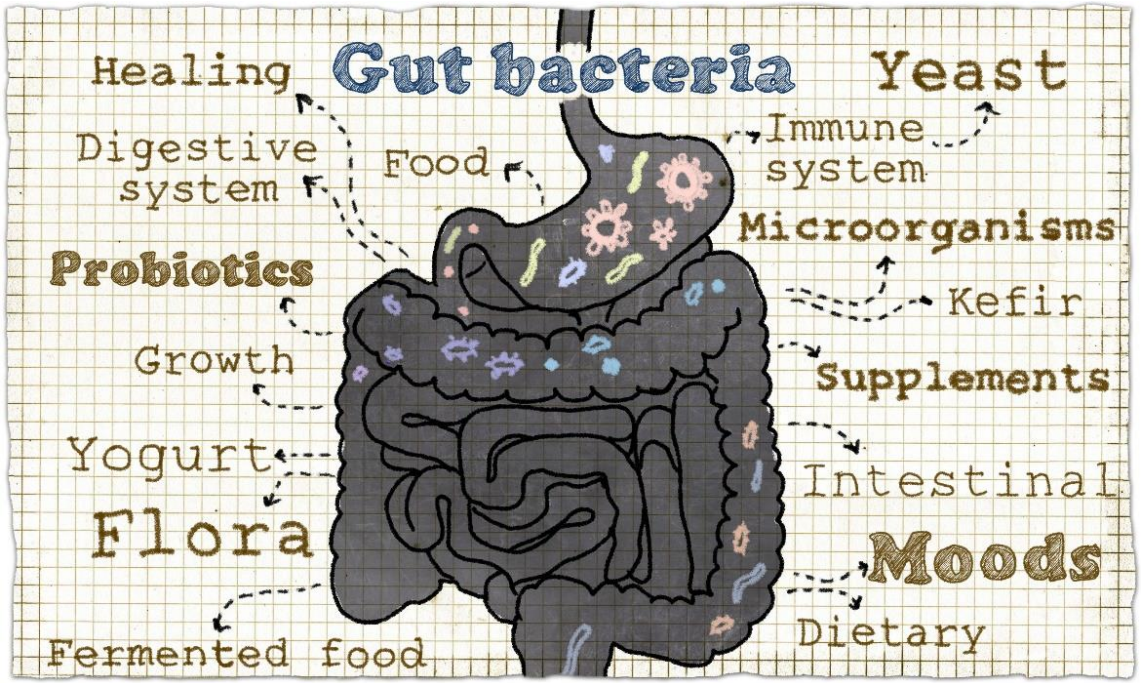
About 75% of the food in the Western diet is of limited or no benefit to the microbiota in the lower gut. Most of it, comprised specifically of refined carbohydrates, is already absorbed in the upper part of the GI tract, and what eventually reaches the large intestine is of limited value, as it contains only small amounts of the minerals, vitamins and other nutrients necessary for maintenance of the microbiota.

Bengmark S. Nutrition of the critically ill — a 21st-century perspective. Nutrients. 2013 Jan 14;5(1):162-207. doi: 10.3390/nu5010162.

Influencing the Microbiome

"Factors including age, genetics, and diet may influence microbiome composition.

Of these, **diet** is easiest to modify and presents the simplest route for intervention."



Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011 Oct 7;334(6052):105-8. doi: 10.1126/science.1208344.

Diets For Microbiome Restoration

Fermented foods

Restore and maintain “inner ecology” through:

- Cultured foods
- Decreasing sugars and carbohydrates

Probiotic Rich Foods

- Yogurt/kefir
- Miso
- Natto
- Tempeh
- Sauerkraut
- Kimchi
- Raw pickles
- Fermented anything
- Root and ginger beers
- Pulke
- Kombucha
- Fermented vegetables/sausages
- Buttermilk
- Raw whey
- Raw vinegars
- Sourdough? Essene bread?
- Beer/Wine

Consistency of Probiotics in Foods: Yogurt

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

- 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**

In your Toolkit

Probiotic and Prebiotic Foods

The digestive tract is home to more than 500 species of bacteria, comprising about 100 trillion bugs altogether. Collectively, they are tremendously important for overall health. We give these bugs a home; in exchange, they do a variety of things for us. For instance, they help digest food, synthesize certain vitamins, and play an important role in immune defense. These bugs also act as a barrier to help our bodies filter and appropriately absorb nutrients from what we eat.

There are 'good' bugs called probiotics, which we can constantly replenish. These probiotics also need nourishing food to help them grow. Prebiotics are the fiber-rich foods that probiotics feed and grow on. As an added bonus, a compound called butyric acid is produced when the probiotics break down prebiotic foods in the colon. Butyric acid is the preferred form of fuel for the cells that line the colon, and it serves to acidify the environment as well, making it harder for harmful bacteria to survive.

Two of the main probiotic bacteria that reside in the digestive tract are *Lactobacilli and Bifidobacteria*. These can be taken in the form of supplements or included in the diet in the form of fermented (or probiotic) foods. The table below lists examples of common probiotic and prebiotic foods.

In order to maintain colonization in the digestive tract, probiotics must be taken or eaten regularly. General recommendations call for ingesting 1 to 25 billion colony-forming units (CFUs) daily. To put these guidelines into perspective, most store-bought probiotic yogurts contain about 1 billion CFUs per serving. To get the maximum benefit from fermented foods, it's important to read product labels and choose only those that contain "active, live cultures" and preferentially raw, unpasteurized, perishable ingredients. Organic brands are the best choices, as they are not typically heat-treated after fermentation, so more of the good bacteria are present. Fermented foods can also be made at home. Though the probiotic content will vary by batch, home fermenting is a safe way to ensure that you are ingesting beneficial bacteria, as various cultures around the world have done for centuries.

Probiotic Foods	Prebiotic Foods
Dairy:	Apple
Acidophilus milk	Asparagus
Buttermilk	Banana
Cheese (aged)	Burdock
Cottage cheese	Chicory
Kefir	Cocoa
Sour cream	Dandelion greens
Yogurt (plain, no added sugar, active cultures)	Eggplant
Non-Dairy:	Endive
Fermented meats	Flaxseed
Fermented vegetables	Garlic
Kimchi	Honey
Kombucha	Jerusalem artichoke (sunchoke)
Kvass	Jicama
Miso	Konjac
Natto	Leek
Pickled vegetables (raw)	Legumes
Sauerkraut	Onion
Tempeh	Peas
Yogurt (plain, no added sugar, active cultures)	Radicchio
	Whole grains
	Yacon

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1. Lipski L. Digestive Wellness. 4th ed. New York, NY: McGraw Hill; 2012.
2. Mahan LK, Escott-Stump S, Raymond JL. Krause's Food and Nutrition Care Process. 13th ed. St. Louis, MO: Elsevier Inc; 2012.
3. Markowiak P, Slizewska K. Effects of Probiotics, Prebiotics, and Synbiotics on Human Health. Nutrients. 2017;9(9):1021. Published 2017 Sep 15. doi:10.3390/nu9091021
4. Parker EC, Gourard CM, Dolan KT, Finley EJ, Burne CM, Gaia MG, Pizano JM, Williamson CH, Lipski EA. Probiotics and Disease: A Comprehensive Summary Part 2, Commercially Produced Cultured and Fermented Foods Commonly Available in the United States. Integr Med (Encinitas). 2016 Dec;15(6):22-30.
5. Vighi G, Marcucci F, Sensi L, Di Cara G, Frati F. Allergy and the gastrointestinal system. Clinical & Experimental Immunology. 2008; 153, 3–6. http://doi.org/10.1111/j.1365-2249.2008.03713.

Version 3

IFM

PREBIOTICS

A prebiotic is a substrate that is selectively utilized by host microorganisms conferring a health benefit.

1. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014 Aug;11(8):506-14. doi: 10.1038/nrgastro.2014.66.
2. Gibson GR, Hutkins R, Sanders ME, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol. 2017;14(8):491-502. doi:10.1038/nrgastro.2017.75

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




SCFA Production in Colon

Starch

+

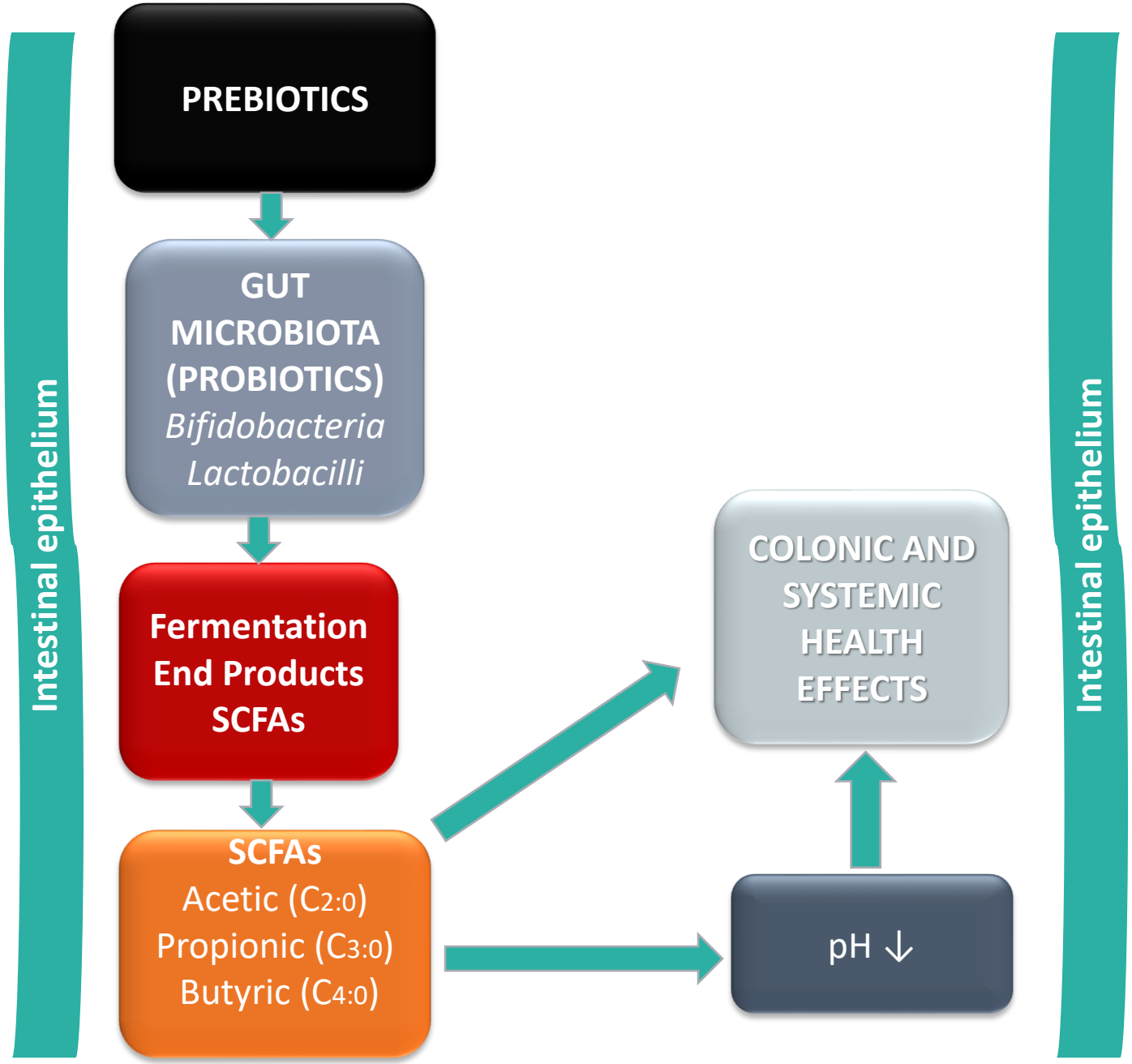
Non-Starch Polysaccharides

Bacterial Enzymes

Short-Chain Fatty Acids

- **Butyric**
- **Acetic**
- **Propionic**

SCFA Production in Colon



Effect Of Prebiotics

Sick Gut
Without nutritional therapies

- ↑ Inflammatory mediators
- ↑ Bacterial translocation
- ↑ Intestinal permeability
- ↑ Firmicutes
- ↓ Bacteroidetes
- ↓ Insulin sensibility

Healthy Gut
With nutritional therapies

- ↓ Inflammatory mediators
- ↓ Bacterial translocation
- ↓ Intestinal permeability
- ↓ Firmicutes
- ↑ Bacteroidetes
- ↑ Insulin sensibility

Adapted from Pimentel, G. D., Micheletti, T. O., Pace, F., Rosa, J. C., Santos, R. V., & Lira, F. S. (2012). Gut-central nervous system axis is a target for nutritional therapies. Nutrition journal, 11, 22. https://doi.org/10.1186/1475-2891-11-22. Licensed under CC BY 2.0.

Butyrate Benefits

- Colon: energy, maintenance & repair (production of 70% of ATP in colonocytes)
- Colon: increase mucus production, < permeability, decrease pH
- Histone deacetylase inhibitor (HDAC)
- Butyrate restored oxidative phosphorylation chain (Complex I-IV) and TCA cycle activity
- G-protein coupled receptor (GPCR) activator
- Reduces oxidative stress
- Promotes neurotrophic factors: BDNF, GDNF and NGF
- Keeps proteins and enzymes activated
- Impacts neurological disease positively (animal models)
  - Parkinson's disease, reduced stroke damage, improves learning and memory in aged mice with Alzheimer's.

Bourassa MW, Alim I, Bultman SJ, Ratan RR. Butyrate, Neuroepigenetics and the Gut Microbiome: Can a High Fiber Diet Improve Brain Health? Neuroscience letters. 2016;625:56-63. doi:10.1016/j.neulet.2016.02.009.

Prebiotic Beneficial Effects

- Improves bowel function
- Promotes growth of Bifidobacteria, Lactobacilli and other beneficial microbes
- Colon pH
- Protects against negative effects of bile acids
- Substrate for SCFA
- Improves intestinal permeability
- Improves metabolism of microbiota
- Adds sweetness to food
- > Satiety
- Stimulates neurochemical production in the gut

- Bone density (+ calcium)
- Serum cholesterol and triglycerides
- Cancer protective
- Used in treatment of atherosclerosis
- Immune function
- Neural and cognitive function
- Skin
- Insulin sensitivity & glucose regulation (in all and Type 2 DM)
- Mineral absorption
- Small but sig. effects body weight

1. Collins S, Reid G. Distant Site Effects of Ingested Prebiotics. Nutrients. 2016;8(9):523. doi:10.3390/nu8090523.
2. Gibson GR et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol. 2017 Aug;14(8):491-502. doi: 10.1038/nrgastro.2017.75.

Prebiotics: Oligosaccharides

- Fructiloogosaccharides (FOS)
- Galactooligosaccharides (GOS)
- Lactulose derived galactooligosaccharides (LDGOS)
- Xylooligosaccharides (XOS)
- Arbinooligosaccharides (AOS)
- Algae derived marine oligosaccharides (ADMO)
- Pectin-derived oligosaccharides (pAOS)
- Human milk oligosaccharides (HMO)

- Modified Starch
- Soluble Fiber

Oligosaccharide is actually a carbohydrate that is extracted using biotechnology. They are not normal carbohydrates. These saccharide polymers have between 3 and 10 linked simple sugars that work wonders for the body. They are found in plants like artichokes, chicory root, onions, legumes, wheatgrass and asparagus.

Benefits of Oligosaccharides

- Promote the growth of bifidobacteria and lacto-bacilli (need 4+ grams daily of FOS to promote growth of Bifidobacteria/dose response)
- Lower colon pH
- Discourage growth of clostridia
- Prevent constipation and diarrhea
- Have low glycemic index
- Lower ammonia levels (liver disease)
- Water soluble and of low viscosity
- Do not bind minerals

Looijer-van Langen MA, Dieleman LA. Prebiotics in chronic intestinal inflammation. Inflamm Bowel Dis. 2009 Mar;15(3):454-62. doi: 10.1002/ibd.20737.

Prebiotic Substances Available Commercially

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

Prebiotics: Summary

- Fructo-oligosaccharides and galacto-oligosaccharides are the two most important groups of prebiotics
- Considerable health benefits
- Strong safety record
- Easy to produce and store




Prebiotics: Practical Issues

Treatment time – indefinite

- **FOS/fructo-oligosaccharides:** 1000-5000 mg, QD-TID
- **Inulin:** 1000-5000 mg, QD-TID
- **Other specific fibers (high soluble):**
  - Larch (arabinogalactans): 500-5000 mg, QD-TID
  - Modified citrus pectin: 3-5 g, BID-TID

See References: Prebiotics

References: Prebiotics

1. Gibson GR, Hutkins R, Sanders ME, Prescott SL et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol. 2017 Aug;14(8):491-502. doi: 10.1038/nrgastro.2017.75.
2. Belorkar SA, Gupta AK. Oligosaccharides: a boon from nature's desk. AMB Express. 2016;6:82. doi:10.1186/s13568-016-0253-5.
3. Barengolts E. Gut Microbiota, Prebiotics, Probiotics, And Synbiotics In Management Of Obesity And Prediabetes: Review Of Randomized Controlled Trials.Endocr Pract. 2016 Oct;22(10):1224-1234.
4. Collins S, Reid G. Distant Site Effects of Ingested Prebiotics. Nutrients. 2016;8(9):523. doi:10.3390/nu8090523.
5. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014 Aug;11(8):506-14. doi: 10.1038/nrgastro.2014.66.

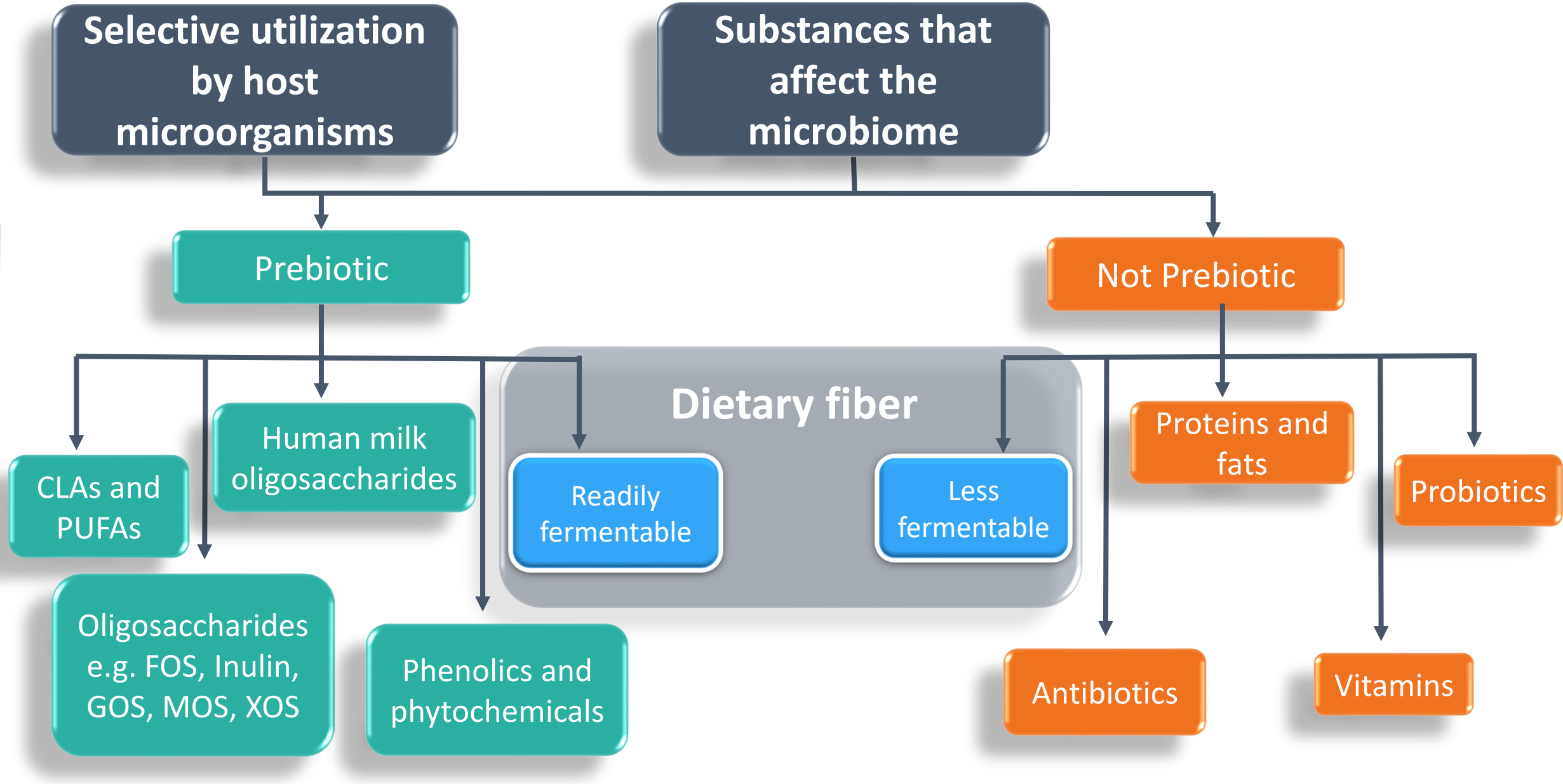
Dietary Fiber

Fiber is broken into ***soluble*** **and** ***insoluble*** components *(cf. resistant starch identified by other chemical method)*

- ***Soluble*** components are pectins, gums, inulin-type fructans, and mucilages that are **completely fermented** by the bacterial flora.
- ***Insoluble*** components are cellulose, waxes, beta-glucan, 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.**

Kuo SM. The interplay between fiber and the intestinal microbiome in the inflammatory response. Adv Nutr. 2013 Jan 1;4(1):16-28. doi: 10.3945/an.112.003046.



Adapted from Gibson, G., Hutkins, R., Sanders, M. et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol 14, 491–502 (2017). https://doi.org/10.1038/nrgastro.2017.75. Licensed under CC BY 4.0.

Dietary Fiber

- Intake of fiber and whole grains - **inverse relationship with:**
  - Obesity
  - Type 2 diabetes
  - Cardiovascular disease
  - Cancer (colorectal, small intestine, oral, larynx, breast)

- **Mechanisms:** > SCFA, > gut hormones, < transit time, change in intestinal viscosity = less contact with mucosal cells, > estrogen excretion, > antioxidant nutrients

Lattimer JM, Haub MD. Effects of dietary fiber and its components on metabolic health. Nutrients. 2010 Dec;2(12):1266-89. doi: 10.3390/nu2121266.

Dietary Fiber Intake

- Paleolithic (estimated) intake **100 - 125 g/day**
- Recommended daily intake **25 - 35 g/day**
- Actual (average) intake in US **8-15 g/day**
- **Physiologic Properties**
  1. Slows transit in small bowel
  2. Increases stool bulk
  3. Holds on to water
  4. Increases estrogen excretion
  5. Binds minerals and organotoxins
  6. Stimulates bacterial growth
  7. Metabolized to SCFA

Dietary Fiber

In Your Toolkit

Food Sources:
Dietary Fiber

Dietary fiber comes from plant foods, including fruits, vegetables, legumes, nuts, seeds, and grains. The fiber in plant foods is not digested by enzymes present in the digestive tract, but it may be digested by the microorganisms that inhabit the intestines.

Dietary fiber is usually described as "soluble" or "insoluble," based on its ability to dissolve in water. As an example, the inner portion of an apple contains soluble fiber, whereas the peel is made of insoluble fiber. Soluble fiber can contribute to a feeling of fullness and helps with weight management. It also helps to decrease the absorption of dietary sugars and fats, thereby helping to manage blood sugar and blood fat levels. Soluble fiber also serves as a food source for the beneficial bacteria that inhabit the digestive tract. The insoluble fiber in plant foods is helpful in moving waste products through the digestive tract. It also provides bulk to the stool and is beneficial in preventing constipation, hemorrhoids, and diverticuli.

The Dietary Reference Intake for dietary fiber (soluble and insoluble fiber, combined) is as follows:

- **Females, age 18-50**: 25 grams per day
- **Females, ages 51 and above**: 21 grams per day
- **Males, ages 18-50**: 38 grams per day
- **Males, ages 51 and above**: 30 grams per day

Food Sources of Soluble Fiber (food, standard serving size)	Amount of Dietary Fiber (g)
Black beans (cooked), 3/4 cup	5.4
Lima beans, 3/4 cup	5.3
Tofu, 3/4 cup	2.8
Avocado, 1/2 whole	2.1
Brussels sprouts, 1/2 cup	2.0
Sweet potato (cooked), 1/2 cup	1.8
Asparagus (cooked), 1/2 cup	1.7
Turnip (cooked), 1/2 cup	1.7

Food Sources of Insoluble Fiber (food, standard serving size)	Amount of Dietary Fiber (g)
Wheat bran, 1/2 cup	12.5
Navy beans (cooked), 1/2 cup	9.5
Kidney beans (cooked), 1/2 cup	8.2
Lentils (cooked), 1/2 cup	7.8
Black beans (cooked), 1/2 cup	7.5
Oat bran, 1/2 cup	7.0
Okra, 1/2 cup	3.1
Turnip (cooked), 1/2 cup	3.1
Peas, 1/2 cup	3.0

References

1. Food Composition Database Nutrients List. Food Composition Database. https://ndb.nal.usda.gov/ndb/nutrients/index. Accessed September 6, 2018.

IFM

Version 1

Summary: Feeding

- Prebiotics from foods may generally be incorporated into a dietary protocol unless contraindicated.
- Prebiotics may often be accompanied with probiotics (from food or supplements) unless contraindicated.

Summary: Feeding

- Prebiotic supplements should be assessed for quality and purchased from a reputable commercial manufacturer.
- Prebiotics supplements are often added initially in a dysbiosis protocol and with an initial treatment time of 6-12 weeks.
- Prebiotic supplements can generally be continued indefinitely.

Summary: Feeding

Laboratory stool assessment of:

(1) Low short chain fatty acids (SCFA) and/or low butyrate

(2) Stool assessment showing a deficiency in the commensal flora

…should result in

> Dietary recommendations incorporating prebiotics

> Supplemental recommendations incorporating prebiotics

FEEDING (Prebiotics)

First Steps	Treatment Considerations	Treatment Based on Labs
Prebiotics from foods may be incorporated into a dietary protocol unless contraindicated. Prebiotics may be accompanied with probiotics (from food or supplements) unless contraindicated.	Prebiotic supplements should be assessed for quality and purchased from a reputable commercial manufacturer. Prebiotics supplements are often added initially in a dysbiosis protocol and with an initial treatment time of **6-12 weeks.** Prebiotic supplements can generally be continued indefinitely.	Laboratory stool assessment indicating: (1) low SCFAs and/or low butyrate (2) a deficiency in the commensal flora **…should result in** Dietary and supplemental recommendations incorporating prebiotics.

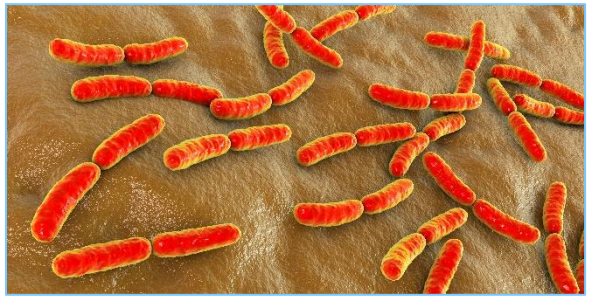
Seeding

Feeding and Seeding the Microbiome

- **Diet** (Food as Medicine)
  - Prebiotics
  - Fermented foods
  - Specific carbohydrates
  - Soluble fiber
  - Synbiotics = Pre- + Pro-biotics

- **Probiotics** (Bugs as Drugs)
  - Dosage?
  - Strains?
  - Safety?

Probiotics Definition



Definition: [Greek, *pro* = for, *biosis* = life]

Non-pathogenic micro-organisms that, when ingested, exert a positive influence of host health or physiology

A probiotic must be of human origin, be resistant to destruction by gastric acid and bile, adhere to intestinal epithelial tissue, and be able to colonize the gastrointestinal tract (if only for a short period).

1. Schrezenemeir J, deVrese M. Prebiotics, probiotics, and synbiotics – approaching a definition. *Am J Clin Nutr* 2001;73:361S-364S.
2. Isolauri E, Sutas Y, Kankaanpaa, et al. Probiotics: effects on immunity. *Am J Clin Nutr* 2001;73:444S-450S.

Probiotic Use: Health Care Costs and Societal Impact

1. When productivity loss is included, total savings for society by use of probiotics: **784 million or 1.4 billion USD** (YHEC and Cochrane scenarios, respectively).

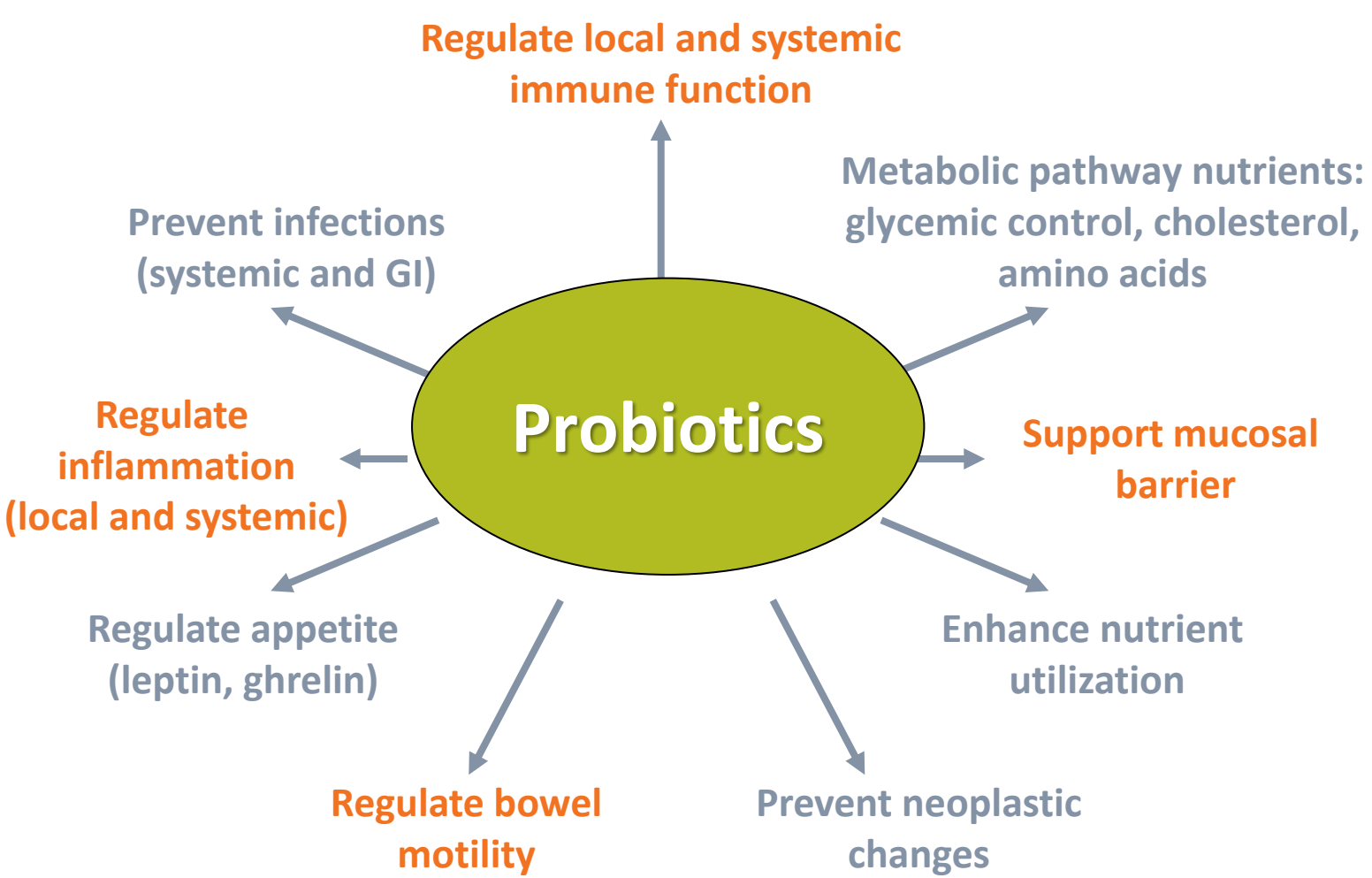
2. Antibiotic prescriptions **decreased with 1.39-2.16 million courses**.

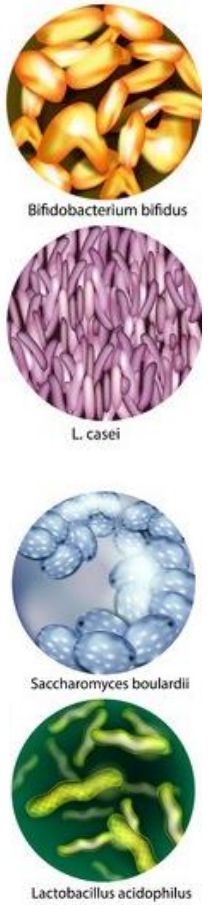
3. Absence from work **decreased by 3.58-4.2 million days** (YHEC and Cochrane data, respectively).

Conclusion: Improved disease outcomes through the use of probiotics translated into considerable cost savings for both the payer and society.

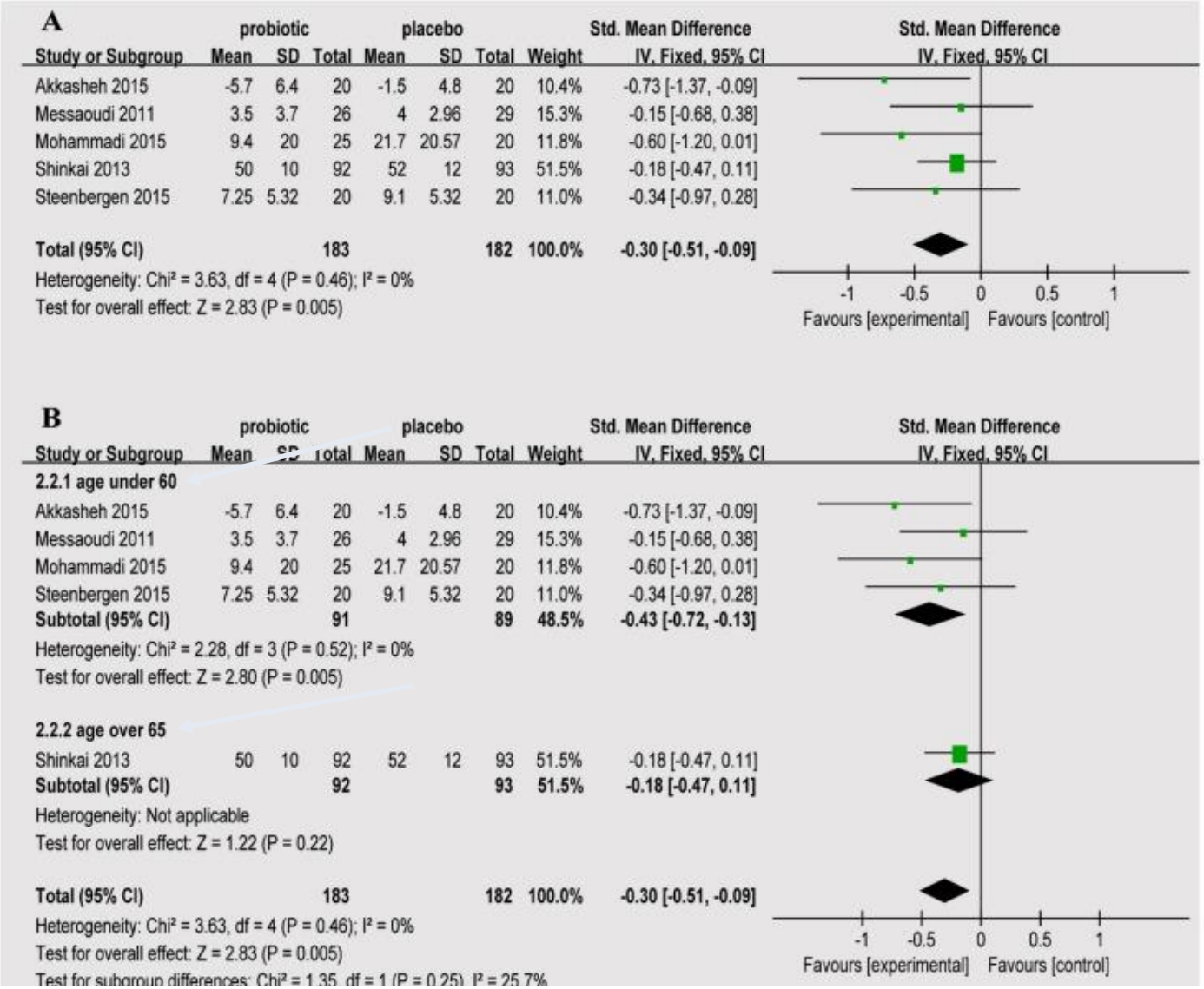
Lenoir-Wijnkoop I, Merenstein D, Korchagina D, Broholm C, Sanders ME, Tancredi D. Probiotics Reduce Health Care Cost and Societal Impact of Flu-Like Respiratory Tract Infections in the USA: An Economic Modeling Study. Front Pharmacol. 2019 Aug 28;10:980. doi: 10.3389/fphar.2019.00980.

Exploring the Mutually Beneficial Effects of Probiotic Bacteria in the Human Host





Can we link Joan's symptoms of IBS and depression to a lack of probiotics in particular?



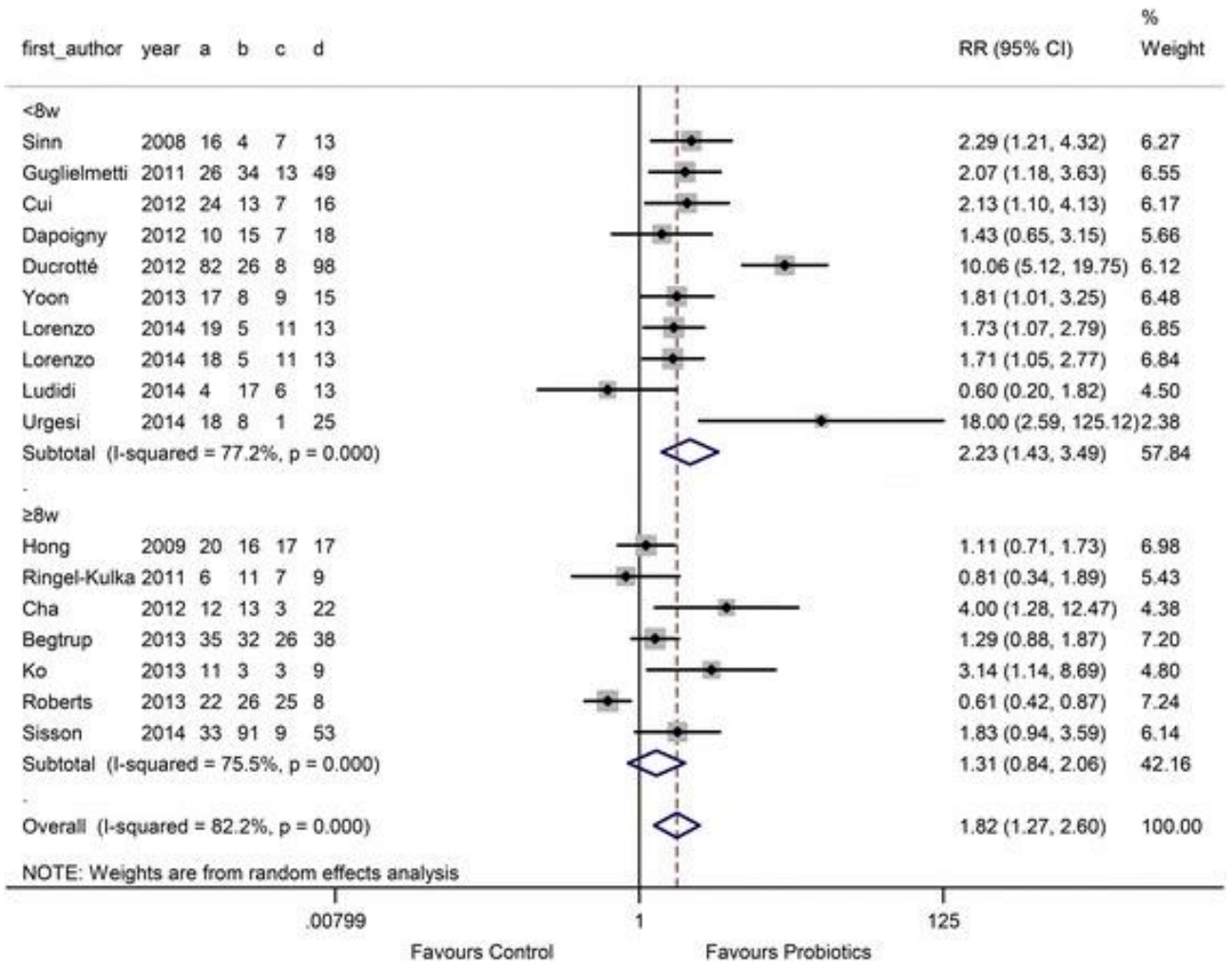
Effect of Probiotics on Depression:

A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Huang R, Wang K, Hu J. Effect of Probiotics on Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2016 Aug 6;8(8):483. doi: 10.3390/nu8080483.

Meta-analysis for Probiotic Use in IBS

- **< 8 weeks=> 8 weeks**
- **Dose <10^{10}=>10^{10}**
- **QOL, IBS symptoms**
- Strain-specific?



Zhang, Y., Li, L., Guo, C. et al. Effects of probiotic type, dose and treatment duration on irritable bowel syndrome diagnosed by Rome III criteria: a meta-analysis. BMC Gastroenterol 16, 62 (2016). https://doi.org/10.1186/s12876-016-0470-z. Licensed under CC BY 4.0.

2015 Yale/Harvard Consensus Opinion

- Various probiotic strains/uses for:
  - Diarrhea
  - IBS
  - IBD
  - Allergy
  - Radiation enteritis
  - Vaginosis and vaginitis
  - Liver Disease

Floch MH et al. Recommendations for Probiotic Use--2015 Update: Proceedings and Consensus Opinion. J Clin Gastroenterol. 2015 Nov-Dec;49 Suppl 1:S69-73. doi: 10.1097/MCG.0000000000000420.

Probiotic Supplements

- >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?

Common Probiotic Supplements

***Lactobacillus* sp.**

- > *reuteri*
- > *casei*
- > *rhamnosus*
- > *acidophilus*
- > *plantarum*

***Bifidobacterium* sp.**

- >*infantis*
- >*lactis*
- >*longum*
- >*breve*
- >*bifidum*

***Streptococcus* sp.**

S. boulardii (nonhuman)

Probiotics: Practical Issues

Which probiotic to prescribe,

at what dose,

and for how long?

Probiotics: Practical Issues

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

Govender M, Choonara YE, Kumar P, du Toit LC, van Vuuren S, Pillay V. A Review of the Advancements in Probiotic Delivery: Conventional vs. Non-conventional Formulations for Intestinal Flora Supplementation. AAPS PharmSciTech. 2014;15(1):29-43. doi:10.1208/s12249-013-0027-1.

Probiotics: Practical Issues

PROBIOTIC

Extreme Strength

----------10 billion extra----------

FRIENDLY BACTERIA

- **Not well regulated**
  - Quality control is poor.
  - Studies conducted worldwide have shown that inconsistencies and deviations from the information provided on the product label are common.
- **Numerous preparations on the market**
  - Which strains work best?
  - Do different strains work better for different diseases?
  - Do combinations work better than single strains?

Kolaček S, Hojsak I, Canani RB, Guarino A et al…ESPGHAN Working Group for Probiotics and Prebiotics. Commercial probiotic products: A call for improved quality control. A Position Paper by the ESPGHAN Working Group for Probiotics and Prebiotics. J Pediatr Gastroenterol Nutr. 2017 Apr 11. doi: 10.1097/MPG.0000000000001603.

Practical Issues: Quality Control is Important

- 2016 UK study:
  - All products evaluated contained viable probiotic bacteria but **only 3 out of the 7** products (43%) contained the claimed culture concentration or more.
  - **None** of the multispecies product contained all the labeled probiotic bacteria.
  - **Misidentification of some species** occurred.
- 2010 US study: **Only 4 of 13 products** (31%) were in accordance with label claims.

1. Fredua-Agyeman, Mansa, Parab, Shruti and Gaisford, Simon. Evaluation of Commercial Probiotic Products. British Journal of Pharmacy. 2016; 1(1). doi: 10.5920/bjpharm.2016.11
2. Drago L, Rodighiero V, Celeste T, Rovetto L, De Vecchi E. Microbiological evaluation of commercial probiotic products available in the USA in 2009. J Chemother. 2010 Dec;22(6):373-7.

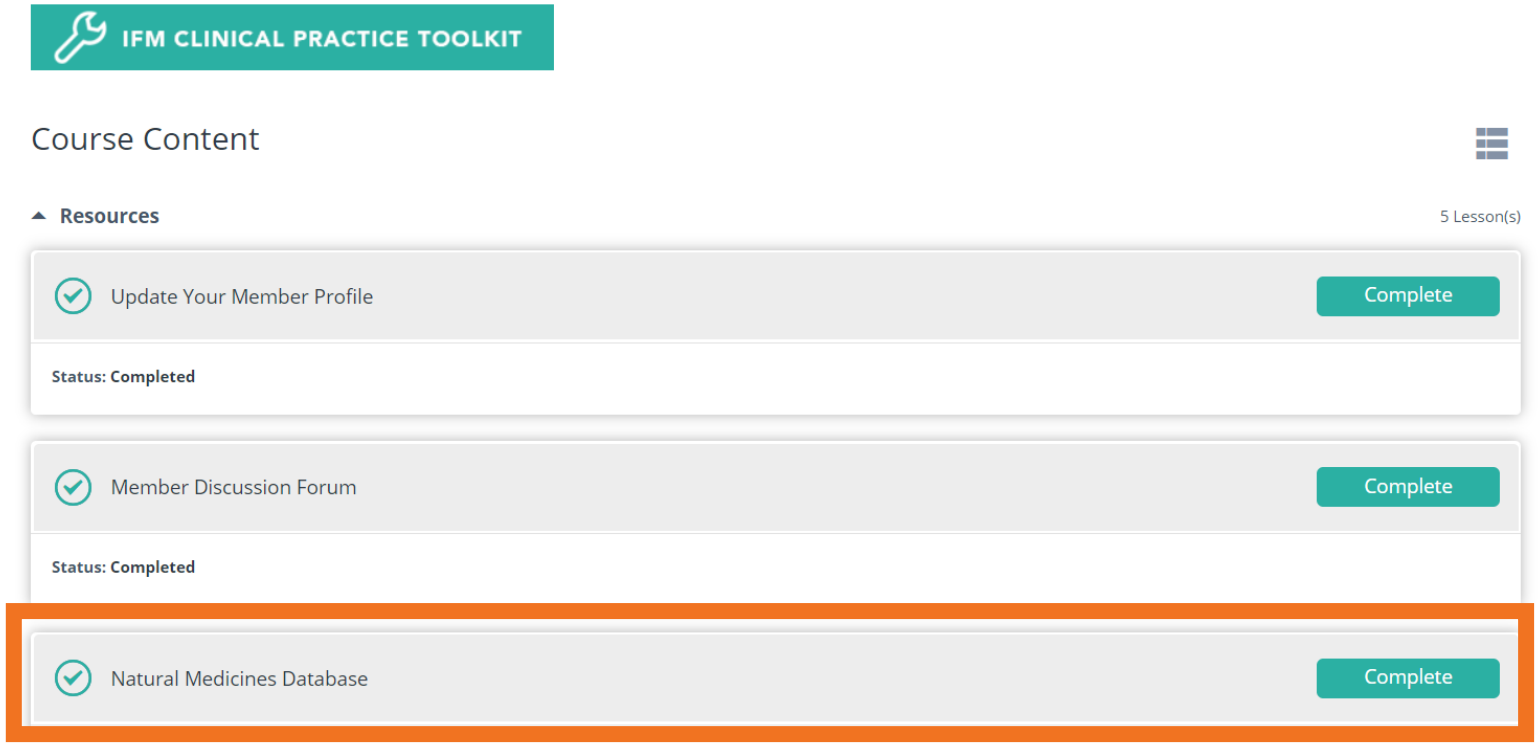
Probiotics: Practical Issues

- Typically $1 to $3 per day
  - VSL#3®: $98 for 30 sachets
  - Culturelle® (LGG): $25 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

Probiotic Prescribing: Resources to Consider

- Natural Medicine Database (free with IFM membership)
- USProbioticguide.com
  - (free)
- Probiotic Advisor
  - *(subscription)*



Lactobacilli and Bifidobacteria: Safety

- Used in pregnancy and infants without incidence of harm
- Normal to human body
- Cases of **infection extremely rare**
  - Account for 0.05% to 0.4% of infective endocarditis and bacteremia
  - Less than 1 case per million people

Summary: Seeding

- Probiotics from foods may generally be incorporated into a dietary protocol unless contraindicated.
- Probiotics from foods or as supplements may generally be prescribed with acute administration of antibiotics [esp. *S. boulardii*]
- Probiotics may often be accompanied with prebiotics (from food or supplements) unless contraindicated.

Summary: Seeding

- Probiotic supplements should be assessed for quality and purchased from a reputable commercial manufacturer.
- Probiotics supplements are often added initially in a dysbiosis protocol and with an initial treatment time of 6-12 weeks.
- Probiotic supplements can generally be continued indefinitely.

Summary: Seeding

Laboratory stool assessment of:

(1) Stool assessment showing a deficiency in the commensal flora

(2) OR stool culture assessment showing elevated potentially pathogenic bacteria

…should result in

> Dietary recommendations incorporating probiotics

> Supplemental recommendations incorporating probiotics

Summary: Seeding

Specific strains, combinations and dosages of probiotic supplements should be based upon:

> Peer reviewed research

and/or

> Clinical experience

	First Steps	Treatment Considerations	Treatment Considerations
SEEDING (Probiotics)	Probiotics from foods may generally be incorporated into a dietary protocol unless contraindicated. Probiotics from foods or as supplements may generally be prescribed with acute administration of antibiotics [esp. *S. boulardii*]. Probiotics may often be accompanied with prebiotics (from food or supplements) unless contraindicated.	Probiotic supplements should be assessed for quality and purchased from a reputable commercial manufacturer. Probiotic supplements are often added initially in a dysbiosis protocol and with an initial treatment time of **6-12 weeks.** Probiotic supplements can generally be continued indefinitely.	Laboratory stool assessment indicating: (1) a deficiency in the commensal flora (2) Elevated potentially pathogenic bacteria **…should result in** Dietary and supplemental recommendations incorporating probiotics.

"Reinoculate" Summary: Joan

- ***Reinoculate*** refers to the **reintroduction of desirable GI microflora** (via prebiotics, probiotics, synbiotics) to obtain a more desirable balance to the intestinal milieu.

- **Clinical approaches may include:**

Probiotics: ✔

- *Bifidobacteria* strains
- *Lactobacillus* strains
- *Saccharomyces boulardii*

Prebiotics: ✔

- Inulin or fructooligosaccharides (FOS)
- Various other soluble fibers

Synbiotics:

- Bifidobacteria and FOS
- Lactobacillus and inulin

Changing The Microflora Of The Gut

- To date **only dietary changes and stool transplants** have been shown to actually *change* the microflora of the gut.

- Probiotics should be thought of as place holders with transient (although important) effects; prebiotics as fertilizer.

Recapping The Treatment Program So Far: Remove, Replace, Reinoculate…

To Start:

- Oligoantigenic elimination diet
- Anti-parasitic protocol
    - Prescriptive medication
    - Botanical combination
- Pancreatic enzymes
- Probiotics/Prebiotics

Part 3

Practical Applications Using The "5R" Approach

Does Joan need to ***Repair*** her GI lining?

- Determine need for support of intestinal lining
  - Foundation
    - Elimination Diet
    - Pre- and Probiotics

Foundational GI Repair Protocol

- Elimination Diet
- Probiotics
- Vitamin D
- Omega-3 Fatty Acids
- L-Glutamine

Vitamin D & Repair: Summary

- Vitamin D **decreases inflammation:**
  - ✓down-regulates nuclear factor-kB (NF-kB) activity
  - ✓increases IL-10 production
  - ✓decreases IL-6, IL-12, IFN-c, and TNF-a production
- **IBD risk:** Vitamin D deficiency may compromise the mucosal barrier, leading to increased susceptibility to mucosal damage and increased risk of IBD.

1. Levin A, Li YC. Vitamin D and its analogues: Do they protect against cardiovascular disease in patients with kidney disease? Kidney International. 2005;68(5):1973–1981. DOI:10.1111/j.1523-1755.2005.00651.x
2. Kong J, Zhang Z, Musch MW, et al. Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. Am J Physiol Gastrointest Liver Physiol. 2008;294(1):G208-16. DOI:10.1152/ajpgi.00398.2007
3. Cantorna MT, Mahon BD. D-Hormone and the Immune System. J Rheumatol Suppl. 2005;76:11-20.

Vitamin D Treatment Protocols

Therapeutic dosages:

30-75 lbs = up to 1000 iu/d

76-125 lbs = up to 2-3000 iu/d

> 125 lbs = up to 4-5000iu/d

***Recheck in 8 weeks**

Acute protocol: 50,000 iu once/twice per week for 8 weeks, recheck 25-OH (D)

If 25-OH (D) levels not normal after 8 weeks, continue protocol and recheck serum calcium every 2 weeks, re-evaluate intestinal absorption efficiency.

Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Jul;96(7):1911-30. doi: 10.1210/jc.2011-0385. Epub 2011 Jun 6. Erratum in: J Clin Endocrinol Metab. 2011 Dec;96(12):3908. PMID: 21646368.

Practical Applications Using The "5R" Approach

Does this patient need to have ***Repair*** for the GI lining?

- Determine need for support of intestinal lining
  - Anti-Inflammatory Foundation
    - Elimination Diet
    - Probiotics
    - Vitamin D
    - Omega-3 Fatty Acids
    - L-Glutamine

Omega 3 Fatty Acids & Repair: Summary

- EPA appears to exert much of its anti-inflammatory benefit by suppressing NF-kappaB activation via activation of PPAR-alpha and thus reducing elaboration of proinflammatory mediators.
- When endoscopic endpoints were used to evaluate the role of fish oil in the treatment of ulcerative colitis, 3 of 3 studies showed statistically significant improvement in the study group that received fish oil supplementation.
- The safety of fatty acid supplementation is high and has been well established in numerous clinical studies. Drug interactions are extremely rare with fatty acids.
- A dose of up to 3 g per day of EPA plus DHA has been determined to be safe for general consumption.

1. Vasquez Alex. (2005). Reducing Pain and Inflammation Naturally. Part ll: New Insights into Fatty Acid Supplementation and Its Effect on Eicosanoid Production and Genetic Expression. Nutritional Perspectives. 28(1): 1-16.
2. Clarke JO, Mullin GE. A Review of Complementary and Alternative Approaches to Immunomodulation. Nutrition in Clinical Practice. 2008;23(1):49–62.

Omega-3 Treatment Protocols (EPA/DHA)

Therapeutic dosages:

30-75 lbs = at least 1 g/d (total Omega 3's)

76-125 lbs = at least 2g/d (total Omega 3's)

> 125 lbs = 3+ g/d (total Omega 3's)

NB: Numerous studies regarding the impact of Omega 3's on Cardiovascular and Cognitive function show **beneficial results with dosages of 3 g/d up to 20 g/d.** Caution is recommended regarding hypocoagulability.

See References: Omega 3 RBC level and disease

References: Omega 3 RBC level and disease

1. Block, R. C., Harris, W. S., Reid, K. J., Sands, S. A., & Spertus, J. A. (2008). EPA and DHA in blood cell membranes from acute coronary syndrome patients and controls. *Atherosclerosis*, *197*(2), 821-828. doi: 10.1016/j.atherosclerosis.2007.07.042
2. Fougère, B., Goisser, S., Cantet, C., Soriano, G., Guyonnet, S., De Souto Barreto, P., Cesari, M., Andrieu, S., Vellas, B., MAPT Study Group (2017). Omega-3 fatty acid levels in red blood cell membranes and physical decline over 3 years: longitudinal data from the MAPT study. *GeroScience*, *39*(4), 429–437. doi:10.1007/s11357-017-9990-x
3. Harris, W. S., Luo, J., Pottala, J. V., Espeland, M. A., Margolis, K. L., Manson, J. E., ... & Robinson, J. G. (2017). Red blood cell polyunsaturated fatty acids and mortality in the Women's Health Initiative Memory Study. *Journal of clinical lipidology*, *11*(1), 250-259. doi: 10.1016/j.jacl.2016.12.013
4. Pottala, J. V., Garg, S., Cohen, B. E., Whooley, M. A., & Harris, W. S. (2010). Blood eicosapentaenoic and docosahexaenoic acids predict all-cause mortality in patients with stable coronary heart disease: the Heart and Soul study. *Circulation: Cardiovascular Quality and Outcomes*, CIRCOUTCOMES-109. doi: 10.1161/CIRCOUTCOMES.109.896159
5. Tan, Z. S., et al. (2012). Red blood cell ω-3 fatty acid levels and markers of accelerated brain aging. *Neurology*, *78*(9), 658-64. doi: 10.1212/WNL.0b013e318249f6a9

Omega-3 Treatment Protocols (EPA/DHA)

- RBC fatty acid composition reflects long-term intake of omega-3 fatty acids.
- Percentage of DHA+EPA in RBC:
  - High Risk = < 4%
  - Intermediate risk = 4–8%
  - Low risk = > 8%

  *Therapeutic Omega-3 Index (>5.5 is good, 8-10 is optimal)

Therapeutic dosages: 1gm EPA+DHA increases Omega-3 Index 1.5%

1. von Schacky C. Use of red blood cell fatty-acid profiles as biomarkers in cardiac disease. Biomark Med. 2009;3(1):25–32. doi:10.2217/17520363.3.1.25
2. Harris WS. Omega-3 fatty acids and cardiovascular disease: a case for omega-3 index as a new risk factor. *Pharmacol Res*. 2007;55(3):217–223. doi:10.1016/j.phrs.2007.01.013

Omega-3 Foods

Regular consumption of *n*-3-enriched foods increased EPA + DHA intake from 0.2 to 1.0 g/d which was also reflected in increased RBC omega-3 levels.

Murphy, K. J., Meyer, B. J., Mori, T. A., Burke, V., Mansour, J., Patch, C. S., ... & Puddey, I. B. (2007). Impact of foods enriched with n-3 long-chain polyunsaturated fatty acids on erythrocyte n-3 levels and cardiovascular risk factors. British Journal of Nutrition, 97(4), 749-757. doi: 10.1017/S000711450747252X (8)

Foundational GI Repair Protocol

- Elimination Diet
- Probiotics
- Vitamin D
- Omega-3 Fatty Acids
- L-Glutamine

L-Glutamine

- Preferred fuel for enterocytes of small intestine
- Increases intestinal villous height
- Stimulates gut mucosal cellular proliferation
- Maintains mucosal integrity
- Prevents intestinal hyperpermeability and bacterial translocation

Miller AL. Therapeutic considerations of L-glutamine: a review of the literature. *Altern Med Rev.* 1999 Aug;4(4):239-48.

L-Glutamine & Repair: Summary

- The gastrointestinal tract is by far the greatest user of glutamine in the body, as enterocytes in the intestinal epithelium use glutamine as their principal metabolic fuel.
- Glutamine-enriched TPN decreases villous atrophy, increases jejunal weight, and decreases intestinal permeability.
- A clinical study of ulcerative colitis patients:
  - 30 g daily of glutamine four weeks
  - Significant clinical and endoscopic improvement, independent of disease state.
  - Disease exacerbation returned when treatment was discontinued.

Monograph: L-Glutamine. Alternative Medicine Review. 2001;6(4):406.

L-Glutamine Treatment Protocols

Dosages vary greatly depending on the clinical situation.

- 2-4 g/d in divided dosages for wound healing and general intestinal support
- 10-40 g/d in divided dosages for critically ill and advanced disease

1. Kjaer M, Frederiksen AKS, Nissen NI, et al. Multinutrient Supplementation Increases Collagen Synthesis during Early Wound Repair in a Randomized Controlled Trial in Patients with Inguinal Hernia. J Nutr. 2020 Apr 1;150(4):792-799. doi: 10.1093/jn/nxz324
2. Chen QH, Yang Y, He HL, et al. The effect of glutamine therapy on outcomes in critically ill patients: a meta-analysis of randomized controlled trials. Crit Care. 2014 Jan 9;18(1):R8. doi: 10.1186/cc13185. Erratum in: Crit Care. 2014;18(3):436. PMID: 24401636; PMCID: PMC4057299.

Remember other "Repair" clinical approaches may include:

- **GI repair and healing:**
  - > Additional considerations: Arginine, Vitamin A, Vitamin C, Zinc, Pantothenic acid, Vitamin E, Carotenoids
- **Other considerations:**
  - > **Mucosal lining support** (e.g., phosphatidylcholine)
  - > **Mucosal secretion protectants** such as phosphatidylcholine, plantain, polysaccharides
  - > **Support for GALT function** (e.g., lactoferrin, lactoperoxidase, whey immunoglobulins)
  - > **Antioxidants** known to function in the GI (e.g., catechins)
  - > Other nutritional and phytonutritional **anti-inflammatories**: curcumin

GI Repair and Healing

- **Arginine**
- **Zinc**
- **Pantothenic acid**
- **Antioxidants (Vitamin A, C, E, carotenoids)**

1. Mijan MA, Lim BO. Diets, functional foods, and nutraceuticals as alternative therapies for inflammatory bowel disease: Present status and future trends. World J Gastroenterol. 2018 Jul 7;24(25):2673-2685. doi: 10.3748/wjg.v24.i25.2673.

2. Masri OA, Chalhoub JM, Sharara AI. Role of vitamins in gastrointestinal diseases. World J Gastroenterol. 2015;21(17):5191–5209. doi:10.3748/wjg.v21.i17.5191

Mucosal Lining Support

Phosphatidylcholine (PC):

- Phospholipids are important for the maintenance of an intact barrier function as they help establish the hydrophobic surface by virtue of their amphipathic nature. Phosphatidylcholine is the major mucus phospholipid.
- A lack of PC could result in a reduction in surface hydrophobicity, enabling the invasion of luminal noxious agents.
- PC also participates in various mucosal pathways including TNFα signaling, activation of NF-κB cytokine expression and mitogen-activated protein kinase.
- PC has been found to be substantially reduced in the mucus of patients with UC compared with patients with Crohn's disease (CD) and healthy controls, independent of the state of inflammation.

1. Torres J, Danese S, Colombel JF. New therapeutic avenues in ulcerative colitis: thinking out of the box. Gut. 2013 Nov;62(11):1642-52. doi: 10.1136/gutjnl-2012-303959.
2. Stremmel W, Ehehalt R, Staffer S, Stoffels S, Mohr A, Karner M, Braun A. Mucosal protection by phosphatidylcholine. Dig Dis. 2012;30 Suppl 3:85-91. doi: 10.1159/000342729.

Mucosal secretion protectants

- **Polysaccharides:** Xyloglucan, a natural polysaccharide derived from tamarind seeds, has a "mucin-like" molecular structure that confers mucoadhesive properties. This allows xyloglucan formulations to act as a barrier, lowering bacterial adherence and invasion while also preserving tight junctions and paracellular flux.
  - In clinical trials, xyloglucan has been seen to reduce symptoms of gastroenteritis in adults and children, nasal disorders and dry eye syndrome.
  - Similar mucosal protectors containing reticulated proteins have also been useful for the treatment of irritable bowel syndrome and urinary tract infections.
- **Phosphatidylcholine:** The colonic mucus serves a first barrier towards invasion of commensal bacteria in stools to prevent inflammation. One essential component of intestinal mucus is phosphatidylcholine (PC).

1. Piqué N, Gómez-Guillén MDC, Montero MP. Xyloglucan, a Plant Polymer with Barrier Protective Properties over the Mucous Membranes: An Overview. Int J Mol Sci. 2018 Feb 27;19(3).
2. Stremmel W, Ehehalt R, Staffer S, Stoffels S, Mohr A, Karner M, Braun A. Mucosal protection by phosphatidylcholine. Dig Dis. 2012;30 Suppl 3:85-91. doi: 10.1159/000342729.

GALT Function

- **Lactoferrin:** A glycoprotein of the primary innate immune-defense system present in milk and other mucosal secretions. It exhibits immunomodulatory activities (up and down-regulating innate and adaptive immune cells) which contributes to the homeostasis in mucosal surfaces.
- **Lactoperoxidase**
- **Whey immunoglobulins**

1. Artym J, Zimecki M. [The role of lactoferrin in the proper development of newborns]. Postepy Hig Med Dosw (Online). 2005;59:421-32.
2. Dix C, Wright O. Bioavailability of a Novel Form of Microencapsulated Bovine Lactoferrin and Its Effect on Inflammatory Markers and the Gut Microbiome: A Pilot Study. Nutrients. 2018 Aug 17;10(8). pii: E1115. doi: 10.3390/nu10081115.
3. Brimelow RE, West NP, Williams LT, Cripps AW, Cox AJ. A role for whey-derived lactoferrin and immunoglobulins in the attenuation of obesity-related inflammation and disease. Crit Rev Food Sci Nutr. 2017 May 24;57(8):1593-1602. doi: 10.1080/10408398.2014.995264.

TGF-β-enriched Formulas for Crohn's Disease Using Whey Protein

- 3 cohort studies evaluated TGF-β-enriched formula in patients with Crohn's disease.

- TGF-β diet for 8 weeks as sole nutrition - **improvements:**
  - **ESR and CRP levels**
  - **Serum albumin levels**
  - **Mucosal healing, Clinical Disease Activity**
  - **Serum IL-1β, IL-8, and IFN-γ**

- ***Remission both clinical and endoscopic was achieved.***

See References: TGF-β-enriched Formulas for Crohn's Disease

References: TGF-β-enriched Formulas for Crohn's Disease

1. Beattie RM, Schiffrin EJ, Donnet-Hughes A, et al. Polymeric nutrition as the primary therapy in children with small bowel Crohn's disease. Aliment Pharmacol Ther. 1994 Dec;8(6):609-15.
2. Fell JM, Paintin M, Arnaud-Battandier F, et al. Mucosal healing and a fall in mucosal pro-inflammatory cytokine mRNA induced by a specific oral polymeric diet in paediatric Crohn's disease. Aliment Pharmacol Ther. 2000 Mar;14(3):281-9.
3. Afzal NA, Van Der Zaag-Loonen HJ, Arnaud-Battandier F, et al. Improvement in quality of life of children with acute Crohn's disease does not parallel mucosal healing after treatment with exclusive enteral nutrition. Aliment Pharmacol Ther. 2004 Jul 15;20(2):167-72.

Antioxidants for GI Function

Green tea *(Camellia sinensis)* standardized to *catechins* 100-300 mg TID

- Catechins can regulate the infiltration and proliferation of immune related-cells as well as exerting their significant anti-inflammatory properties by regulating the activation or deactivation of inflammation-related oxidative stress-related cell signaling pathways.

1. Fan FY, Sang LX, Jiang M. Catechins and Their Therapeutic Benefits to Inflammatory Bowel Disease. Molecules. 2017 Mar 19;22(3). pii: E484. doi: 10.3390/molecules22030484.

Other Nutritional and Phytonutritional Anti-Inflammatories

Curcumin:

- Best evidence was found for herbal therapy, ie plantago ovata and curcumin in UC maintenance therapy

1. Langhorst J et al. Systematic review of complementary and alternative medicine treatments in inflammatory bowel diseases. J Crohns Colitis. 2015 Jan;9(1):86-106. doi: 10.1093/ecco-jcc/jju007.
2. Burge K, Gunasekaran A, Eckert J, Chaaban H. Curcumin and Intestinal Inflammatory Diseases: Molecular Mechanisms of Protection. Int J Mol Sci. 2019 Apr 18;20(8). pii: E1912. doi: 10.3390/ijms20081912.

"Repair" Summary: Joan

Repair refers to **providing nutritional support for healing and regeneration of the GI mucosa.**

- **Clinical approaches include:**
  - Nutrients important for GI repair and healing: Glutamine, arginine, vitamin A, vitamin D, vitamin C, zinc, pantothenic acid, vitamin E, carotenoids
  - Nutritional and phytonutritional anti-inflammatories (e.g., curcumin, EPA, and DHA)

Recapping The Treatment Program So Far: Remove, Replace, Reinoculate, Repair…

To start:

- **Oligoantigenic elimination diet**
- **Anti-parasitic protocol**
    - Prescriptive medication
    - Botanical combination
- **Pancreatic enzymes**
- **Probiotics/Prebiotics**

Consider:

- Repair **medical food/individual nutrients**

Practical Applications Using The “5R” Approach

Does Joan need to have her gut ***ReBalanced*****?**

FUNCTIONAL MEDICINE MATRIX

Retelling the Patient's Story

Antecedents

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

Triggering Events

Parents div @7; blended fm @9
Abd pn @10
Dx Lactose Intol. Part improvement
2 kids@27&29 wt post part dep.
Div at 34yo (has two teen boys)

Mediators/Perpetuators

SAD
Weight gain in college

Physiology and Function: Organizing the Patient's Clinical Imbalances

Assimilation

- Gas and Bloating
- Freq stools
- Low pancreatic elastase
- Dysbiosis (SCFA,n-Butyrate decreased

Defense & Repair

SAD (inflammatory diet)

Structural Integrity

Mental **Emotional**

Stressful job
Family Dynamic?

Energy

History of Depression

Communication

Depression
Stress (adrenal)

Biotransformation

Transport

Modifiable Personal Lifestyle Factors

Sleep & Relaxation	Exercise & Movement	Nutrition	Stress	Relationships
Poor; has to be up t get the kids ready	NONE; "no time"	SAD; quick meals dt being busy	Kids are a "handful" Job is stressful (bank exec asst.)	"boys are a handful" Not dating

Name: _____ Date: _____ CC: _____

IFM

The 5th “R”

Rebalance

Modify attitude, diet, and lifestyle of the patient to promote a healthier way of living

"Rebalance" Summary: Joan

- ***Rebalance*** refers to **providing support for restorative processes in a patients life.**
- **Clinical approaches may include:**
  - 'Scheduling' and relaxation ✔
  - Mindful eating and better choices
  - Heart rate variability/ biofeedback
  - Yoga, meditation, prayer, breathing, or other centering practices
  - Psychotherapy etc.
  - Neuroplasticity (Retraining the Brain)

References: Rebalance

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Recapping The Treatment Program So Far: 5Rs

To start:

- **Oligoantigenic elimination diet**
- **Anti-parasitic protocol**
    - Prescriptive medication
    - Botanical combination
- **Pancreatic enzymes**
- **Probiotics/Prebiotics**

Consider:

- Repair **medical food/individual nutrients**
- **Immune support** for decreased SIgA
- Rebalance

Psycho-emotional impact on the microbiome

1. Stress suppresses Lactobacillus, Bifidobacteria, & sIgA
2. Catecholamines stimulate growth of gram-negative organisms (Yersinia, Pseudomonas)
    - 45-50% of total body production of norepinephrine occurs in mesenteric organs
3. Anger or fear increases *Bacteroides fragilis*

See References: Psycho-emotional impact on the microbiome

References: Psycho-emotional impact on the microbiome

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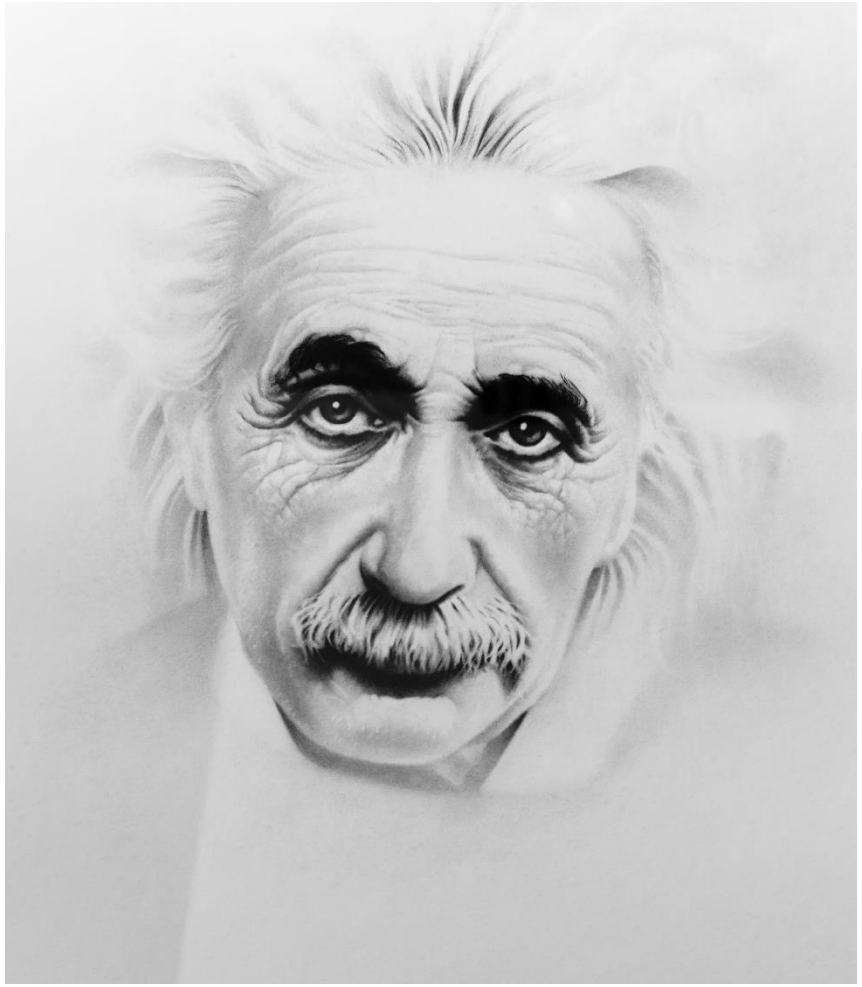
Patterns That Connect The Web:

"It is a wonderful feeling to recognize the unity of complex phenomena that, to direct observation, appear to be quite separate things.

Albert Einstein



Prof. Walter Kotschnig told Holyoke College students to…

Keep their minds open—"but not so open that your brains fall out."

Unless there is a compelling reason to do otherwise –

TREAT THE GUT.

The GI system is an integral and central "node" of the complex web of functional medicine.

- Dysregulation of the GI system can have a profound impact on health.
- Consider the inter-relationships of:
  - Digestion and absorption
  - Intestinal permeability
  - GI flora (all types)
  - Immune regulation and inflammation.
  - Nervous system relationships

GI Dysfunction (5R Protocol): Clinical Takeaways

- **R**emove
- **R**eplace
- **R**einoculate
- **R**epair
- **R**ebalance

The Conceptual Approach **Asks 5 Basic Questions**:

1. What does this patient need to have ***Removed?***
2. What does this patient need to have ***Replaced?***
3. What does this patient need in terms of support and/or re-establishment of a healthy balance of microflora; that is, what does he/she require to ***Reinoculate*** the gut?
4. What does this patient require to support healing and ***Repair*** of the GI epithelial barrier?
5. What does this patient need to do to ***Rebalance*** their lifestyle; that is, are there ways to modify their attitude and lifestyle to promote a healthier way of living, and thus healthier gut balance?

"Remove"

Remove refers to the elimination of factors such as:

- **Foods** to which an individual is sensitive, intolerant, or allergic
- **Pathogenic microflora** (e.g., bacteria, fungi, parasites)
- **Environmental stressors** such as pollutants
- **Stress**

Clinical approaches may include:

- Oligoantigenic elimination diet
- Botanical antimicrobials or bacteriostatic/bacteriocidal phytonutrients
- Antibiotics/Antifungal medications
- Removal of toxins and stressors

"Replace"

Replace refers to the replacement of factors that may be inadequate or lacking.

Clinical approaches may include:

- Digestive factors
- Hydrochloric acid
- Pancreatic enzymes
- Bile salts
- Fiber to support transit and general GI function

"Reinoculate"

Reinoculate refers to the **reintroduction of desirable GI microflora** (prebiotics, probiotics, synbiotics) to obtain a more desirable balance to the intestinal milieu.

Clinical approaches may include:

Probiotics may include:

- *Bifidobacteria* strains
- *Lactobacillus* strains
- *Saccharomyces boulardii*

Prebiotics may include:

- Inulin or fructooligosaccharides (FOS)
- Various other soluble fibers

Synbiotics may include:

- Bifidobacteria and FOS
- Lactobacillus and inulin

"Repair"

Repair refers to **providing nutritional support for healing and regeneration of the GI mucosa.**

Clinical approaches may include:

- Nutrients important for GI repair and healing: glutamine, arginine, vitamin A, vitamin D, vitamin C, zinc, pantothenic acid, vitamin E, carotenoids
- Mucosal lining support (e.g., phosphatidylcholine)
- Mucosal secretion protectants such as phosphatidylcholine, plantain, polysaccharides
- Support for GALT function (e.g., lactoferrin, lactoperoxidase, whey immunoglobulins)
- Antioxidants known to function in the GI (e.g., catechins)
- Nutritional and phytonutritional anti-inflammatories (e.g., curcumin, EPA, and DHA)

"Rebalance"

Rebalance refers to **providing support for restorative processes in a patients life.**

Clinical approaches may include:

- 'Scheduling' relaxation
- Mindful eating and better choices
- Heart rate variability/ biofeedback
- Yoga, meditation, prayer, breathing, or other centering practices
- Psychotherapy

"The microbe is nothing. The terrain (milieu) is everything."

- *Statement that Louis Pasteur is purported to have made on his deathbed*